Nipple-Sparing Mastectomy Update

One Hundred Forty-Nine Procedures and Clinical Outcomes

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Objectives: To describe our experience with patients who underwent the nipple-sparing mastectomy procedure developed and standardized at our institution and to report clinical outcomes for those patients with a breast cancer diagnosis.

Design: Prospective study for consecutive nipple-sparing mastectomy procedures.

Setting: Multidisciplinary breast center at a large tertiary care facility.

Patients: One hundred ten consecutive patients underwent nipple-sparing mastectomy between July 2001 and June 2007.

Intervention: Nipple-sparing mastectomy was offered to carefully screened patients; the nipple-areola tissue was cored and sent for histologic frozen-section analysis intraoperatively.

Main Outcome Measures: Assessment of nipple-areola cored tissue for neoplastic involvement; postoperative stability of retained nipple-areola complex; and clinical outcomes.

Results: Data were available for 149 nipple-sparing mastectomies performed on 110 patients. No procedure performed for prevention had neoplastic involvement of the cored nipple-areola tissue, while 9 procedures performed for breast cancer treatment were found to have neoplastic involvement. Postoperatively, 2 patients had partial loss of the nipple-areola complex due to sloughing and a third patient developed an infection that required surgical removal of the nipple-areola complex. Among patients with breast cancer, none with ductal carcinoma in situ has developed a recurrence, while 4 patients with infiltrating breast cancer have, including 2 patients with distant metastases only, a third with a chest wall recurrence, and a fourth with an axillary recurrence.

Conclusion: A low incidence of neoplastic involvement of the nipple-areola cored tissue leads to successful completion of nipple-sparing mastectomy for most patients.

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Achieving improved cosmesis by preservation of the nipple-areola complex (NAC) for patients undergoing mastectomy has been a goal of breast surgeons for several decades.1,2 Historically, an incomplete understanding of the breast ductal system and its relationship to disease within the breast2-4; concerns over neoplastic involvement of the NAC,3,5-16 including those autotransplanted for later reimplantation; and an inability to accurately predict which tumors would likely have associated NAC involvement3-10 rightly disposed cosmesis second to therapeutic intent.

A thorough anatomical description of the duct system and its common histopathologic findings was presented by Snyder and Chaffin,4 who appear to have coined the term carcinoma in situ, to the Western Surgical Society in 1954. This significant contribution, complete with detailed illustrations and descriptions of surgical techniques and pathologic guidelines, enhanced and furthered the understanding of duct anatomy and, in particular, breast disease with concomitant NAC involvement, whether benign or malignant. Although Snyder and Chaffin make no claim to originating a distinction between diseases predominantly of the nipple with those of the breast, their comprehensive work likely focused some attention to possible preservation of the NAC by permitting the means to more carefully screen patients based on clinical and pathologic findings.

Clinical, pathologic, and radiologic predictors of NAC involvement have met with conflicting reports, in part because of varying assessment techniques, disparate inclusion and exclusion criteria and other study design attributes, quality and quantity of preserved mastectomy specimens, and incon-
sistent statistical approaches. One study of 26 NACs\textsuperscript{17} reported no neoplastic involvement in any specimens, while another study of 33 NACs reported 58\% involvement.\textsuperscript{7} The first study considered only those tumors located in the periphery of the breast, while the second included all mastectomy specimens, including those with gross nipple involvement and centrally located tumors. These 2 studies, each too small to extrapolate a reliable estimate of neoplastic involvement of the NAC, illustrate the irreconcilable differences in study design and, although widely referenced, particularly to support a bias either for or against NAC preservation, their findings are spurious and should be set aside. Many studies that are more moderate in their approach and somewhat more compatible in their designs report between 8\%\textsuperscript{13} and 30\%\textsuperscript{6,8} NAC involvement, with the majority reporting approximately 25\%.\textsuperscript{9-12}

Concurrent to the early research activity in NAC assessment, a cosmesis-preserving nipple-areola harvesting procedure was developed in which the NAC was transplanted, or banked, often to the thigh and sometimes after cryopreservation\textsuperscript{19} for later heterotopic implantation on the reconstructed breast mound. Although highly touted at the time, this procedure was quickly abandoned for 2 reasons. First, for some patients, breast cancer developed at the transplantation site, often with spread to the surrounding lymph nodes; pleas were urgently issued to screen patients more carefully or to abandon the procedure altogether.\textsuperscript{10-22} Second, implantation during reconstruction was sometimes compromised or failed because of insufficient blood supply, which resulted in necrosis of the NAC\textsuperscript{19,26} or ultimate poor cosmetic, particularly hypopigmentation or fibrosis.\textsuperscript{6,25,26} These problems overwhelmed the feasibility of this technique for patients with breast cancer and it was rapidly abandoned. Persistent inconsistencies in NAC neoplastic assessment studies and an inability to predict NAC involvement preoperatively with some level of accuracy led to the development of statistically oriented prediction tests. In 1979, Lagios et al.\textsuperscript{6} who reported 30\% NAC involvement, determined that distance between the tumor and NAC, the tumor size, multicentricity, tumor differentiation, and positive axillary nodes were correlates for neoplastic involvement of the NAC. These correlates were similar to those gleaned from the many contemporaneous studies that assessed NAC involvement pathologically.\textsuperscript{7-17} Subsequent prediction models have been developed.\textsuperscript{27-30} Interestingly, although these models are inconsistently designed, making direct comparisons impossible, and with reported NAC involvement of 16\% to 42\%, each essentially validates the original Lagios et al correlates, particularly regarding tumor size and distance from the NAC. It seems reasonable to conclude, therefore, that likely predictors of neoplastic involvement of the NAC are, at least, tumor size and distance from the NAC and, possibly, tumor differentiation, involved axillary nodes, and associated angiolymphatic invasion. Being able to speculate preoperatively about the likelihood of NAC involvement, particularly during discussions with patients about treatment options, is certainly useful and serves as an adjunct to sound clinical judgment and common sense. Nevertheless, it is also reasonable to conclude that there is no sure way to assess neoplastic involvement of the NAC other than to core the tissue and analyze it.

In 2004, we described the nipple-sparing mastectomy (NSM) technique developed by Crowe et al.\textsuperscript{23} and detailed our findings for the initial 54 patients who underwent NSM at our institution. Since our first report, we have continued to offer NSM to carefully selected patients, monitor the findings, and accrue clinical outcomes data. The purpose of this study is to update our initial experience with NSM, describe the findings of a much larger patient population, report clinical outcomes for patients who underwent NSM for cancer treatment, and share lessons we have learned.

**METHODS**

Data were collected prospectively between July 11, 2001, and June 30, 2007, in our institutional review board-approved breast center patient registry. Patients requested NSM for either prophylaxis if at high risk of developing breast cancer or for the treatment of newly diagnosed breast cancer, which was defined as any infiltrating breast cancer (IBC) or ductal carcinoma in situ (DCIS). Neoplastic involvement of the NAC was defined as either the presence of IBC or DCIS in the cored nipple tissue or subareolar tissue. Clinical outcomes, if available, were collected for all patients with breast cancer.

**SURGICAL TECHNIQUE**

As previously reported,\textsuperscript{31} the NSM technique developed at our institution includes immediate breast reconstruction. Our previous experiences suggested that medial incisions may inhibit postoperative viability of the NAC; all NSMs have been performed through a lateral incision since. Incision placement and reconstruction method are determined by the plastic surgeon and surgical oncologist, in collaboration with the patient, during the informed consent process. The biopsy incision, including either the core biopsy tract or previously excised area, is incorporated in the incision and elliptically excised. The tissue within the nipple is dissected completely and removed (the nipple core) and sent for frozen-section analysis. If neoplastic involvement is identified in the nipple core, the NAC is resected. Throughout the mastectomy and reconstruction, the NAC is monitored for viability.

**PATIENT SELECTION**

Patients were carefully screened for NSM and selected based on tumor size, location of the tumor within the breast, clinical and mammographic findings, and informed consent. Generally, patients whose tumors measure (clinically) larger than 3.5 cm or have clinical axillary node involvement; whose tumors are centrally located; who have inflammatory breast cancer, Paget disease, or other gross involvement of the nipple; or who have undergone preoperative chemotherapy are not candidates for NSM. Patients must also be suitable candidates for breast reconstruction, and suitability is determined by the plastic surgeon. These recommendations, previously reported,\textsuperscript{13} remain, with the caveat that clinical assessment of tumor size and axillary node involvement may, at times, underestimate actual pathologic measurements and findings.

**RESULTS**

Data were available for 110 patients (median age, 43 years; range, 20-72 years) who underwent 149 NSMs for either prophylaxis or treatment of newly diagnosed breast cancer (Figure).
Twenty-seven patients elected to undergo NSM for prophylaxis, including 13 who had never developed breast cancer but who were at high risk and desired bilateral NSM (26 procedures); 3 patients who had been treated in the remote past for breast cancer with unilateral mastectomy and reconstruction and now desired to reduce their risk in the nonaffected breast (3 NSMs); and 11 patients who were ineligible for NSM for a newly diagnosed breast cancer in one breast but who desired prophylaxis in the contralateral breast (11 NSMs). Reasons for NSM ineligibility included tumor location (n=3); tumor size (n=4); both location and size (n=3); and NAC distortion from prior excisional biopsy at a different institution (n=1). None of these 40 NSM specimens was found to have breast cancer in either the breast tissue or NAC cored tissue (39 evaluated). Breast mound reconstruction was completed by tissue expander implant (n=31) or autologous tissue transfer procedure (n=9); all 40 NSMs remain intact.

Another 24 patients underwent bilateral NSM (48 procedures) for newly diagnosed unilateral breast cancer treatment, including 17 with IBC and 7 with DCIS, and contralateral prophylaxis. None of these 24 prophylactic NSM specimens was found to have breast cancer in either the breast tissue or the NAC cored tissue (23 evaluated). Of 24 treatment NSMs, neoplastic involvement of the NAC cored tissue was confirmed in 4 specimens, including 3 involved with DCIS and 1 with IBC; these 4 NACs were removed intraoperatively, although only the nipple was removed for the NAC with IBC involvement, leaving the areola intact. The associated breast pathologic findings for these NACs were DCIS (n=2) and IBC (n=2). Two additional NACs were removed, including 1 in which an infection developed 5 weeks postoperatively for a patient who had undergone bilateral NSM with tissue expander implants placed; the contralateral breast did not develop an infection. Another patient underwent bilateral NSM for a diagnosis of unilateral DCIS, described as multifocal and widespread. Preoperatively, she had requested removal of both NACs if either were found to have neoplastic involvement. The NAC tissue core for the affected breast did reveal DCIS involvement; therefore, both NACs were removed. The 42 intact NSMs in this group were all reconstructed using tissue expander implants.

The remaining 59 patients underwent NSM for the treatment of newly diagnosed breast cancer, including 57 with unilateral disease (IBC=42 and DCIS=15) and 2 with bilateral disease (IBC=4). Of these 61 NSMs, 60 NACs were cored for histologic analysis: 5 tissue cores were found to have DCIS involvement and 5 were found to have atypical hyperplasia. Four of those with DCIS involvement were removed intraoperatively, but for the fifth NAC tissue core, the intraoperative frozen-section analysis revealed only benign changes and it was left intact. The permanent-section analysis, however, identified DCIS and the patient was instructed to have the NAC removed. She postponed for 14 months, at which time the NAC was removed without any evidence of recurrence. Two of 5 NAC tissue cores with atypical hyperplasia identified were described as having multiple foci and were removed intraoperatively, but the remaining 3 NACs were left intact because only a single focus of atypia was identified in each. Another 2 NACs had postoperative sloughing, resulting in partial permanent loss, but remained mostly intact and have now been stable for several years. Of the 54 intact NSMs, 36 were reconstructed by tissue expander implants and 18, by an autologous tissue transfer procedure.

Overall, 146 NACs were cored and sent for frozen-section analysis intraoperatively. Of these, 63 NSMs were for prevention, including 26 NSMs for 13 patients who elected bilateral prophylaxis having never had breast cancer and 37 NSMs for 37 patients who had either newly diagnosed contralateral breast cancer or who had been previously treated for contralateral breast cancer; 61 NACs were cored and none was found to have neoplastic involvement of the NAC. The remaining 86 NSMs were for breast cancer treatment; 85 NACs were cored and 9 (11%) were found to have neoplastic involvement and were removed, including 8 during the NSM procedure and 1 during a separate operation after DCIS was identified only on the permanent sections. Only 1 NAC tissue core was involved with IBC; the nipple only was removed during the NSM. This patient had a recurrence in the areola 14 months postoperatively, at which time it was removed; the reconstructed breast remains intact.

The associated breast pathologic findings for the 8 NAC tissue cores in which DCIS was identified were DCIS in the breast (n=2); DCIS with microinvasion (n=2); and IBC (n=4) ranging from 0.3 to 1.2 cm. Only 1 patient in this group had metastases to axillary nodes; her tumor measured 1.2 cm and she had 3 involved nodes. The associated breast pathologic findings for the 1 NAC tissue core in which IBC was identified was a 2.6-cm infiltrating ductal carcinoma with metastases identified in 10 axillary nodes.

Two additional NACs were removed because multiple foci of atypical hyperplasia were identified in the tissue core on frozen section; another 3 NACs were found to have a single focus of atypical hyperplasia in the tissue core and were left intact. The associated breast pathologic findings for the 2 NAC tissue cores in which multiple foci of atypical hyperplasia were identified were infiltrating ductal carcinoma measuring 1.3 and 2.5 cm; axillary nodes for both patients were benign. Another NAC was removed at the patient's request and a final NAC was removed because of infection 5 weeks postoperatively. Therefore, of 49 attempted NSMs, 9 NACs were removed for neoplastic involvement, 2, for widespread...
atypical hyperplasia; 1, for infection; and 1, at the patient's request. The remaining 136 remain intact, including 2 with partial loss due to sloughing.

Clinical outcomes were available (median, 41 months; range, 14-64 months) for 58 patients who underwent successful NSM for newly diagnosed breast cancer, including 15 with DCIS and 43 withIBC, of which 39 were classified as infiltrating ductal carcinoma; 3, infiltrating lobular; and 1, infiltrating medullary. Ten of the infiltrating tumors had associated metastases to the axillary lymph nodes identified at the time of NSM: 5 tumors had 1 involved node; 2 had 2 involved nodes; and 3 had more than 2 involved nodes.

All patients diagnosed with DCIS remain disease-free. Four patients, all with infiltrating ductal carcinoma, developed a recurrence. The first patient developed liver and bone metastases at 36 months; her original tumor measured 2.5 cm and she had negative axillary nodes. The second patient developed a chest wall recurrence at 21 months; her original tumor was palpable and not located near the chest wall. Although it initially appeared to be consistent with a lactating adenoma, her mastectomy specimen revealed a 3.5-cm tumor with negative surgical margins; she had 14 involved axillary nodes and extensive angiolymphatic invasion. The third patient developed pulmonary metastases at 47 months, brain metastases at 55 months, and died of her disease at 59 months; her original tumor measured 0.6 cm and she had negative axillary nodes. The fourth patient developed a recurrence in her axilla at 27 months; her original tumor measured 1.1 cm and she had 2 involved axillary nodes.

The 11% incidence of NAC involvement in this series among patients who underwent NSM for breast cancer is lower than that reported in other studies,6,9,16,18,30 higher than some others,5,13,17 similar to others,10,11,24,25,26 and consistent with our previous report.31 Differences in study design, specimen assessment, statistical approaches, and, perhaps most importantly, patient selection and inclusion criteria certainly contribute to these differences. Retrospective studies that sample NAC tissue from preserved mastectomy specimens have as their objective to identify the incidence of NAC involvement in all available specimens to determine overall incidence. The most commonly reported correlates of NAC involvement are tumor size and its nearness to the NAC.6,17,24,27-30 In this study and in our prior experience,31 patients were carefully screened for NSM candidacy: patients whose tumors were centrally located or measured (clinically or mammographically) more than 3.5 cm were not candidates for NSM. Neither were patients who had undergone neoadjuvant chemotherapy, had been diagnosed with inflammatory breast cancer, or had clinical NAC involvement. Nevertheless, our findings demonstrate that even after screening, some patients will have neoplastic involvement of the NAC, suggesting preoperative assessment may be aided by adherence to these widely published and generally agreed on clinical indicators, but that absolute certainty is unattainable without intraoperative assessment of the nipple-areola cored tissue.

Although descriptions of NSM procedures are equitable in recent published reports,29,30,32-35 the technique developed at our institution in 2001 and described previ-ously31 includes excision of the prior biopsy site, lateral incision, intraoperative assessment of the NAC cored tissue, and immediate reconstruction. Patients are advised during the consent process that the NAC will be removed if neoplastic involvement is identified or if it becomes necrotic. Patients are also advised that, although some erectile ability and nipple sensation may remain postoperatively, it is more likely those characteristics will be permanently lost and that NSM should, therefore, be viewed as a procedure to conserve cosmesis, rather than function.

Candidates for partial mastectomy, who most often have peripherally located tumors in which wide local excision is performed with preservation of the NAC, do not routinely undergo any additional pathologic analysis of the NAC. Studies have repeatedly shown that preservation of the NAC, if possible, has a significant effect on subsequent perceived body image and quality of life.36-42 Although it has been suggested that NSM should be abandoned if erectile function and sensation cannot be preserved,43 the benefit of conserved cosmesis overrides this restrictive viewpoint among patients in this study, all of whom were counseled to expect loss of function and sensation, but who, nevertheless, chose NSM to preserve cosmesis.

The data presented in this report have accrued over 7 years and represent consecutive NSMs performed at this institution for either prophylaxis or breast cancer treatment; we have learned some lessons over this period. Early in our experience we suspected that several NSMs that had been performed through medial incisions were the cause of necrosis of the NAC. Since then, we have performed all procedures through lateral incisions and no additional NACs have been lost to necrosis. Although we make careful assessment preoperatively of tumor size for patients with breast cancer, and prefer to limit NSM to patients whose tumors measure no more than 3.5 cm, a few patients with larger tumors (per the pathologic measurement) did undergo this procedure. Finally, to avoid unrealistic expectations and disappointment, comprehensive informed patient consent remains mandatory.

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REFERENCES

When considering NSM, the most important factor is the oncologic safety of the procedure. There are populations of patients, specifically those undergoing prophylactic mastectomy, where NSM is a good choice. However, in patients with breast cancer, the oncologic safety becomes paramount. The Crowe et al article is a triumph in number of cases and developed technique, but it provides less convincing evidence that NSM is oncologically sound.

To know if this is a safe cancer operation, we must determine if the risk of local recurrence is increased by leaving the NAC. Of the 43 patients with invasive breast cancer reported, 4 developed recurrence, a 9% recurrence rate. The recurrence rate after mastectomy is 3% to 6%, and for lumpectomy and radiation therapy, it is 6% to 8%. One must question whether NSM results in equivalent local control compared with standard therapies. While the recurrences reported herein are not at the NAC, the recurrence rate is relatively high in a breast cancer population selected for low-risk disease. Crowe et al report strict selection criteria that would predict a low risk for local recurrence; however, the evidence establishing those selection criteria is not described nor is the expected local recurrence after standard mastectomy in the same population.

In counseling patients regarding risks and benefits, the Crowe et al article provides information regarding the risk of NSM but provides no information of the benefits, primarily an expected improvement in patient satisfaction. We make the assumption that patient satisfaction is high but have no accurate measure. While we applaud Crowe et al on this endeavor with the second largest number of patients in the literature, we ask them to assure us that presumed benefits are real and that NSM is truly oncologically safe.

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