Areola-Sparing Mastectomy: Defining the Risks

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The recent development and popularity of skin-sparing mastectomy (SSM) is a likely byproduct of high-quality autogenous tissue breast reconstruction. Numerous non-randomized series suggest that SSM does not add to the risk of local recurrence.[1–3] Although there is still some skepticism,[4] SSM has become a standard part of the surgical armamentarium when dealing with small or in situ breast cancers requiring mastectomy and in prophylactic mastectomy in high-risk patients. Some have suggested that SSM also compares favorably with standard mastectomy for more advanced local breast cancer.[2] Recently, areola-sparing mastectomy (ASM) has been recommended for a similar subset of patients in whom potential involvement by cancer of the nipple-areola complex is thought to be low or in patients undergoing prophylactic mastectomy.[5] For ASM, the assumption is that the areola does not contain glandular tissue and can be treated the same as other breast skin. Because no large series exists to define the risks of preserving the areola, it seems appropriate to critically review our knowledge of the areola and thereby attempt to define those patients in whom ASM might be appropriate. Some topics thought to be relevant to ASM are:

1. What is the histologic anatomy of the areola?
2. Does the areola contain ductal tissue or breast lobules? If not, it would seem appropriate to apply the same rules to the areola as one applies to removal of breast skin.
3. What is the risk of occult involvement of the areola in patients with established breast cancer?
4. Based on histopathologic data, what are the risk factors that can favor areola involvement?
5. What is the incidence of cancer involvement of nonareola skin?
6. What is the incidence of Paget's disease of the breast involving the areola in the absence of nipple involvement? This is an important question to answer because it speaks to actual risk of cancer arising in the areola and is pertinent to any application of ASM in prophylactic operations.
7. Based on clinical studies, what are the outcomes when some degree of nipple-areola complex (NAC) is preserved as part of the surgical treatment?

ANATOMY OF THE AREOLA

In 1719, Morgagni first observed that there were mammary ducts present within the areola. In 1837, William Fetherstone Montgomery (1797–1859) described the tubercles that would bare his name.[6] In a series of scholarly articles from 1970 to 1974, William Montagna and colleagues described in great detail the histologic anatomy of the nipple and areola.[7,8] He noted that there was "confusion about the structure of the glands of Montgomery being referred to as accessory mammary glands or as intermediates between mammary and sweat glands."[9] He found that the glands of Montgomery were true mammary glands, the ducts and parenchyma of which were no different from the mammary glands and ducts that opened into the tip of the nipple.

Perhaps the most enlightening work on the anatomic structure of the areola came from Smith and colleagues.[10] Serial sections of the areola were performed from 12 patients who had undergone modified radical mastectomy for invasive ductal carcinoma. Thirty-six areola tubercles were sampled in the 12 patients. In 4 of the 12 patients, pathologic abnormalities were identified in the areola tubercle, including 2 patients showing features consistent with fibrocystic disease, 1 showing intraductal hyperplasia, and 1 showing both hyperplasia and ductal carcinoma in situ. They noted that the "ducts coursed from the underlying mammary lobules, through the SC tissues and into the region of the sebaceous apparatus." The ducts terminate by joining the sebaceous gland ducts or through a separate opening in the epidermis nearby (Fig. 1).[9] These findings were in agreement with Montagna and colleagues, who also found that the ducts extending from the breast lobules can at times empty directly into the secretory ducts of the sebaceous glands or directly into the epidermis.[9]

In an attempt to address ASM, which was termed

Abbreviations and Acronyms

ASM = areola-sparing mastectomy
LR = local recurrence
NAC = nipple-areola complex
NSM = nipple-sparing mastectomy
SCM = subcutaneous mastectomy
SSM = skin-sparing mastectomy

Figure 1. Tubercle of Montgomery. (Reprinted from Smith DM Jr, Peters DG, Donegan WL. Montgomery's areolar tubercle. Arch Pathol Lab Med 1982;106:60–63, with permission. © 1982 American Medical Association.)

nipple-coring in 1991, Schnitt and colleagues[11] published data on histology of the areola in 8 patients who underwent mastectomy for cancer. They noted that the ducts present in the areola dermis consisted of two cell layers, including a cuboidal to columnar layer and a layer of myoepithelial cells. They noted that in some instances the ducts were seen to arise from the underlying breast tissue. They also noted that "the histologic appearance of these ducts was identical to that of extralobular ducts within the breast parenchyma... ."

RISK OF OCCULT INVOLVEMENT OF THE AREOLA IN PATIENTS WITH ESTABLISHED BREAST CANCER

Nipple-areola complex involvement

Innumerable studies have been published looking at the incidence of occult nipple-areola complex (NAC) involvement with an established breast cancer (Table 1). Unfortunately, most have not specifically looked at areola involvement and tend to focus on nipple involvement. Lagios and colleagues[12] examined 149 consecutive mastectomy specimens for frequency of nipple involvement. Using serial subgross and correlated radiographic examination they found carcinoma in the nipple in 30.2% of cases. Poor differentiation, tumor size >20 mm, and axillary metastases were found to be risk factors for occult NAC involvement.

In examining pathologic specimens from the NSABP B-04 study (radical mastectomy versus total mastectomy ± radiation) occult nipple involvement was noted in 107 of 967 cases (11.1%). Fisher and colleagues[13] noted that when cancer had invaded the skin, there was greater likelihood that the tumor was beneath the nipple-areola region. It was also more likely that the tumor was ≥4.1 cm, had an extensive intraductal component, and had lymphovascular or perineural invasion.

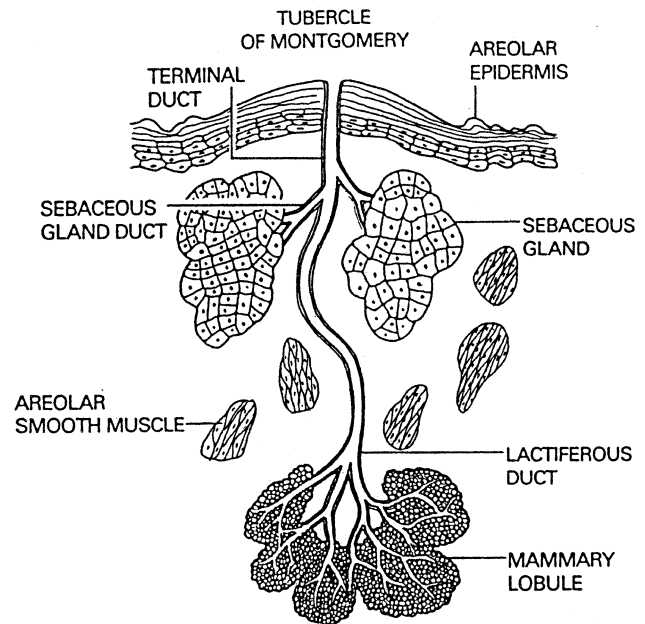A series of 286 mastectomy specimens was reviewed at MD Anderson Cancer Center for presence of occult NAC involvement.[14] Occult tumor in the NAC was detected in 5.6%. In this instance, tumor size, nuclear grade, and histologic subtype did not impact risk. Location of the tumor in the subareola region, multicentricity, and axillary nodal involvement did adversely impact risk of NAC involvement.

Morimoto and colleagues[15] published data from a study of 141 mastectomy specimens. Forty-four (31%) demonstrated neoplastic involvement of the NAC.[15] They also measured the distance from the tumor to the nipple and found that there were no cases of NAC involvement with a distance of ≥4 cm.

The largest study of NAC involvement is by Santini and colleagues,[16] from Bologna, Italy. They studied 1,291 consecutive mastectomy specimens with primary invasive carcinoma. Overall, 12% were found to have NAC involvement with 8% of the total being unsuspected clinically. They found that occult NAC involvement was directly related to tumor size, but not to type of, or presence of, an extensive intraductal component. Again, the data did not allow one to distinguish between nipple and areola involvement.

Several smaller studies have been published with the aim of examining incidence of occult NAC involvement, presumably to determine feasibility of retaining

Table 1. Studies Examining Occult Involvement of the Nipple-Areola Complex

Study	Cases	NAC involvement (%)	Risk factors
Lagios et al[12]	149	30.2	>2 cm, poor differentiation, positive axillary nodes
NSABP B-04[13]	967	11.1	≥4.1 cm, beneath nipple, ≥4 positive axillary nodes, EIC
Laronga et al[14]	286	5.6	Subareola location, multicentricity, positive axillary nodes
Morimoto et al[15]	141	31	<4 cm from NAC
Santini et al[16]	1,291	12	Tumor size

EIC, extensive intraductal component; NAC, nipple-areola complex.

the NAC during skin-sparing mastectomy.[17–22] All fail to distinguish between cancerous involvement of the nipple and areola, making it difficult to determine the true risk of areola involvement in patients with established breast cancer.

Occult involvement of the areola

Aside from the study by Smith and colleagues[10] describing a single case of ductal carcinoma in situ involving the areola, only the study by Simmons and associates[5] specifically examined occult involvement of areola. Both the nipple and areola were examined histologically in a retrospective review of 217 mastectomy specimens. Nipple involvement was discovered in 10.7% of patients, but only 2 patients (0.9%) were found to have cancer involving the areola. Both patients had tumors >5 cm. The authors concluded that their study supported ASM in selected patients. The authors voiced concern about leaving the nipple because of the cancer potential of ductal cells and noted that the areola differs from the nipple because it does not contain breast parenchymal ducts.

CANCEROUS INVOLVEMENT OF THE NONAREOLA SKIN

Because the areola is in continuity with the breast skin, it would seem reasonable to consider that those factors favoring occult involvement of breast skin in general would similarly apply to the areola. Again, Fisher and colleagues,[13] examining the pathologic specimens from the NSABP B-04 study, noted involvement of the skin overlying the index tumor in 4.4% of 946 cases.

Ho and colleagues[23] examined the skin in 30 mastectomy specimens using step-serial sectioning technique. They found that the skin showed tumor infiltration in 23% of specimens and was significantly related to skin tethering, tumor size, and perineural invasion.

The largest study on skin involvement from established breast cancer was by Wertheim and Ozzello,[24] who examined skin flaps in 1,000 mastectomy specimens to determine frequency of neoplastic involvement. They found skin involvement away from the nipple areola complex in 12.7% of evaluable cases, most of which were by direct infiltration and approximately a third of which were clinically occult. In 1.3% of patients, tumor emboli were noted in clinically uninvolved skin and over half involved more than one quadrant. Again, there was noted to be a correlation between tumor size and skin involvement.

Paget's disease of the areola

In 1995, van der Putte and colleagues[25] reported the first case of Paget's disease involving the areola without nipple involvement. The patient described gave a 10-year history of a slowly growing lesion of the areola that at the time of diagnosis measured 2 × 1.5 cm. No underlying cancer was discovered and it appeared that the disease process was limited to the areola. Serial sections of the areola demonstrated 39 glands, some of which were simple tubules, although others showed branching into lobules. Clusters of clear cells resembling Paget cells were also noted in seven uninvolved areas of the areola. The patient underwent a partial mastectomy and, at the time of publication, was without evidence of recurrence with only 2 years followup.

CLINICAL STUDIES
Skin-sparing mastectomy

Because the term *skin-sparing mastectomy* was coined in 1991, several nonrandomized series have appeared in the medical literature addressing both its technical aspects and its oncologic safety. It is important to note that most studies of SSM include removal of the NAC. Newman and colleagues[1] reviewed 372 patients undergoing 437 SSM at MD Anderson Cancer Center. With a minimum of 5 years followup, they reported a local recurrence (LR) rate of 6.2%. Carlson and colleagues[3] reported on a se-

ries of 539 patients who underwent SSM with a median followup of 65.4 months. The LR for the entire series was 5.5%. Medina-Franco and colleagues[26] reported on a series of 173 patients from the University of Alabama in Birmingham. With a median followup of 73 months, they reported an LR rate of 4.5%.[26]

Nipple-sparing mastectomy

More recently, a series of articles appeared in the literature exploring the possibility of sparing the entire NAC in selected patients. The largest series of NAC preservation is by Gerber and coworkers,[27] who compared the results of 112 patients undergoing SSM with preservation of the NAC to 134 patients having standard mastectomy incisions. All patients had tumors >2 cm from the nipple. Using histologic examination of the tissue beneath the NAC as preservation criteria, they were able to preserve the NAC in 61 patients (54.5%). With an average followup of 59 months, there was no statistical difference in the rate of LR.

Crowe and colleagues,[28] found that from the Cleveland Clinic, 54 nipple-sparing mastectomies (NSM) were performed in 44 patients. Six patients were found to have nipple involvement when the core of the nipple tissue was analyzed and these were converted to total mastectomies. They noted that superficial tissue loss was common but that all cases were only partial thickness and healed well. Patients did not undergo NSM if their tumors exceeded 3.5 cm, were centrally located, or had neoadjuvant chemotherapy or inflammatory breast cancer. They concluded that sparing the NAC was a reasonable option for carefully screened patients.

Bishop and colleagues[29] reported on 87 women with breast cancer who underwent total mastectomy with nipple preservation and reconstruction using a myocutaneous flap. There were no recurrences in 63 women who underwent the procedure for tumor recurrence and had received earlier radiotherapy. Recurrence in the nipple did occur in 3 of 24 women who underwent NSM for multifocal disease without radiation.

Cheung and colleagues[30] performed subcutaneous mastectomy in 323 women over 20 years for both invasive and noninvasive cancer.[30] Minimum followup was 30 months. Local recurrence was 16%, compared with 14% for a similar group undergoing total mastectomy during the same period. Ductal carcinoma in situ recurred in five of the patients, four recurred in the nipple. In this group of patients, LR after subcutaneous mastec-

tomy compared favorably to total mastectomy. The areola was not mentioned as a site of recurrence. The authors recommended radiation therapy to the nipple alone in patients in whom microscopic disease is discovered in the nipple.

Areola-sparing mastectomy

In the only reported cases of ASM by Simmons and colleagues,[31] 17 procedures were performed. Ten of the procedures were performed for cancer prophylaxis and four for ductal carcinoma in situ. Only three ASMs were performed for invasive cancer. There were minimal complications and cosmetic results were judged as excellent. Because of the small numbers and short followup, no conclusions can be drawn about efficacy for cancer treatment.

Autotransplantation of NAC

In the 1970s and 1980s, several studies appeared recommending autotransplantation of the NAC to improve cosmetic results of breast reconstruction.[32,33] In many instances, the NAC was temporarily transplanted to a distant site, eg, the groin, before replacing it on the breast. The procedure fell into disfavor when reports began to appear of cancer arising in the graft and in the temporary graft bed.[34–36]

Subcutaneous mastectomy

Subcutaneous mastectomy (SCM), which saves both the nipple and areola, has enjoyed ebbs and flows in popularity over the last 3 to 4 decades. It has been used to treat established breast cancers and for risk-reduction operations. Studies examining SCM as the surgical treatment for established breast cancer are small and fail to show survival differences between SCM and standard mastectomy.[37–39] The largest study from Horiguchi and with colleagues[37] compared 133 SCMs with 910 cases of radical mastectomy. There was no difference in disease-free or overall survival between the two groups. But, in node-negative patients there was a significant difference in local recurrence between SCM and standard mastectomy (3.8% versus 1.3%, p < 0.05).

More commonly, SCM has been used as a risk-reduction strategy for women at high risk for breast cancer. There are numerous anecdotal reports of breast cancer developing in women who had undergone SCM.[40–43] Pennisi and Capozzi[44] reported on a series of 1,244 patients who underwent SCM for prophylaxis. The degree

of risk for this group of patients was unclear. Cancer developed in only 6 patients (0.5%) during a 7-year followup period.

In a series from the Mayo Clinic, Hartmann and colleagues[45] reported on 639 women who had undergone bilateral prophylactic mastectomy and were thought to be at high risk for breast cancer based on family history. Approximately 90% underwent SCM and 10% total mastectomy. In an earlier description of the SCM technique, it was noted that approximately 1 cm of breast tissue was left beneath the NAC to ensure viability.[46] With a median followup of 14 years, breast cancer developed in 7 women. All seven had undergone SCM. In a followup report, Hartmann and coworkers[47] noted that only 18 of the original 639 patients could be documented as carrying a mutation in the BRCA1-2 genes. Seventeen of the 18 had SCM. No breast cancer developed with a median followup of 13.4 years.

DISCUSSION

Because there are no large studies of ASM, it is difficult to assess oncologic risk. Surrogate information must be used to determine whether it is appropriate to spare the areola in women undergoing mastectomy, whether for cancer or for prophylaxis. Judging the cosmetic value of sparing the areola is beyond the scope of this article.

It seems clear from the available anatomic studies that the areola is not just pigmented skin with sebaceous elements, but contains breast ductal structures that are indistinguishable from normal breast with connections to underlying breast lobular units.[7–11] The presence of only one reported case of Paget's disease involving only areola, without nipple involvement, suggests that incidence of de novo cancers originating in the areola is extremely low.

Making blanket recommendations for ASM in patients with established breast cancer is difficult. Data suggest several features of the primary cancer that should make one hesitate before performing ASM (Table 2). As noted, with rare exception, studies of occult involvement of the areola have concentrated on nipple involvement with no mention of the areola. Data from NSABP B-04[13] and from Ho and colleagues[23] suggest that tumors that closely approximate the skin, skin tethering, and larger tumors (>4 cm) are at higher risk for occult involvement of the overlying skin. Although the areola does contain ductal elements, there is every reason to expect that risk of occult involvement from a proximate

or large tumor is no different from that of nonareola breast skin. Although it has been suggested that breast-conserving therapy for subareola tumors fare quite well when negative margins are achieved,[48–50] it is likely that most, if not all, of these patients undergo radiation therapy, potentially eliminating this area of recurrence as a major problem. Radiation therapy is not generally a consideration for most patients undergoing SSM with immediate reconstruction. Recently, Petit and colleagues,[51] from the European Institute of Oncology in Milan, published preliminary results in 25 patients who had undergone NSM with intraoperative electron beam therapy delivered to the NAC. Until such data are expanded and matured, it would be appropriate to eliminate patients with large tumors and tumors beneath the areola when considering ASM.

Data from several studies also suggest that multicentricity is a risk factor for occult involvement of the NAC. Again, in studies in which multicentricity was found to be a risk factor for occult NAC involvement, the ducts within the nipple were found to contain occult tumor with no specific mention of the areola. Despite this general lack of pertinent information about occult areola involvement with multicentric tumors, it would seem prudent at this time to restrict ASM to those patients without multicentricity.

There are several general categories of patients in which ASM might be considered. The first is in patients with established breast cancer who require or who elect to undergo mastectomy with reconstruction. Based on the evidence presented, we would suggest that the procedure be limited to those patients in whom the index cancer is ≤4 cm, that the tumor is not multicentric, and, most importantly, that the tumor is not located beneath the areola.

ASM would also be appropriate in patients undergoing contralateral prophylactic mastectomy after treatment of opposite side breast cancer or in patients who

Table 2. Features of the Primary Breast Cancer Reported to Increase Risk of Occult Nipple-Areola Involvement

Feature
<2 cm from areola
Dimpling (tethering) of areola
Tumors >4 cm
Multicentric tumors
Multifocal tumors
Lymphovascular invasion
Perineural invasion

elect to undergo mastectomy for lobular carcinoma in situ or other high-risk conditions. In these situations, ASM is likely to offer minimal risk.

More problematic are patients who are undergoing prophylactic mastectomy for a deleterious mutation in the BRCA1-2 genes or those with histories highly suggestive of hereditary breast cancer. Although, as noted previously, the incidence of carcinoma originating in the areola is thought to be extremely low, the impact of a deleterious mutation in each ductal cell gives cause for caution in performing risk-reduction operations. Admittedly, our surgical approach to breast cancer patients in many instances represents compromise in the name of cosmetics and quality of life. We perform limited resections for ductal carcinoma in situ despite evidence that more can be better. In some instances, we maintain the inframammary fold in mastectomy patients when reconstruction is planned, despite the proved presence of breast tissue that lies inferior to the fold.[52] We perform SSM in BRCA1-2 mutation patients despite the knowledge that we are likely to be leaving behind more breast tissue on the skin flaps than would have been left with a more standard mastectomy incision. Yet, in all of these instances, we attempt to remove all visible breast tissue. When we retain the areola, we are knowingly leaving behind breast ducts with a risk of cancer that, to date, is unknown. Data from the study by Hartmann and colleagues[47] would suggest that even in this group of patients the risk of developing cancer in the NAC is extremely low. With only 18 patients carrying the BRCA1-2 gene mutation, there are insufficient numbers to draw definitive conclusions. With our current level of knowledge about risk of cancer in the areola, it is our recommendation that, aside from a clinical trial setting, the areola be removed during mastectomy in this high-risk group of patients.

In conclusion, areola-sparing mastectomy is thought to enhance cosmetic results in patients undergoing SSM and immediate reconstruction, but there is little clinical evidence from which to identify those patients in whom this procedure would be oncologically appropriate. An extensive literature review revealed that the areola is not pigmented breast skin but a discrete anatomic structure containing sebaceous and ductal elements indistinguishable from normal breast tissue. Based on studies of the anatomy and data addressing occult involvement of the NAC

and occult skin involvement it is recommended that ASM might be considered in patients with an ipsilateral cancer that is <4 cm in size, not multicentric, and does not lie beneath the NAC. ASM is not recommended in patients at high risk for hereditary breast cancer or a proved BRCA1-2 mutation.

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