

## Expanding the Indications for Total Skin-Sparing Mastectomy: Is It Safe for Patients with Locally Advanced Disease?

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### ABSTRACT

**Background.** Indications for total skin-sparing mastectomy (TSSM) continue to expand. Although initially used only for early-stage breast cancer, TSSM currently is offered in many centers to patients with locally advanced disease. However, despite this practice change, limited data on oncologic outcomes in this population have been reported.

**Methods.** A retrospective review of a prospectively collected database of all patients undergoing TSSM and immediate reconstruction from 2005 to 2013 was performed. The outcomes for patients with stage 2b and stage 3 cancer were included in the analysis. The primary outcomes included the development of locoregional or distant recurrences.

**Results.** Of 753 patients undergoing TSSM, 139 (18 %) presented with locally advanced disease. Of these 139 patients, 25 (18 %) had stage 2b disease, and 114 (82 %) had stage 3 disease. Most of the patients (97 %) received chemotherapy (77 % neoadjuvant, 20 % adjuvant), whereas 3 % received adjuvant hormonal therapy alone. Of the neoadjuvant patients, 13 (12 %) had a pathologic complete response (pCR) to treatment. During a mean follow-up period of 41 months (range 4–111 months), seven patients (5 %) had a local recurrence, 21 patients (15.1 %) had a distant recurrence, and three patients (2.2 %) had simultaneous local and distant recurrences.

None of the local recurrences occurred in the preserved nipple–areolar complex skin.

**Conclusions.** Patients with locally advanced breast cancer are most at risk for distant rather than local recurrence, even after TSSM. When used in conjunction with appropriate multimodal therapy, TSSM is not associated with an increased risk for local recurrence in this population, even in the setting of low pCR rates.

Total skin-sparing mastectomy (TSSM) entails preservation of the entire breast skin envelope, including the nipple–areolar complex (NAC) skin, while all underlying breast tissue is removed. Although TSSM techniques raised early concerns regarding oncologic safety and technical feasibility, the approach has become more widely accepted as longer-term follow-up evaluation and improvements in technique have been reported.

With the increasing adoption of TSSM, the patient selection criteria for the approach also have expanded. Early studies described its use only for prophylactic indications or for patients with small tumors located far from the NAC without skin or nodal involvement.<sup>1–4</sup> However, more recently, many groups have begun offering the approach to patients with larger tumors and no longer require preoperative magnetic resonance imaging (MRI) to document distance from the NAC, but instead just ensure that examination shows no clinical involvement of the NAC.<sup>5–8</sup>

One group of patients now offered TSSM at some centers are those with locally advanced breast cancer,<sup>9–11</sup> although outcomes analysis of these patients after TSSM is limited and often grouped within larger studies that include earlier-stage and prophylactic patients.

The current study aimed to focus specifically on a high-risk group of patients with locally advanced disease (stage

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2b or 3) who had undergone TSSM to determine oncologic outcomes for this population.

## METHODS

### *Selection Criteria*

Over time, our group's selection criteria for TSSM have evolved, and currently, nearly all our patients choosing or requiring mastectomy are offered TSSM. The exclusion criteria for the procedure rule out clinical involvement of the NAC in examination or imaging, significant ptosis, and large breast size. Patients initially presenting with skin involvement who have a good response to neoadjuvant chemotherapy and no longer have tumor involvement of the skin at the time of mastectomy are also offered TSSM.

### *Surgical Technique*

Our TSSM technique involves inversion of the nipple with complete excision of all nipple tissue at the dermal junction to ensure the removal of all breast tissue during the mastectomy. Excised nipple tissue then is evaluated for tumor involvement during final pathologic analysis of the surgical specimen. Our preferred mastectomy incisions are inframammary and superior areolar/mastopexy incisions, with other less commonly used incisions including radial and lateral incisions and incisions incorporating prior partial mastectomy scars. Immediate breast reconstruction is performed for all patients using standard prosthetic and autologous reconstructive techniques, including two-stage expander-implant reconstruction, microvascular flaps, and transverse rectus abdominis myocutaneous (TRAM) flaps.

The patients in this study requiring postmastectomy radiation therapy underwent radiation consisting of opposed tangential fields to the reconstructed breast with the field-in-field technique. A boost dose of radiation to the mastectomy scar or reconstructed breast was not included. Patients with four or more positive axillary nodes received treatment to the supraclavicular region. Prophylactic irradiation of the internal mammary nodes was not performed and was reserved for patients with documented (via imaging or biopsy) positive internal mammary nodes. Patients undergoing expander-implant reconstruction received radiation before the expander-implant exchange without deflation of the expander.

### *Patients and Outcomes*

A prospectively maintained database of patients who underwent TSSM and immediate breast reconstruction at our institution from 2005 to 2013 was queried for patients

presenting with stage 2b or 3 disease. The key variables included tumor histology, stage, receptor subtype, history of radiation therapy or receipt of postmastectomy radiation therapy, receipt of neoadjuvant or adjuvant chemotherapy, and pathologic response to treatment in patients who received neoadjuvant chemotherapy.

The oncologic outcomes included locoregional recurrence, defined as a tumor recurrence within the chest wall, breast skin, or ipsilateral regional lymph nodes, and distant recurrence. Complications data collected included infections, mastectomy skin flap or NAC necrosis, and expander-implant or flap loss.

Kaplan–Meier curves were constructed using Stata 13 software (StataCorp LP, College Station, TX, USA) for overall and disease-free survival. The patients were stratified based on their first event: locoregional recurrence, distant recurrence, or simultaneous presentation of locoregional and distant recurrences.

This study was approved by the University of California, San Francisco Committee on Human Research.

## RESULTS

### *Patients and Tumor Characteristics*

Of 753 TSSM patients during the study period, 139 (18 %) presented with locally advanced disease; 25 (18 %) had stage 2b disease, and 114 (82 %) had stage 3 disease (Table 1). Tumor receptor status is shown in Table 1. The mean age of the patients was 46.9 years (range 30.4–70 years), and the mean body mass index (BMI) was 24.4 kg/m<sup>2</sup> (range 17–36 kg/m<sup>2</sup>). The rates of diabetes and active tobacco use were both less than 2 %.

### *Treatment Characteristics*

Treatment and response to treatment details are presented in Table 1. Neoadjuvant chemotherapy was administered to 77 % of the patients. Of the patients who received neoadjuvant chemotherapy, 13 (12 %) had a pathologic complete response (pCR) to treatment seen at the time of mastectomy. Postmastectomy radiation therapy was administered to 88 patients (63 %).

### *Oncologic Outcomes*

During a mean follow-up period of 41 months (range 4–111 months), seven patients (5 %) had a locoregional recurrence, 21 patients (15 %) had a distant recurrence, and three patients (2 %) had simultaneous local and distant recurrences (Figs. 1, 2). All locoregional recurrences were experienced by patients with residual disease in the breast

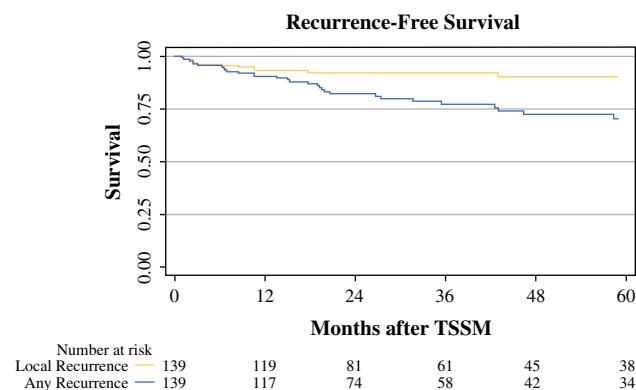
**TABLE 1** Tumor and treatment characteristics

	<i>n</i> (Total = 139)	%
<b>Chemotherapy</b>		
Neoadjuvant	107	77
Adjuvant	28	20
None <sup>a</sup>	4	3
<b>Radiation therapy</b>		
Postmastectomy	88	63
History	5	4
None	46	33
<b>Pretreatment stage</b>		
Stage 2b	25	18
Stage 3	114	82
<b>Posttreatment stage<sup>b</sup></b>		
0	13	12
1	4	4
2	36	34
3	54	50
<b>Receptor status</b>		
HR+/HER2/neu+	19	14
HR+/HER2/neu-	92	66
HR-/HER2/neu+	7	5
HR-/HER2/neu-	21	15

HR hormone receptor, HER2 human epidermal growth factor receptor 2

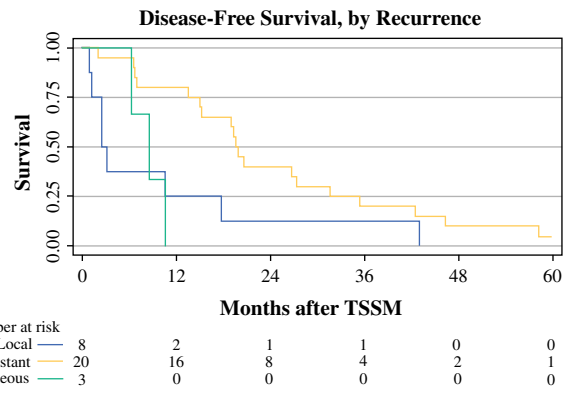
<sup>a</sup> All received adjuvant hormone therapy

<sup>b</sup> Neoadjuvant patients only



**FIG. 1** Local recurrence-free survival compared to overall recurrence-free survival

at the time of mastectomy. All the patients who initially presented with a locoregional recurrence alone subsequently experienced a distant recurrence, the majority (88 %) of which occurred within 18 months. None of the local recurrences developed in the preserved NAC skin. Overall event-free survival was 70 % at the 5-year follow-



**FIG. 2** Disease-free survival stratified by recurrence type

up visit. By subtype, recurrence-free survival rates were as follows: hormone receptor-positive (HR+)/human epidermal growth factor receptor 2 (HER2)/neu+ (84 %), HR+/HER2/neu- (93 %), HR-/HER2/neu+ (57 %), and HR-/HER2/neu- (57 %).

*Complications*

The reconstructions performed included 128 (92 %) expander-implant reconstructions, 10 pedicled TRAM flaps (7 %) and 1 DIEP flap (1 %). The surgical complications included 2 cases (1.4 %) of NAC necrosis, 5 cases (3.6 %) of mastectomy skin flap necrosis, 14 cases (11 % of expander-implant reconstructions) of implant loss, and 17 cases (12 %) of severe infection requiring intravenous antibiotics. All the cases of mastectomy skin flap necrosis and implant loss involved patients who had received postmastectomy radiation therapy. Additionally, 10 (59 %) of the 17 patients with severe infections then went on to experience implant loss, all of whom had received postmastectomy radiation therapy. Both cases of nipple necrosis involved patients who had immediate autologous reconstruction, neither of whom received radiation. No instances of partial or total flap loss occurred in patients who had autologous reconstruction.

**DISCUSSION**

The expansion of total skin-sparing mastectomy criteria over time has allowed greater numbers of patients to experience the aesthetic and psychological benefits that TSSM approaches provide. However, these benefits need to be weighed within the context of oncologic safety, particularly for patients presenting with extensive disease. Our patient population included a significant number of patients with locally advanced disease, nearly all of whom were offered TSSM approaches unless they had tumor involvement of the skin or clinical involvement of the nipple.

Review of our outcomes for these patients demonstrates low rates of local recurrence without any recurrences in the preserved NAC skin, supporting the oncologic safety of this approach.

Although no prior study has specifically focused on TSSM outcomes for patients with locally advanced disease, other studies have included a significant number of patients with more advanced disease in their larger series. A recent study including 42 patients with locally advanced disease<sup>11</sup> showed a 1.6 % local recurrence rate in the overall study of 105 patients, although follow-up evaluation was somewhat limited at 26 months. Another study investigating a subset of patients with locally advanced disease who underwent TSSM or skin-sparing mastectomy<sup>9</sup> reported a 10.3 % locoregional recurrence rate for the 39 patients who underwent TSSM during a mean follow-up period of 25.3 months. None of the recurrences developed in the preserved NAC.

In addition to being a high-risk cohort from an oncologic standpoint, patients with locally advanced disease also are at high risk for reconstructive complications given the more extensive procedures (e.g., axillary node dissection) and adjuvant treatment, particularly radiation therapy, often required. Other large series of patients with significant rates of adjuvant chemotherapy and radiation therapy have shown necrotic complication rates in the range of 5–20 %, <sup>9,12–14</sup> which is similar to rates seen in this series. Certainly, post-mastectomy radiation therapy is a major contributor to reconstructive complications, particularly in the setting of expander-implant-based reconstruction. Prior studies of patients undergoing TSSM and postmastectomy radiation therapy have shown complication rates as high as 30 %.<sup>12,15</sup>

Despite the increased risk of complications, our protocol involves offering immediate reconstruction routinely to all patients, regardless of radiation status, given the acceptable rates of complications and high rates of successful reconstruction seen even for patients who receive postmastectomy radiation therapy.<sup>16</sup> However, for patients with a high likelihood of needing postmastectomy radiation therapy, we try to achieve the option of breast conservation whenever possible through approaches such as the use of neoadjuvant chemotherapy to minimize complications.<sup>17</sup> Neoadjuvant chemotherapy can help to reduce the need for postmastectomy radiation therapy because many patients with a significant response to treatment, even those initially presenting with advanced disease, can achieve good oncologic outcomes without radiation therapy<sup>18,19</sup> or avoid mastectomy altogether and achieve breast conservation.<sup>20</sup>

These results also highlight how tumor biology and use of systemic therapy are the primary drivers of patient outcomes rather than local treatment. Similar to what has been shown with other studies of neoadjuvant chemotherapy,<sup>21–24</sup> patients presenting with advanced disease had high rates of systemic recurrence irrespective of the

surgical management of their cancer. Therefore, use of neoadjuvant chemotherapy to downstage tumors and allow for less invasive or more aesthetic procedures should be considered for patients presenting with locally advanced disease because it not only optimizes quality of life and avoids the increased complications of postmastectomy radiation therapy in the setting of reconstruction but also provides valuable information about response to treatment. This is particularly true for patients with anticipated poor prognosis based on their tumor biology (i.e., HR–/HER2/neu– tumors), who can often achieve breast conservation after an initial strong response to neoadjuvant chemotherapy<sup>24,25</sup> but still have high rates of distant recurrence.

Our series shows a disproportionately high number of patients with hormone-positive tumors compared with an overall population presenting with stage 2B or higher disease, which usually is enriched with triple-negative tumors.<sup>26</sup> This finding is not surprising because patients with hormone-positive disease are less likely to respond well to neoadjuvant therapy,<sup>25,26</sup> which means that many of the patients in this series may not have had the option of breast conservation based on their clinical response to treatment. The low rates of pCR seen in our population confirm the overall poor response to treatment, as does the high rate of postmastectomy radiation therapy. However, despite the significant disease burden still present at the time of mastectomy in many of our patients, local recurrence rates were not elevated at the 5-year follow-up assessment after TSSM and were comparable with those of other series showing 5-year local recurrence rates after non-TSSM approaches in the range of 5–21 %.<sup>27–29</sup> These findings lend support to the use of TSSM in this high-risk population as a strategy for improving aesthetic outcomes without compromising local control, although longer-term follow-up evaluation is needed for further confirmation of this approach.

To our knowledge, this study represents the largest series of patients with locally advanced breast cancer who have undergone total skin-sparing mastectomy, documenting low rates of local recurrence despite initial presentation with extensive disease. By specifically assessing the subset of patients with locally advanced disease, the safety of TSSM approaches in this population can be determined and used to guide patient decision making. These results support the expansion of the selection criteria for TSSM that our center and others have adopted in recent years, particularly with the growing use of neoadjuvant chemotherapy to downstage disease and optimize systemic control.

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