

## Tumor Involvement of the Nipple in Total Skin-Sparing Mastectomy: Strategies for Management

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### ABSTRACT

**Background.** Despite a growing body of literature on oncologic and reconstructive outcomes after total skin-sparing mastectomy (TSSM), some questions related to this approach remain unanswered, including strategies for managing tumor involvement of the nipple while maintaining the aesthetic benefits of TSSM.

**Methods.** A prospectively maintained database of patients undergoing TSSM and immediate breast reconstruction from 2005 to 2013 was reviewed. Outcomes included tumor involvement of resected nipple tissue and subsequent management, recurrences after nipple involvement, and trends in management of involved nipple tissue.

**Results.** The study included 1176 breasts in 751 patients treated with TSSM. The follow-up period was 31.3 months. The nipple–areolar complex (NAC) of 32 breasts (2.7 %) had a positive margin or involvement of nipple tissue. Of these breasts, 56 % contained invasive cancer, and 44 % had in situ disease. Management included repeat excision (11 cases, 34 % of cases), radiation of the NAC (as part of the postmastectomy breast field) without further excision (5 cases, 16 %), complete NAC removal (8 cases, 25 %), and no further treatment (8 cases, 25 %). Management by complete NAC skin excision significantly decreased during the study period ( $p = 0.003$ ). The overall local recurrence rate was 6.2 %. No patients had recurrence in the preserved NAC skin.

**Conclusions.** Despite expanding indications for TSSM, it can be performed safely with low rates of nipple involvement. Over time, tumor involvement of the nipple has been treated with re-excision or other alternative approaches to NAC removal that preserve the aesthetic benefits of total skin-sparing approaches without an early adverse impact on local recurrence.

Total skin-sparing mastectomy (TSSM) and nipple skin-sparing mastectomy (NSSM) evolved from skin-sparing mastectomy as a way to provide patients with added aesthetic and psychological benefits by preserving the entire breast skin envelope, including the nipple–areolar complex (NAC) skin. The TSSM procedure can be distinguished from subcutaneous mastectomy and some nipple-sparing mastectomy techniques because all breast tissue, including nipple tissue, is removed with the TSSM technique.<sup>1</sup>

Although NAC skin preservation initially raised concerns about a potential increase in locoregional recurrence rates, the growing body of studies reporting oncologic outcomes after TSSM present recurrence rates similar to those after skin-sparing mastectomy, demonstrating that TSSM does not appear to compromise oncologic safety.<sup>2–5</sup> As a result, and as surgeons are becoming increasingly comfortable with the TSSM technique, the selection criteria for TSSM have expanded over time. The selection criteria currently include patients with larger tumors, locally advanced disease, and tumors closer to the NAC, especially in the setting of neoadjuvant therapy and tumor volume shrinkage.<sup>2,6–11</sup>

As the indications for TSSM have expanded, the rates of tumor involvement of the NAC could potentially increase. Characteristics such as tumor size, histologic type, staging, location, human epidermal growth factor receptor 2 (HER2) amplification, lymphovascular invasion,

intraductal spread, and clinical appearance of the NAC (including the presence of nipple discharge) all have been shown to affect tumor involvement of the NAC.<sup>12</sup>

Pathologic studies of patients undergoing NSSM or TSSM have reported a wide range of NAC involvement risk ranging from 2.5 to 14%.<sup>2,10,11,13–15</sup> Few data exist on the optimal way to manage TSSM cases with NAC involvement or on the oncologic outcomes for these patients, particularly in high-risk populations. This report presents our experience managing patients with tumor involvement of the NAC at the time of TSSM and the oncologic outcomes for this patient cohort.

## METHODS

### *Patient Selection*

We reviewed prospectively collected clinical data from all TSSM and immediate breast reconstruction cases performed from 2005 to 2013. Patients with a positive margin for invasive cancer or ductal carcinoma in situ (DCIS) at the NAC or tumor involvement of resected nipple tissue then were selected from this cohort for further analysis. This study was approved by the University of California, San Francisco Committee on Human Research.

### *Surgical Technique*

At our institution, all patients without clinical involvement of the NAC or skin at the time of mastectomy and no significant ptosis or macromastia are eligible for TSSM. Patients who initially present with skin involvement but subsequently have a good response to neoadjuvant chemotherapy also are offered the procedure. Whereas we initially performed magnetic resonance imaging (MRI) for all patients planning TSSM to assess for radiographic evidence of NAC involvement, we no longer routinely perform MRI unless indicated for other reasons (e.g., assessment of response to neoadjuvant chemotherapy).

Our TSSM technique involves removal of all nipple tissue through inversion of the nipple and excision of the nipple tissue at the dermal junction. Once the mastectomy is complete, the subareolar margin deep only to the NAC is marked with a suture on the mastectomy specimen so the area can be closely examined by the pathologists at sectioning. After removal of the mastectomy specimen, the nipple is completely cored out, and the new nipple margin is sent as a separate specimen.

The incisions in the current series included inframammary, superior periareolar, lateral and radial incisions, as well as incisions incorporating prior breast surgery scars. Standard breast reconstruction options were offered to patients, including autologous reconstruction with pedicled

transverse rectus abdominis myocutaneous (TRAM) flaps or microvascular free flaps and prosthetic reconstruction with two-stage tissue expander-implant reconstruction or immediate implant placement.

Surgical management of positive nipple margins involved either complete resection of the preserved NAC skin in an elliptical fashion around the areola or assessment of the area beneath the preserved NAC skin with re-excision of any residual tissue or scar present. Typically, NAC resection or nipple margin re-excision is performed at the second stage of reconstruction so that it does not have to be performed as a separate procedure.

### *Oncologic Outcomes*

Ultrasound and MRI imaging reports were used to determine the location of the tumor relative to the nipple for data analysis. Pathologic analysis determined the tumor size at the time of surgery. Serial sectioning of the nipple tissue during the final pathologic analysis determined tumor involvement. Locoregional recurrences were defined as subsequent diagnoses of breast cancer of the ipsilateral chest wall or locoregional lymph nodes after TSSM, and negative margins were achieved at pathology. Management of tumor involvement of the nipple specimen and locoregional and distant recurrences were collected via medical record review. All re-excisions of positive nipple margins were submitted for pathologic analysis at the time of re-excision.

### *Statistical Analyses*

The year of surgery was used as an instrumental variable for our ongoing change in practice. The Kendall–Mann test for monotonic trend was used to analyze the significance of our change in practice. Statistical analyses were performed using the R programming language, and *p* values lower than 0.05 were considered significant.

## RESULTS

### *Patient Characteristics*

From January 2005 through January 2014, TSSM and immediate reconstruction were performed on 1173 breasts in 748 patients. Final pathologic analysis showed a positive margin at the NAC or involvement of nipple tissue in 32 breasts (2.7%). In the overall cohort, 440 (38%) of the TSSM cases were prophylactic. None of the prophylactic cases ultimately had tumor involvement within the NAC.

The patient characteristics are displayed in Table 1. The mean follow-up time was 31.3 months. The median age

**TABLE 1** Patient, tumor, and treatment characteristics of total skin-sparing mastectomy (TSSM) cases

| Characteristic      | Overall TSSM cohort, <i>n</i> (%) | Cohort with IDC or DCIS in nipple, <i>n</i> (%) |
|---------------------|-----------------------------------|---|
| Patient age (years) |                                   |   |
| Median              | 46                                | 49.5  |
| Range               | 18–76                             | 36–71   |
| Chemotherapy        |                                   |   |
| Any                 | 408 (55)                          | 23 (6)  |
| Neoadjuvant         | 263 (35)                          | 14 (5)  |
| Adjuvant            | 145 (19)                          | 9 (6)   |
| Radiotherapy        |                                   |   |
| Any                 | 248 (21)                          | 15 (6)  |
| History             | 103 (9)                           | 1 (1)   |
| Postmastectomy      | 146 (12)                          | 15 (10)   |
| Tumor stage         |                                   |   |
| Clinical            |                                   |   |
| Prophylactic        | 440 (38)                          | 0 (0)   |
| 0                   | 186 (16)                          | 6 (19)  |
| 1                   | 224 (19)                          | 10 (31)   |
| 2                   | 227 (19)                          | 9 (28)  |
| 3                   | 84 (7)                            | 7 (22)  |
| 4                   | 7 (1)                             | 0 (0)   |

IDC invasive ductal carcinoma, DCIS ductal carcinoma in situ

was 46 years (range 18–76 years), and the mean body mass index (BMI) was 23.9 kg/m<sup>2</sup>, which was not statistically different from that of the subset identified as having positive nipple involvement (median age 49.5 years; range 36–71 years; mean BMI 22.6 kg/m<sup>2</sup>).

*Tumor and Treatment Characteristics*

Table 1 presents the tumor stages and treatment characteristics for the TSSM cases at our institution since 2005. A total of 263 patients (35 %) received neoadjuvant chemotherapy, whereas 145 patients (19 %) received adjuvant chemotherapy. In the group that had positive nipple involvement, 14 (44 %) had neoadjuvant chemotherapy and 9 (28 %) had adjuvant chemotherapy. Postmastectomy radiation was performed in 145 (20 %) of all the therapeutic TSSM cases, although the proportion was significantly higher among the cases that had positive nipple tissue, with 14 (44 %) of the 32 cases receiving postmastectomy radiation (*p* < 0.0001). The cases that had no tumor involvement of the nipple included 6 (3 %) of 186 stage 0 TSSM cases, 10 (4 %) of 224 stage 1 cases, 9 (4 %) of 227 stage 2 cases, and 7 (8 %) of 84 stage 3 cases. None of the seven stage 4 cases (0 %) had positive nipple involvement.

Table 2 presents the treatment and tumor characteristics of the 263 patients (414 cases) that received neoadjuvant

**TABLE 2** Tumor and treatment characteristics of total skin-sparing mastectomy (TSSM) cases treated with neoadjuvant chemotherapy<sup>a</sup>

| Characteristic             | Overall TSSM neoadjuvant cohort, <i>n</i> (%) | Neoadjuvant cohort with IDC or DCIS in nipple, <i>n</i> (%) |
|----------------------------|---|---|
| Radiotherapy               |   |   |
| Any                        | 133 (32)                                      | 12 (86)   |
| History                    | 28 (7)  | 0 (0)   |
| Postmastectomy             | 105 (25)                                      | 12 (86)   |
| Tumor stage                |   |   |
| Pretreatment (clinical)    |   |   |
| Prophylactic <sup>b</sup>  | 141 (34)                                      | 0 (0)   |
| 0 <sup>b</sup>             | 19 (5)  | 0 (0)   |
| 1                          | 41 (10)                                       | 1 (7)   |
| 2                          | 134 (32)                                      | 6 (43)  |
| 3                          | 72 (17)                                       | 7 (50)  |
| 4                          | 6 (2)   | 0 (0)   |
| Posttreatment (pathologic) |   |   |
| Prophylactic               | 141 (34)                                      | 0 (0)   |
| 0                          | 62 (15)                                       | 0 (0)   |
| 1                          | 55 (13)                                       | 1 (7)   |
| 2                          | 95 (23)                                       | 4 (29)  |
| 3                          | 55 (13)                                       | 9 (64)  |
| 4                          | 6 (2)   | 0 (0)   |

IDC invasive ductal carcinoma, DCIS ductal carcinoma in situ

<sup>a</sup> Overall TSSM neoadjuvant cohort includes 414 cases

<sup>b</sup> Treated because of a contralateral breast cancer

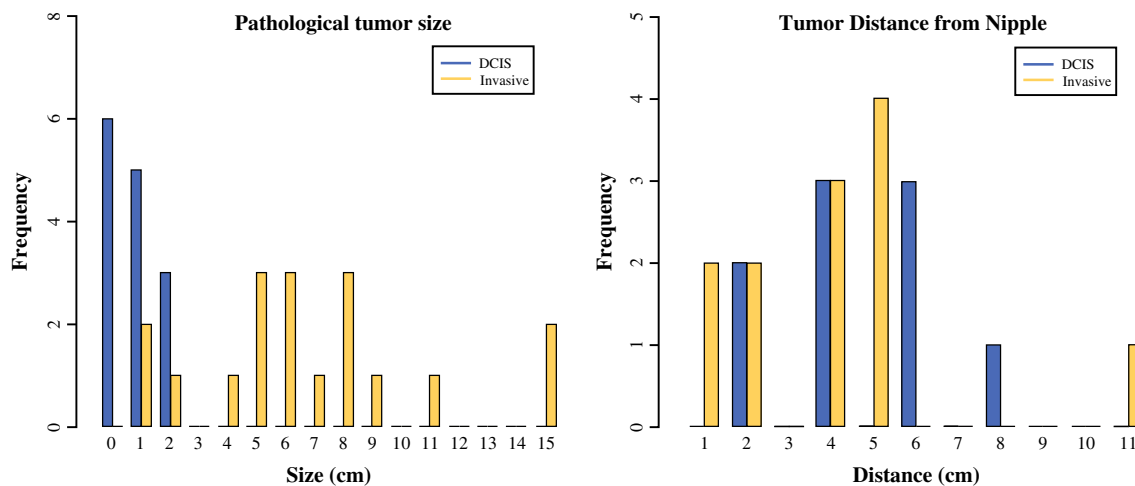
chemotherapy. Positive nipple tissue was observed in 14 (3.4 %) of these neoadjuvant cases, and the distributions of both the pre- and post-treatment tumor stages of those cases also are presented in Table 2.

*Surgical Characteristics*

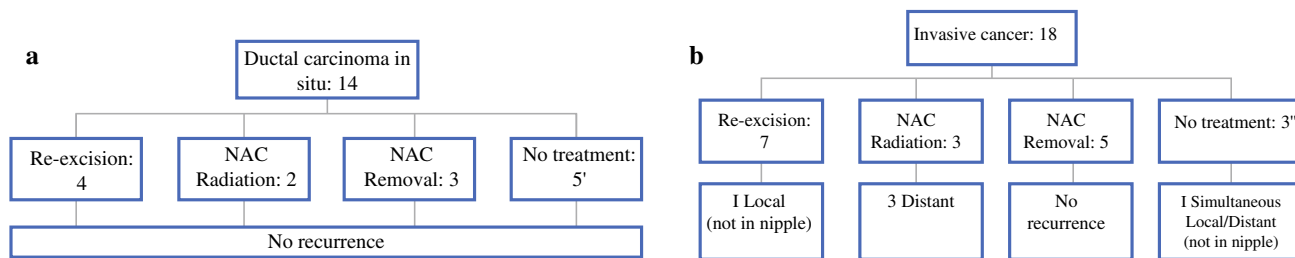
The incisional approaches for TSSM included inframammary, lateral, superior areolar, and radial incisions, as well as incisions designed to incorporate prior breast surgery scars. Overall, the preferred incisions were inframammary incisions (616 cases, 53 %) and superior areolar incisions (444 cases, 38 %). These incisions were similarly preferred in the subset that had positive nipple involvement, with inframammary incisions used in 20 cases (63 %) and superior areolar incisions used in 8 cases (25 %).

*Oncologic Outcomes*

Of the 32 cases (2.7 %) with either invasive or in situ involvement of the nipple specimen, 14 (44 %) had in situ cancer in the nipple specimen, and 18 (56 %) had invasive



**FIG. 1** Distribution of final pathologic tumor sizes (*left*) and distance of the tumor from the nipple (*right*)



<sup>a</sup>All five cases had tumor within the nipple without extension to the margins.

<sup>a</sup>All three cases had tumor within the nipple without extension to the margins.

**FIG. 2** Management of ductal carcinoma in situ (DCIS) involvement of the nipple and recurrence rates (*left*). Management of invasive cancer involvement of the nipple and recurrence rates (*right*)

cancer. In these cases, tumor size varied significantly at the final pathology (median 2.15 cm; range 0–15 cm), as did tumor distance from the nipple (median 4 cm; range 1–11 cm), as shown in Fig. 1.

Management of the positive margins at the NAC in the 32 cases included re-excision of nipple tissue in 11 cases (34 %), NAC radiation without further excision in 5 cases (16 %), complete NAC resection in 8 cases (25 %), and no further treatment in 8 cases (25 %). Management of in situ cancer within the nipple included re-excision of nipple tissue in 4 cases (29 %), NAC radiation without further excision in 2 cases (14 %), complete NAC resection in 3 cases (21 %), and no further treatment in 5 cases (36 %) (Fig. 2a). Of the cases with in situ cancer in the nipple specimen, 10 cases (71 %) involved patients treated for invasive disease. Management of invasive cancer within the nipple included re-excision of nipple tissue in 7 cases (39 %), NAC radiation without further excision in 3 cases (17 %), complete NAC resection in 5 cases (28 %), and no further treatment in 3 cases (17 %) (Fig. 2b). All the patients who underwent radiation without further excision had primary indications for postmastectomy radiation (i.e., large tumor size or involved axillary lymph nodes) leading

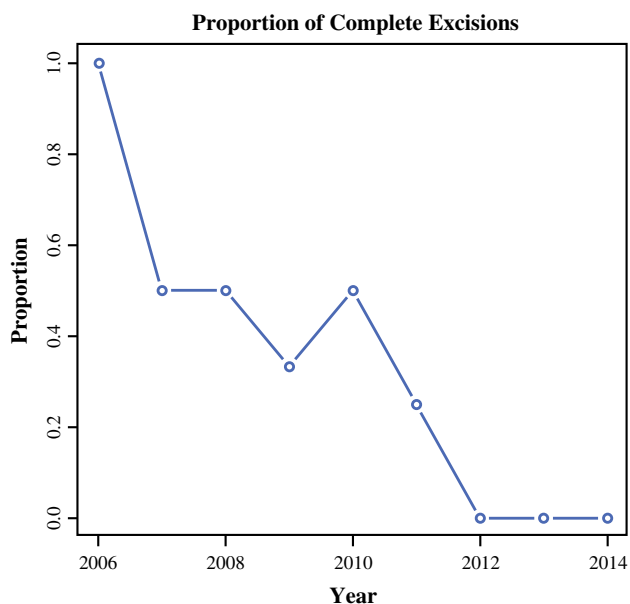
to recommendation for radiation therapy aside from the positive nipple margin.

Management by complete NAC excision significantly decreased during the study period ( $p = 0.003$ ), as shown in Fig. 3. For the nine nipple margin re-excisions already performed, the final pathology in five cases (56 %) showed only scar or other fibrous tissue. The remaining four cases (44 %) yielded benign breast tissue. At this writing, two additional re-excisions with upcoming expander-implant exchange procedures are scheduled.

The overall locoregional recurrence rate was 6.2 %, which did not differ statistically from the 3.3 % seen in the larger cohort that had no tumor involvement of the nipple ( $p = 0.3$ ). One local recurrence was experienced by a patient with stage 2 disease, and one simultaneous locoregional and distant recurrence was experienced by a patient with stage 3 disease. Both local recurrences occurred away from the preserved NAC skin.

## DISCUSSION

The practice of our group has been to assess tumor involvement of the NAC only on the permanent final



**FIG. 3** Decline in the proportion of complete excisions performed each year over time

pathology, which differs from some other high-volume centers.<sup>2,3,11</sup> This decision stems from a number of factors, including the potential false-negative results with frozen section.<sup>13,14</sup> Additionally, because our technique involves coring out all nipple tissue for every patient regardless of tumor location, the only intraoperative option for patients with a positive frozen section of the nipple tissue would be complete NAC removal, which we currently believe is likely unnecessary for most patients without extensive disease in the nipple. Finally, with the low overall rate of tumor involvement seen in our cohort, despite our high-risk population, performing frozen section analysis for every patient is not justified.

The low rates of NAC involvement in this study are similar to findings from other large studies. Other recent studies investigating final pathology to determine tumor involvement of the resected nipple tissue or subareolar margin have shown rates of 3–8%.<sup>2,15</sup> Interestingly, in our series, the distance from the nipple to the primary tumor on imaging and the tumor size on final pathology varied significantly, indicating that consideration of tumor size and distance from the nipple may not be necessary in patient selection for the approach. When tumor involvement of the nipple is found, management is varied, with many groups recommending complete NAC excision.<sup>2,11,13</sup> However, authors of some recent studies have advocated re-excision rather than complete excision.<sup>15</sup>

Over time, our practice has changed significantly (as shown in Fig. 3). Currently, the only clear indication for NAC removal is extensive tumor involvement of the subareolar margin and nipple specimen in the final pathologic analysis. If a patient will not be receiving postmastectomy

radiation therapy for another indication and if review of the pathology specimen shows definitive involvement of the anterior aspect of the excised nipple tissue, we perform re-excision of the margin, typically at the time of expander-implant exchange or another reconstruction revision procedure. However, even when we do go back for re-excision of the nipple margin, we often do not find any residual breast tissue beneath the NAC skin to excise and instead find only scar or fibrous tissue, which occurred in more than half of the re-excisions in this series. Even in cases with a small amount of residual breast tissue, none of the re-excised nipple margins have shown any remaining invasive or in situ cancer.

Although the follow-up period in this series still is short, the low rates of local recurrence seen in this study support the patient selection criteria as well as the strategies for management of the positive nipple specimens. Most importantly, none of the patients in this study (or in our entire TSSM cohort) have experienced a local recurrence in the preserved NAC skin, highlighting the importance of careful removal of all breast and nipple duct tissue at the time of mastectomy. When all breast tissue is entirely resected, TSSM can be safely performed, with patients given the aesthetic and psychological benefits the approach provides.

**DISCLOSURE** The authors declare no conflict of interest.

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