

The Incidence of Occult Nipple-Areola Complex Involvement in Breast Cancer Patients Receiving a Skin-Sparing Mastectomy

Christine Laronga, MD, Bonnie Kemp, MD, Dennis Johnston, PhD,
Geoffrey L. Robb, MD, and S. Eva Singletary, MD

Background: Surgical treatment of breast cancer traditionally has included resection of the nipple-areola complex (NAC), in the belief that this area had a significant probability of containing occult tumors. The purpose of this study was to investigate the true incidence of NAC involvement in patients who underwent a skin-sparing mastectomy (SSM) and to determine associated risk factors.

Methods: A retrospective chart review was conducted of 326 patients who had a SSM at our institution from 1990 to 1993. NAC involvement was reviewed in 286 mastectomy specimens. The charts were analyzed for tumor size, site, histology, grade, nodal status, recurrence, survival, and NAC involvement.

Results: Occult tumor involvement in the NAC was found in 5.6% of mastectomy specimens (16 patients). Four patients would have had NAC involvement identified on frozen section if they had been undergoing a skin-sparing mastectomy with preservation of the NAC. There were no significant differences between NAC-positive (NAC+) and NAC-negative (NAC-) patients in median tumor size, nuclear grade, histologic subtype of the primary tumor, or receptor status. There were significant differences in location of the primary tumor (subareolar or multicentric vs. peripheral) and positive axillary lymph node status. NAC involvement was not a marker for increased recurrence or decreased survival.

Conclusions: Occult NAC involvement occurred in only a small percentage of patients undergoing skin-sparing mastectomies. NAC preservation would be appropriate in axillary node-negative patients with small, solitary tumors located on the periphery of the breast.

Key Words: Occult nipple involvement—Skin-sparing mastectomy.

Although conservative surgery has been shown to be an oncologically sound strategy for most early-stage breast cancer, mastectomy remains the treatment of choice for many women, either because of patient preference or because of tumor characteristics that are not compatible with a more conservative approach.¹ The standard of care for women receiving mastectomies who

desire surgical restoration of a breast mound is immediate breast reconstruction. A skin-sparing mastectomy preserves a maximal amount of breast skin, providing an ideal color, size, and texture match between the reconstructed breast mound and the contralateral breast.

Surgical treatment of breast cancer, including skin-sparing mastectomies, traditionally has included the nipple-areola complex (NAC), in the belief that this area had a significant probability of containing occult tumors. Studies that support this idea have been difficult to interpret, however, because of wide variation in nipple sampling technique and the number of patients examined.^{2–9} In general, these studies found that the risk of occult NAC involvement was greater when the primary tumor was close to the NAC, larger than 2 cm, poorly differentiated, and associated with positive axillary lymph nodes.^{2–9}

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From the Departments of Surgical Oncology (CL, SES), Pathology (BK), Biomathematics (DJ), and Plastic Surgery (GLR), The University of Texas M.D. Anderson Cancer Center, Houston, Texas.

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Address correspondence to: S. Eva Singletary, MD, Dept. of Surgical Oncology, The University of Texas M.D. Anderson Cancer Center, 1515 Holcombe Blvd., Box 106, Houston TX 77030; Fax: 713-792-0722.

In a preliminary study, we examined the feasibility of preserving the NAC during skin-sparing mastectomy with immediate reconstruction (Fig. 1).¹⁰ The patient was a 50-year-old postmenopausal woman who requested a bilateral mastectomy after a diagnosis of ductal carcinoma subsequent to earlier treatment for adenocarcinoma metastatic to the left axilla (Fig. 2). Because the blood supply to the NAC is more reliable when it comes from the inferior mastectomy flap, the skin incision was made along the superior border of the NAC and then extended out laterally toward the axilla. The dissection of the superior skin flap was the same as when performing a skin-sparing mastectomy. When fashioning the inferior skin flap, however, the incision was extended onto the undersurface of the NAC in this superficial plane, yielding flaps approximately 3 mm thick. The NAC is highly vascularized and tolerates this thickness well. The cosmetic results were excellent, with symmetrical breasts, good nipple projection, and some sensation in both NACs (Fig. 3). There has been no tumor recurrence at 20 months follow-up.

To assess the more general feasibility of NAC preservation during skin-sparing mastectomy, we reviewed all skin-sparing mastectomies performed during a 4-year period at the M. D. Anderson Cancer Center to determine the true incidence of occult NAC involvement and the risk factors for NAC involvement. We also examined recurrence and survival statistics to determine whether NAC involvement was a marker for unfavorable outcomes.

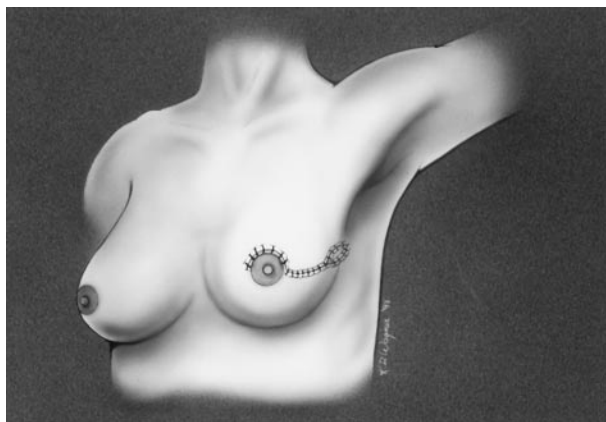


FIG. 1. Preservation of the NAC during a skin-sparing mastectomy, with an incision along the superior border of the NAC followed by a lateral extension incision. A small skin island protrudes from the lateral incision to serve as a window for flap viability.



Figure 2. Fifty-year-old patient seen 3 months after bilateral skin-sparing mastectomies with preservation of the NAC.

MATERIALS AND METHODS

A retrospective chart review was conducted of 326 patients who had a skin-sparing mastectomy with immediate reconstruction at The M. D. Anderson Cancer Center from 1990 to 1993. Patients were excluded from the study if the mastectomy was prophylactic (2 patients); the pathology was lobular carcinoma in situ only (6 patients); or gross nipple involvement, including Paget's disease, was present based on preoperative clinical or diagnostic examination (41 patients). Involvement of the NAC on clinical examination was defined as induration, retraction, fixation, or ulceration of the NAC or presence of nipple discharge. Occult NAC involvement was reviewed in 286 mastectomy specimens. Nine patients had bilateral breast cancer, and both mastectomy specimens were available for review. Charts were analyzed for the type of clinical and diagnostic evidence of breast cancer, NAC involvement, or both. The demographics of the

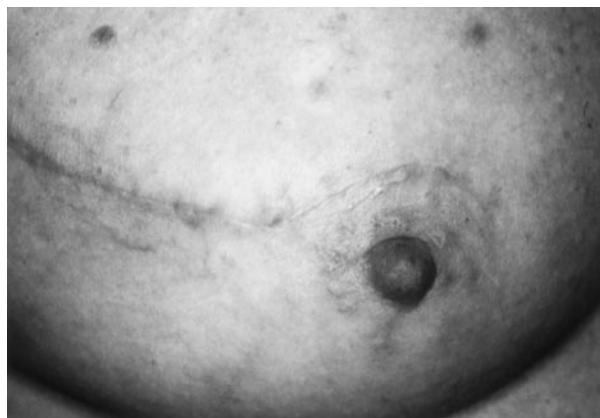


Figure 3. Close-up view of a superior circumareolar skin incision with lateral extension toward the axilla.

TABLE 1. NAC involvement as a function of primary tumor location and histology

Patient	Primary Tumor		NAC	
	Histology	Location	Histology	Description
1	IDC + DCIS	Multicentric	DCIS	Contiguous with primary tumor Subareola margin positive on frozen section
2	IDC + DCIS	Multicentric	Lymphatic embolization	Subareola margin positive on frozen section
3	IDC	Multicentric	Pagetoid spread	Involving only one duct
4	IDC + DCIS	Multicentric	DCIS	Involving multiple ducts
5	DCIS	Subareola	DCIS + pagetoid	Involving multiple ducts
6	IDC	Subareola	Pagetoid spread	Involving only one duct
7	DCIS	Subareola	DCIS	Involving only one duct
8	IDC, DCIS, IL	Subareola	Pagetoid spread	Large primary tumor (5 cm)
9	IDC + DCIS	Subareola	Pagetoid spread	Contiguous with primary tumor, subareola margin positive on frozen section
10	IDC	Subareola	Stromal infiltration	Contiguous with primary tumor, subareola margin positive on frozen section
11	DCIS	Subareola	Atypical duct	Involving only one duct
12	IDC + DCIS	Periphery	Pagetoid spread	Involving multiple ducts
13	DCIS	Periphery	DCIS	One duct close to skin surface
14	DCIS	Periphery	Paget's disease	Primary just superior to NAC
15	IL	Periphery	Stromal infiltration	Close to skin surface
16	DCIS	Periphery	DCIS	Involving multiple ducts

DCIS, ductal carcinoma in situ; IDC, infiltrating ductal carcinoma; IL, infiltrating lobular carcinoma; NAC, nipple-areola complex.

tumor [i.e., size, location, histology, nuclear grade, receptor status (estrogen, progesterone, Ki-67), and lymph node status] were obtained from the pathology reports. NAC involvement was determined by horizontally sectioning the entire NAC from the mastectomy, followed by vertically sectioning the complex for gross and microscopic evaluation.

In patients in whom occult tumor involvement of the NAC was identified, the pathology slides were reviewed again by an independent pathologist (BK) who was blinded to the clinical, mammographic, and histopathologic information. New sections of the original specimen were made as needed for clarification by the pathologist. This review was conducted for four reasons: (1) to confirm the original diagnosis; (2) to identify the exact histologic involvement of the NAC; (3) to note whether the primary tumor was contiguous with the NAC involvement; and (4) to determine if a frozen section on the NAC side of the superficial fascial plane would have identified the NAC involvement. During a skin-sparing mastectomy, the skin flaps are raised in the superficial fascial plane. When performing a skin-sparing mastectomy with preservation of the NAC, the dissection of the inferior skin flap would extend onto the undersurface of the NAC in this same plane. A frozen section of the base of the NAC would then be obtained to rule out either contiguous involvement or a second occult primary of the NAC.

The study concluded in August 1998, at which time the length of follow-up and patient status (alive or deceased) were recorded for each patient. During this fol-

low-up period, any development of local recurrence or distant metastasis was noted. If a local recurrence did occur, the distance from the circumareolar incision or the lateral extension incision of the skin-sparing mastectomy was noted.

RESULTS

Occult tumor involvement of the NAC was identified and confirmed in 16 (5.6%) of the 286 mastectomy specimens. Histologic involvement of the NAC consisted of ductal carcinoma in situ, pagetoid spread of ductal carcinoma in situ, lymphatic embolization, and stromal infiltration (Table 1). In four patients, the NAC involvement would have been identified on frozen section if they had been undergoing a skin-sparing mastectomy with preservation of the NAC. In three of these patients, the NAC involvement was contiguous with the primary tumor.

Tumor characteristics were compared in patients with occult NAC involvement (NAC+) and patients without NAC involvement (NAC-) to determine whether any

TABLE 2. Staging of primary tumors in NAC+ and NAC- patients

Primary Tumor Stage	NAC+ (n = 16) No. (%)	NAC- (n = 270) No. (%)
Stage 0	6 (38)	45 (17)
Stage I	0 (0)	94 (35)
Stage IIA	5 (31)	89 (33)
Stage IIB	5 (31)	40 (15)
Stage IIIA	0 (0)	2 (<1)

TABLE 3. Primary tumor characteristics as a function of occult NAC involvement

Tumor characteristics	NAC Involvement	
	Positive (n = 16)	Negative (n = 270)
Tumor size (median, range)	1.2 (0.5–5 cm)	1.5 (0.15–7.5 cm)
Location (subareola or multicentric)	68.8%	22.6%*
Nuclear grade		
Moderate to high	75.0%	73.3%
Low	11.1%	6.3%
Histologic subtype of primary		
IDC + DCIS	37.5%	44.0%
DCIS	36.5%	18.0%
IDC	18.8%	30.0%
Other	6.2%	8.0%
Positive receptor status		
ER	46.7%	58.0%
PR	35.7%	56.4%
Positive axillary nodes	56.3%	28.1% [†]

* $P \leq .001$; [†] $P = .017$.

DCIS, ductal carcinoma in situ; IDC, infiltrating ductal carcinoma. ER, estrogen receptor; PR, progesterone receptor.

statistically significant differences between these two groups existed (Tables 2 and 3). There were no significant differences between the two groups in median tumor size, nuclear grade, histologic subtype of the primary tumor, or receptor status (ER or PR). There were significant differences in location of the primary tumor (subareolar or multicentric; $P < .001$) and positive axillary lymph node status ($P = .017$).

There were no significant differences between the groups in incidence of local recurrence or distant metastases. Of the 286 mastectomies, 18 patients (6%) developed local recurrences, and only one of these occurred within 1 cm of the circumareolar incision of the skin-sparing mastectomy. In this patient, the NAC was negative for cancer. Two patients with NAC involvement had a local recurrence, one within 1 cm of the lateral extension incision, and the other distant from any incisions. Distant metastases occurred in 28 (13%) patients, most commonly in the bone, followed by liver and lung. The median follow-up for the occult NAC+ and the NAC- groups was 59.6 months and 59.1 months, respectively. This interval was judged to be adequate, because up to 90% of recurrences following mastectomy are detected within 5 years of initial treatment.¹¹ The 5-year overall survival calculated by Kaplan-Meier analysis was 93% for both groups.

DISCUSSION

Rationale for preserving the NAC

Recent trends in breast cancer surgery have been directed at balancing oncologically sound treatment with

improved cosmesis. The development of skin-sparing techniques with immediate reconstruction has meant that even patients who want or need a mastectomy can anticipate an improved cosmetic outcome.

Because the NAC area typically has been included in the resection, cosmetic approaches have involved nipple-areola reconstruction. In most patients, small flaps of skin from the breast mound are used for the nipple, while the areola is simulated by means of tattooing. Although this approach can give excellent cosmetic results, there are potential disadvantages. The use of surrounding skin flaps for reconstruction can lead to a nipple with little or no sensitivity, pale color, and possible loss of projection as the scars soften over time. In a series of 21 women who received nipple reconstruction with local skin flaps, Lossing and colleagues¹² found that only one third of them retained sensation in the nipple, and that two thirds of the women had nipples that were noticeably pale compared with the contralateral nipple. Tanabe and colleagues¹³ have investigated the inclusion of rolled auricular cartilage in the nipple reconstruction to combat the tendency for the height of the nipple to flatten over time. Spear and Arias¹⁴ examined the effectiveness of nipple-areola tattooing over a 6-year period. They found that 10% of tattoos had excessive fading, and nearly 60% ultimately were lighter than normal, requiring one or more subsequent touch-ups for an appropriate color match.

Although preservation of the NAC offers the possibility of preserving sensitivity and providing a good cosmetic match to the contralateral breast, this approach could be recommended only if there were a reasonable certainty that no occult tumor was located at the NAC site.

Determining the Oncologic Safety of NAC Preservation

Previous studies have reported an incidence of occult NAC involvement in mastectomy specimens ranging from 8% to 50%.²⁻⁹ The lower incidence found in the present study (5.6%) may be a reflection of patient selection criteria for skin-sparing mastectomy, or of the limited amount of tissue behind the areola disc included in the pathologic diagnosis of NAC involvement. In any case, the observed incidence suggests that NAC preservation during a skin-sparing mastectomy could be a viable option for patients undergoing this surgery, whether from personal preference or because of primary tumor characteristics. Nonetheless, identification of remaining patients at high risk for NAC involvement is still important.

Of the 16 NAC+ cases identified here, only 4 would have been found by frozen section at the subareolar margin. This suggests that, for 75% of cases with unknown occult tumor involvement, a decision on whether to proceed with NAC preservation would have to be based on other identifiable risk factors. Previous studies have concluded that the risk of NAC involvement was higher in primary tumors that were larger than 2 cm, located in a subareolar region, poorly differentiated, or associated with positive axillary node disease.²⁻⁹ Because the median tumor size was only 1.2 cm in the NAC+ group, the association of large tumor size with occult NAC involvement could not be verified in this study. Likewise, because most of both the NAC+ and the NAC- tumors in this study had a moderate to high nuclear grade, the association with poorly differentiated tumors could not be reproduced. However, our study did confirm a positive correlation between occult NAC involvement and primary tumor location (subareolar or multicentric) and axillary node involvement. These results suggest that NAC preservation would be appropriate in axillary node-negative patients with tumors located on the periphery of the breast. In this subset of patients, the probability of missing occult tumor involvement of the NAC would be less than 2%.

CONCLUSIONS

The results of this study indicate that occult NAC involvement is a fairly rare phenomenon, occurring in only about 6% of women who were undergoing a skin-sparing mastectomy. Women who are clinically N0 and who have small, solitary tumors on the periphery of the breast are at especially low risk, and would be good candidates for NAC preservation.

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