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Nipple-Sparing Mastectomy: Critical Assessment of 51 Procedures and Implications for Selection Criteria

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Background: Retrospective studies have shown that occult nipple–areolar complex (NAC) involvement in breast cancer is low, occurring in 6–10% of women undergoing skin-sparing mastectomy (SSM). The cosmetic result and high patient satisfaction of nipple-sparing mastectomy (NSM) has prompted further evaluation of the oncologic safety of this procedure.

Methods: We conducted a retrospective chart review of 36 self-selected patients who underwent 51 NSM procedures between 2002 and 2007. Criterion for patient selection was no clinical evidence of nipple–areolar tumor involvement. All patients had the base of the NAC evaluated for occult tumor by permanent histologic section assessment. We also evaluated tumor size, location, axillary node status, recurrence rate, and cosmetic result.

Results: Malignant NAC involvement was found in 2 of 34 NSM (5.9%) completed for cancer which prompted subsequent removal of the NAC. Of the 51 NSM, 17 were for prophylaxis, 10 for ductal carcinoma in situ (DCIS), and 24 for invasive cancer. The average tumor size was 2.8 cm for invasive cancer and 2.5 cm for DCIS. Nine patients had positive axillary nodes. Overall, 94% of the tumors were located peripherally in the breast. After mean follow-up of 18 months, only two patients (5.9%) had local recurrence.

Conclusion: Using careful patient selection and careful pathological evaluation of the subareolar breast tissue at surgery, NSM can be an oncologically safe procedure in patients where this is important to their quality of life. A prospective study based on focused selection criteria and long-term follow-up is currently in progress.

Surgical technique for breast cancer has evolved over the last 100 years from extremely invasive and disfiguring, to minimally invasive and cosmetically acceptable. Increased screening and use of chemotherapeutic agents have allowed for continued progression to the current standard of breast conservation. However, total mastectomy is still being performed for extensive cancer, risk reduction, and patient preference. The evolution of the mastectomy procedure has brought us to the threshold of using another form of cosmetic enhancement, the nipple-sparing mastectomy. It should be noted that the nipple-sparing mastectomy is essentially the same operation as the subcutaneous mastectomy.

Many studies confirm that the type of surgery a women under goes for her breast cancer is important for body image and feelings of attractiveness.[1,2] Some

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studies indicate that women undergoing breast conservation experience more positive outcomes than women undergoing mastectomy, with or without reconstruction.[1,2] This may be so since a mastectomy is perceived as a loss of a body part that connotes femininity and womanhood.[3] However, other studies indicate that mastectomy with immediate reconstruction yields comparable results in terms of quality of life while delivering improved cosmetic outcome.[4] A nipple-sparing mastectomy with immediate reconstruction may alter a perceived loss while providing an oncologically safe mastectomy that achieves good cosmetic results. Our surgical ability to reconstruct the nipple–areolar complex (NAC) fails to achieve cosmetic satisfaction.[5] The NAC defines the breast and to some it defines femininity; to leave it in place may provide a more acceptable body image. However, nipple-sparing mastectomy (NSM) is still controversial. The prevailing argument is that, if the NAC is left in place, there is a chance of leaving either occult tumor or a concentration of breast tissue that is at risk to develop a subsequent cancer.

The NSM is a skin-sparing mastectomy (SSM) with retention of the NAC. When reviewing the literature concerning the safety of SSM several studies show that local recurrence (LR) is similar to conventional mastectomy.[6–11] Furthermore, LR of breast cancer after SSM is not associated with systemic relapse.[9–11] LR after mastectomy has shown to range from 3% to 7% for early-stage breast cancer and up to 32% for advanced stages.[12,13] LR for skin-sparing mastectomy ranges from 5.5% to 6.2%.[6,8] LR for NSM ranges from 1.5% up to 28.4% with a mean of 5.4%.[14–18] Additionally, studies that specifically assess LR in NSM also show equivalency to SSM and conventional mastectomy.[14–18] It has become apparent that, despite the surgical approach for breast cancer, LR has remained relatively constant, and other tumor characteristics are more predictive of recurrence.[19] Still, patients should be carefully selected for NSM, which we propose should be based on associated predictive factors of NAC tumor involvement. All reviewed studies, including our own, support further investigation and provide preliminary data from which to develop criteria for patient selection.

METHODS

Patient Selection

After obtaining Institutional Review Board authorization, we retrospectively reviewed the charts of 36 patients who underwent 51 NSM procedures between 2002 and 2007 at a single institution. All patients were self-selected in that they initiated the possibility of NSM. Patients who clinically presented without evidence of involvement of the NAC were felt to be acceptable candidates.

All patients had the NAC base assessed for permanent histological evaluation, and if shown to be positive the NAC was removed at a second surgical setting. If the NAC appeared to be involved at the primary surgical setting, a sample was sent for frozen section. Permanent histological evaluation was preferred, as the fatty nature of the breast makes it difficult to freeze the tissue, leading to subsequent lose of diagnostic accuracy and potential lose of important tissue. We reviewed tumor size, tumor location, tumor-to-nipple distance (TND), axillary node status, local recurrence (LR), and cosmetic outcome. Tumor location and TND were based on clinical description, mammograms, ultrasounds, or magnetic resonance imaging (MRI). Cosmetic result was based on subjective description of the surgical oncologist. Mean follow-up was 18 months (range 2–68 months).

Literature Review

An extensive review of the literature concerning SSM, and NSM was undertaken. Using PUBMED the keywords "nipple sparing mastectomies," "skin sparing mastectomies," and "nipple–areolar complex" in association with "breast cancer" were used. Papers between 1960 and 2007 were reviewed. Over 300 hits were retrieved; 100 abstracts were reviewed based on title relevance. From this review, 14 papers were chosen for inclusion and comparison based on actually pertaining to NSM.

Surgical Technique

Our current surgical technique is to remove the breast tissue through a lateral incision measuring 4–6 cm in length that is at least 2 cm from the edge of the areola. The incision follows the curve of the breast. This incision may need to be extended medially above or below the NAC in order to access the internal mammary vessels for autologous free flap anastomosis and inset. The standard mastectomy borders are utilized. To assess the NAC base for tumor on permanent histological evaluation, the NAC is inverted through the incision and a thin slice of tissue is removed from the base to establish a true margin. This ensures viability of the NAC while obtaining an adequate tissue sample. We do not

TABLE 1. *Nipple-sparing mastectomy: 36 patients, 51 procedures*

Number of patients	Type of procedure	Number of procedures
5	Bilateral prophylactic mastectomy	10
3	Bilateral mastectomy for bilateral breast cancer	6
7 (5 invasive; 2 DCIS)	Bilateral mastectomy for unilateral breast cancer, and unilateral prophylaxis	14
21 (13 invasive; 8 DCIS)	Unilateral mastectomy for unilateral breast cancer	21

advocate coring out the nipple duct bundle. Evidence suggests that breast cancer originates in the terminal duct lobular unit (TDLU) and only 9% of nipples contain TDLU.[20] The low occurrence of TDLU in the nipple may be why Fisher found no primary breast cancers occurring in the nipple in his review of the pathology of breast cancer.[21] Additionally, coring out the nipple duct bundle could disrupt the vasculature, increasing nipple necrosis and diminishing cosmetic results.[22] The sentinel node is obtained through a separate axillary incision in the usual standard fashion, routinely done prior to the mastectomy. Immediate reconstruction ensues, either with autologous free flap, tissue expander, or implant.

RESULTS

Of the 36 patients in this series, 5 chose bilateral prophylactic mastectomy. Two of these women were *BRCA* positive, two had Gail model scores greater than 25% lifetime risk, and the fifth patient had severe chronic pain and deformity from multiple silicone injections performed in another country. Seven patients had unilateral breast cancer (five with invasive and two with DCIS) and chose bilateral mastectomy, including unilateral prophylaxis. The largest group of 21 patients had unilateral breast cancer (13 with invasive and 8 with DCIS) and choose unilateral mastectomy. Three patients had bilateral synchronous breast cancer and chose bilateral mastectomy (Table 1). Two of these women were stage 2A on one side and stage 1 on the contralateral side, while the third woman with bilateral breast cancer was stage 2A and stage 2B.

Interestingly, of the 18 women with unilateral invasive breast cancer, six (33%) were stage 1, although one was multicentric, one was multifocal, and one was *BRCA* positive. Nine (50%) of the total patients had multicentric or multifocal disease, and five (27%) had tumors larger than 5 cm. Of the five tumors larger than 5 cm, two were purely DCIS and three were infiltrating carcinoma. Two of the infiltrating had neoadjuvant chemotherapy and one refused chemotherapy altogether. Of the ten women with DCIS, one was recurrent post radiation and the other nine had multifocal or multicentric disease. Of the 51 NSM, 34 were performed on a breast with cancer. Only 25% of all invasive and noninvasive cancers were eligible for breast conservation.

The mean tumor size for the invasive breast cancer patients was 2.8 cm with a range of 0.8–7 cm, and for DCIS it was 2.5 cm with a range of 0.5–5 cm. The mean TND was only documented for 17 patients and was 4.9 cm with a range of 1.5–10 cm. Nine patients had positive lymph nodes; one of them had bilateral axillary disease. Multicentric disease (tumor in two or more quadrants) was noted in seven (39%) of the invasive breast cancer patients, while two (11%) were multifocal (two or more foci of tumor in the same quadrant). Multicentric disease was seen in five (50%) of the DCIS patients, and four (40%) had multifocal DCIS. Mean follow-up was 18 months with a range of 2–68 months. The majority of the NSM (66%) were done in the last 2 years (Table 2).

Of particular importance is that only 2 (5.9%) of the 34 cancerous patients had an NAC base that was histologically positive for occult tumor. One had clinical evidence of tumor extending to the NAC at the time of surgery, which was confirmed by frozen section. The NAC was removed at the initial surgical setting. This patient had a 7-cm tumor that was 2 cm from the NAC, and the sentinel node was negative. The tumor was estrogen and progesterone receptor positive and Her-2/neu receptor negative. She is currently being treated with chemotherapy. The second patient was found to have DCIS in the NAC base on permanent histologic evaluation. The NAC was removed 3 weeks later at a second surgical setting. This patient had a multicentric invasive ductal tumor, 1.7 cm and 0.6 cm in size. The TND was not assessed. The sentinel node was negative, the estrogen and progesterone receptors were negative, and the Her-2/neu receptor was positive (Table 3). This patient also received chemotherapy, including Herceptin, and remains cancer free at 14 months follow-up. None of the patients who had risk-reducing prophylactic NSM had occult tumor in the NAC or the breast by histologic section examination.

TABLE 2. *Nipple-sparing mastectomy: statistical data*

Age, average (range), years	Average tumor size, mean (range), cm		Tumor–nipple distance, mean, cm	Positive lymph nodes	Positive nipple–areolar complex	Multicentric (MC), multifocal (MF)		Follow-up, mean (range), months	Local recurrence rate
	CA	DCIS				CA	DCIS		
48 (35–72)	2.8 (0.8–7)	2.54 (0.5–5)	4.97 (17 total patients)	29% (10)	5.9% (2/34)	MC = 7 MF = 2	MC = 5 MF = 4	18 (2–68)	5.9% (2/34), none seen in the NAC

TABLE 3. *Positive NAC characteristics*

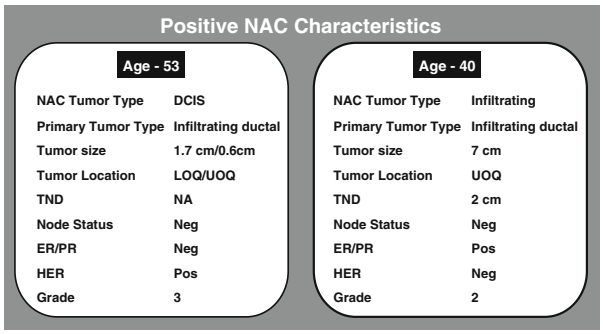
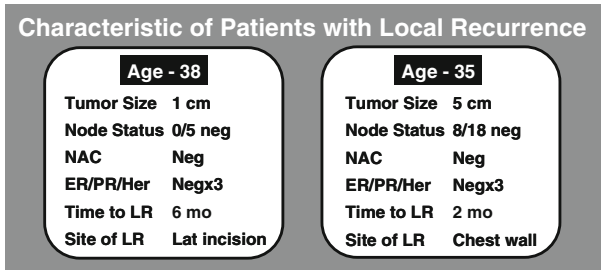


TABLE 4. *Characteristic of patients with local recurrence*



The local recurrence rate was 5.9% (2 of 34) with a mean follow-up of 18 months (range 2–68 months). The two local recurrences were in young patients with aggressive infiltrating triple negative receptor tumors without any evidence of DCIS in which one patient had a 5-cm tumor with eight positive nodes. This patient had a local chest wall recurrence 2 months after surgery. She presented with a locally advanced tumor but clinically negative axilla. She refused neoadjuvant chemotherapy, and subsequently refused adjuvant chemotherapy or radiation. She insisted on the nipple-sparing mastectomy when told she needed a mastectomy to locally control the tumor. Unfortunately she passed away 6 months after surgery. The second patient with a LR initially presented with a 1-cm tumor in the lower inner quadrant and was node negative. On return to the operating room 6 months later to exchange the tissue expander for an implant the patient was found to have tumor in the lateral incision. This patient subsequently had chemotherapy and radiation therapy. Of importance is that neither had recurrence in the NAC (Table 4).

A total of 12 patients (35%) had chemotherapy, 2 of whom had neoadjuvant therapy. Five (15%) of these 12 patients also had radiation therapy. One of the patients who had neoadjuvant therapy also had radiation therapy. The other four who underwent adjuvant radiation therapy had adjuvant chemotherapy. The short time to follow-up and small number of patients and procedures limits further statistical analysis at this time.

Cosmetic result was based on the subjective description of the surgical oncologist. Ten patients (29%) were described as having a "good" cosmetic result, 22 patients (65%) were described as having an "excellent" cosmetic result, and only 2 patients (6%) were described as having a "poor" result. One patient described as having a "poor" cosmetic result had scleroderma and had used a heating pad on the postoperative breast, subsequently injuring the NAC. She went on to have a full-thickness burn to the NAC, and it had to be removed. The second patient with a "poor" descriptive outcome had a cellulitis and the implant had to be removed. She refused to have it replaced and thus obtained a poor cosmetic outcome, although the NAC was intact. The reconstructive procedures consisted of 15 (42%) autologous free flaps and 21 (58%) implants. Cosmetic outcome is based on the number of patients (36) rather than the number of procedures (51).

DISCUSSION

Our results are consistent with the majority of the studies reported in the literature. Our LR of 5.9% is also consistent with local recurrences seen in standard mastectomy patients.[12,13] The two local recurrences seen are independent of the patients having under

gone NSM and are, however, a reflection of the aggressive tumor biology. Specifically, neither of the two local recurrences was in the NAC. We do not suggest planning surgical treatment according to aggressive tumor biology, but rather the standard of care and clinical stage of the tumor. Certainly with accrual of data this recommendation may change in the future.

Of particular interest was the finding of NAC involvement with occult tumor, as this would have been an absolute exclusion criterion if suspected preoperatively. The two patients in the current study who had demonstrated NAC tumor involvement (one found at surgery and the other on final pathology assessment) were at high risk for NAC involvement based on criteria reported in the reviewed studies: large, multicentric tumors presumably close to the NAC.[18,21,23–27] While this may be arguably true, the 5.9% NAC involvement seen in our study is still in the lower half of estimates reviewed. Of note is that our sole criterion for patient selection was no clinical evidence of nipple–areolar tumor involvement. However, our mean TND was 4.9 cm, and the mean tumor size was 2.6 cm, which are both consistent with the suggested predictive factors associated with low occurrence of NAC tumor involvement, and this most likely contributes to the finding of low NAC tumor involvement in the current study.

While only 34 of the 51 procedures were performed for breast cancer (the remainder for prophylaxis), our patient population represents the spectrum of breast cancer ranging from stage 0 to stage 3A. Thus, 73.5% of the patients had early-stage breast cancer (stages 0, 1, 2A), while 26.5% had advanced stage (2B, 3A). Of the women with early-stage breast cancer 60% had multicentric or multifocal disease, which excluded them from breast conservation. Of the women with advanced 2B or 3A stage, 56% were not candidates for breast conservation. Only 25% of the patients in the current study were deemed as candidates for breast conservation. The majority of studies reviewed limit their indications for nippe–areolar preservation to early-stage disease with the intent of selecting patients with reduced risk of NAC tumor involvement. Interestingly, of the patients in the current study who had NAC involvement, one had stage 1 multicentric disease while the other had stage 2B node-negative disease. The sample size is too small to make any significant associations, but again this seems to imply that the biology of the primary tumor cannot be overemphasized. While some studies suggest exclusion of women with positive nodes or evidence of lymphovascular invasion this does not seem warranted without further study, and is certainly not borne out by our data.

Cosmetic outcomes in this series were subjectively assessed by the primary surgical oncologist. In future prospective studies cosmetic results will be objectively examined by the oncologic and plastic surgeons, as well as by the patient. Objective evaluation is especially important since one reason to preserve the nipple is to improve cosmesis. Improving body image is a second reason to retain the NAC, and this needs to be studied further to establish this intuitive concept. To establish cosmetic and body image outcomes definitively, objective validated questionnaires will be used in the prospective study.

Skin-sparing mastectomy (SSM) has been shown to be safe in selected patients; the prevailing evidence is that LR after SSM is most likely a manifestation of the tumor biology rather than preservation of the skin.[8,9] Similarly, NSM appears to be safe in selected patients, since the current evidence suggests that LR is a manifestation of tumor biology rather than preservation of the NAC. Most importantly the LR after NSM is consistent with LR after mastectomy, SSM, and breast conservation. Evidence also suggests that retention of the NAC does not increase the risk of subsequent breast cancer occurrence. Only 1 patient out of 961 (0.1%) patients in all the studies we reviewed had a local recurrence in the nipple. Fisher also failed to show any primary breast cancers originating in the nipple.[21] Current literature and this study indicate that, with careful patient selection using associated predictive factors, the occurrence of occult tumor in the NAC is low: 2–6%. The NSM may be equally safe in screened women who choose prophylactic mastectomy for risk reduction based on the same evidence.

A total of 14 studies on NSM in the literature were reviewed in order to derive selection criteria.[7,8,11,14–18,21,23–27] Discrepancies in the design of these studies prevents valid statistical comparison, however common themes of associated predictive factors for occult tumor in the NAC are seen. A study derived from the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-04 protocol assessed the pathology of invasive breast cancer and found that the nipple was involved in 11.1% of the specimens.[21] The study further analyzed associated factors and assessed when the nipple would more likely be positive for tumor. From these studies and our own data we have extrapolated criteria to be tested for the NAC to be retained. Furthermore, this demonstrates that the majority of breast cancer patients do not have occult tumor in the NAC.

CONCLUSIONS

Our retrospective results and those reported in the reviewed literature suggest that NAC preservation may be oncologically safe in patients with defined clinical and pathologic criteria. We propose the following selection criteria for NSM: tumors less than or equal to 4.5 cm in size, tumors greater than or equal to 2.5 cm from the areola edge or greater than or equal to 4 cm from the nipple center, and no gross involvement of the NAC, including bloody nipple discharge or Paget's disease. The tumor-to-nipple or tumor-to-areolar distance is assessed clinically if possible, and/or mammographically, with ultrasound, or MRI to obtain a precise distance. Tumors that are multicentric, multifocal, or contain extensive DCIS and otherwise meet the stated criteria can be included. Women who have undergone neoadjuvant therapy and subsequently meet the stated criteria for tumor size and location can also be considered. Inflammatory breast cancer is absolutely excluded. Soft tissue from the base of the NAC is removed separately at the time of the NSM and sent for permanent pathologic examination. The nipple duct bundle is not cored out. If the NAC base is positive for tumor on permanent pathology review, the NAC is removed at a second setting. Adjuvant chemotherapy and radiation therapy is given according to the standard of care.

In summary, we have recommended a set of selection criteria based on predictive associations with NAC tumor involvement as well as described a surgical approach for NSM. To assess the safety of the proposed selection criteria and surgical approach, a prospective longitudinal study is currently being conducted. A primary objective is to assess the ability of these predetermined criteria to predict NAC tumor involvement so as to achieve a safe oncologic outcome. Cosmetic outcomes and body image perception will also be evaluated using validated patient and physician questionnaires.

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