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Evidence of the Oncologic Safety of Total Skin-Sparing Mastectomy

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Abstract Total skin-sparing mastectomy or nipple skin-sparing mastectomy (TSSM/NSSM) techniques preserve the entire breast skin envelope and nipple-areolar complex (NAC) skin with resection of the underlying nipple tissue. In this review, we distinguish TSSM/NSSM techniques from other techniques that preserve the nipple appearance and provide clarity for evaluating and comparing these techniques. With longer follow-up and maturity of data sets, the oncologic safety of TSSM is emerging. The risk of breast cancer after prophylactic TSSM and locoregional recurrence after therapeutic TSSM are similar to those seen with other mastectomy techniques, with extremely low rates of recurrence within the NAC. The superior cosmetic outcome of TSSM/NSSM in conjunction with immediate reconstruction, the reduced complications with greater experience with the technique, and the accumulation of evidence on safety provide support for the inclusion of TSSM/NSSM techniques as standard approaches for mastectomy.

Keywords Total skin-sparing mastectomy · Nipple skin-sparing mastectomy · Nipple-sparing mastectomy · Prophylactic mastectomy · Recurrence after mastectomy

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Introduction

Total skin-sparing mastectomy or nipple skin-sparing mastectomy (TSSM/NSSM) and nipple-sparing mastectomy (NSM) techniques evolved as extensions of skin-sparing mastectomy techniques. The goal was to improve aesthetic and psychological outcomes for patients by preserving the entire breast skin envelope. The subcutaneous mastectomy, described by Freeman in 1962 for prophylactic mastectomy, was the first mastectomy technique to spare the nipple-areola complex (NAC) [1]. This approach was abandoned because of its high rate of complications and high rates of recurrence/occurrence which raised concern about the oncologic safety [2]. Relative to subcutaneous mastectomy, the NSM technique creates thinner skin flaps and removes the tissue beneath the areola. However, the nipple tissue may be left intact and is sometimes treated with radiation [3]. In this approach, patients can receive prophylactic or therapeutic irradiation (in the setting of microscopic tumor involvement of the nipple area) to the NAC with electrons [4].

TSSM differs from subcutaneous mastectomy and NSM in that all of the breast tissue, including the nipple parenchyma and ducts, is removed with the mastectomy specimen [5]. There is wide variation in the terminology used for these approaches in the literature, but the key differentiation is the approach to the nipple tissue and whether it is left intact or completely cored out. In this review, we use the term NSM to indicate techniques that may leave some nipple duct tissue behind and the terms TSSM or NSSM to indicate techniques that entail coring out the nipple duct tissue (Fig. 1).

There is a significant learning curve associated with TSSM as the thin skin flaps portend a high risk of skin flap and nipple-areolar complex (NAC) necrosis compared to other techniques. Many studies have focused on reporting postoperative complications and strategies to improve outcomes. Although skin-sparing mastectomy is well established

Fig. 1 Differences in the levels of dissection of techniques that spare the nipple-areola complex (NAC) skin. Subcutaneous mastectomy—thick flaps may leave some breast tissue without removal of nipple tissue. Nipple-sparing mastectomy (NSM)—thinner flaps without routine removal of nipple tissue. Total skin-sparing mastectomy (TSSM) or nipple skin-sparing mastectomy (NSSM)—thinnest flaps with removal of all nipple tissue

and has demonstrated that the preservation of skin does not impact oncologic results, concerns have still remained about the oncologic risk of preserving the NAC skin in TSSM, as the technique is new, and longer-term follow-up has only recently begun to be reported.

This study reviews patient selection, management in the setting of tumor involvement of resected nipple tissue, and rates of subsequent local-regional occurrence (prophylaxis) and recurrence (therapeutic) in patients who have undergone TSSM/NSSM. We have categorized all approaches involving nipple tissue resection as TSSM, regardless of what they are called by the authors, in order to bring clarity to the non-standard terminology that has been used to date. Thus, we differentiated TSSM approaches from NSM approaches, and we evaluate outcomes from papers that describe TSSM techniques with resection of nipple tissue.

Patient Selection for Total Skin-Sparing Mastectomy

The selection criteria for patients who are eligible for TSSM vary across centers and have changed significantly over time (Table 1). Although TSSM with excision of the nipple parenchyma was first performed for non-therapeutic indications in 1998 [6], it was not until 2004 that surgeons began to discuss and report on their experiences with TSSM for treatment of breast cancer. In the first case series of TSSM performed for cancer, Crowe et al. excluded patients with tumors that were >3.5 cm in size, centrally located, or treated with neoadjuvant chemotherapy [7]. They performed frozen sections on all nipple cores and resected the NAC when these were positive. In another early report, Margulies et al. reported offering TSSM to all patients except for those who were heavy smokers, those with obvious NAC involvement, and those with prior radiation [8]. They performed routine intraoperative touch preparation cytology and excised the NAC when these were positive. Valjcic et al. performed a prospective study evaluating predictors of NAC involvement in 108 patients with invasive breast cancer, and they recommended NAC preservation in patients with tumors <2.5 cm that were >4 cm from the NAC with negative axillary lymph nodes and negative for lymphovascular invasion [9]. These considerations are similar to those that were adopted in the early experience of TSSM at most centers. Some early experience also integrated MRI imaging into preoperative patient selection criteria to rule out patients with risk of nipple tissue involvement [5].

Other large centers used similar criteria in their initial experience with TSSM approaches. Spear et al. reported their experience in patients who were offered TSSM if they had tumors <3 cm in size or >2 cm from the NAC with clinically negative axillae [10]. de Alcantara Filho et al. reported using similar criteria, but their minimum tumor to NAC distance was reduced to >1 cm in 2005, and preoperative MRI was not routinely performed or required [11]. Both Boneti et al. and Kneubil et al. reported performing TSSM on patients as long as there was no NAC involvement on clinical exam or preoperative imaging studies, but they still performed intraoperative frozen sections and resected the NAC when these were positive for malignancy [12, 13].

Over our 12-year experience with TSSM, our group's inclusion criteria have expanded significantly over time. We initially offered TSSM only to women with tumors <2 cm in size with no clinical evidence of nipple/skin involvement and MRI confirmation of at least 2 cm distance between the NAC and the tumor [5]. After 2005, preoperative MRI was performed only selectively in patients who had tumors that were close to the NAC, and TSSM was offered as long as there was no direct tumor involvement of the NAC or the skin [14, 15]. We have also been offering TSSM to patients initially presenting with locally advanced disease involving the skin who subsequently have a good response to neoadjuvant chemotherapy and have no residual skin involvement by the time of mastectomy [15]. The relaxation of the oncologic inclusion criteria across centers in the USA was noted in a recent review of the National Cancer Institute's Surveillance, Epidemiology, and End Results database with a gradual increase in the percentage of tumors >2 cm in size over time [16]. These criteria were extended based on the data that skin-sparing mastectomy was as safe and effective as modified radical mastectomy where the central skin was removed.

Table 1 Oncologic tumor size and distance selection criteria for TSSM/NSSM and NAC involvement in selected studies

Author	Year	Tumor size (cm)	Distance to NAC (cm)	MRI used	Additional exclusion criteria	NAC involvement	Management
Crowe et al. [2]	2004	>3.5	"Central"	No	Neoadjuvant chemotherapy Positive nipple core frozen section		
Petit et al. [17]	2009	>3	<1	No	Positive retroareolar frozen section	63/579 (11 %)	NAC resection
Spear et al. [6]	2011	>3	<2	No	Axillary nodal involvement		
de Alcantara Filho et al. [7]	2011	>3	<2 <1 (after 2005)	Selective	Axillary nodal involvement Positive retroareolar frozen section	11/157 (7 %)	NAC resection
Wijayanayagam et al. [5]	2008	>2	<2	Yes	Axillary nodal involvement		
Marguilies et al. [3]	2005	–	–	No	Heavy smokers Prior radiation Positive intraoperative touch preparation		
Boneti et al. [8]	2011	–	–	Selective	Positive intraoperative touch preparation	4/156 (3 %)	NAC resection
Kneubil et al. [9]	2012	–	–	No	Positive retroareolar frozen section		
Coopey et al. [19]	2013	–	–	Selective	–	24/315 (8 %)	NAC resection
Eisenberg et al. [18]	2014	–	–	No	–	29/208 (14 %)	20 NAC resections 9 without additional treatment
Wang et al. [11]	2014	–	–	Selective	–	32/626 (5 %)	12 NAC resections 8 radiations 12 without additional treatment

Tumor Involvement of Nipple Tissue

Historically, studies based on non-TSSM mastectomy specimens have been used to assess the involvement of the NAC in an attempt to define risk factors for NAC invasion. The results were widely variable due to differences in the inclusion criteria. The relatively high rate of tumor reported in the nipple was used as a reason not to perform TSSM type procedures.

More recent pathology studies with inclusion criteria similar to what is currently used for TSSM have reported the risk of NAC involvement to be around 5–21 % [17–20]. The predictors of the tumor involvement of the NAC include tumor size, histological type, HER2 amplification, grade, staging, location, the clinical appearance of the NAC, the presence of nipple discharge, lymphovascular invasion, and intraductal spread [13]. Brachtel et al. performed a review of 232 consecutive therapeutic mastectomy specimens and found that 49 (21 %) had carcinoma contained within the nipple, with the majority of cases being DCIS [17]. However, when gross nipple involvement is excluded, the incidence of NAC pathology is much less. Weidong et al. evaluated 2240 mastectomy specimens without obvious nipple involvement and reported occult nipple involvement in 248 (11 %) cases [19]. D'Alonzo et al. studied 100 cases of total mastectomy without obvious skin involvement that had either preoperative mammogram or MRI available [20]. In their series, 14 (14 %) specimens contained tumor cells in the NAC. Laronga et al. reviewed the NAC pathology in 286 skin-sparing mastectomy specimens, excluding cases with gross nipple involvement and found only 16 of the 286 (5.6 %) specimens had occult NAC involvement [18].

In clinical practice, the larger case series of therapeutic TSSM have reported incidences of NAC involvement in pathology specimens of 2.5–14 % (Table 1), which is similar to results from the pathology studies. Groups differ in their management of assessing NAC involvement, with some surgeons performing intraoperative frozen section analysis of the tissue and others solely assessing permanent pathology. These results suggest that it is important to use TSSM techniques to remove all of the breast and ductal tissue.

Many groups use frozen section analysis to determine whether or not to excise the NAC at the time of mastectomy, although false-negative rates of 5–11 % have been reported [21, 22•]. Boneti et al. noted that 4 of the 156 (2.5 %) cases they had originally planned for TSSM were positive for malignancy on frozen section and thus required NAC excision [12]. Eisenberg et al. obtained frozen sections in 159 of their therapeutic cases and found that they were quite specific (99 %) but not sensitive (64 %), with a false-negative rate of 5 % [22•]. They also evaluated the histopathologic findings of

retroareolar nipple margins separately submitted for permanent pathology and found that 29 of the 208 (14 %) of the nipple margins demonstrated occult malignancy. Petit et al. reported their experience in 579 therapeutic NSM cases that had negative retroareolar frozen sections but found that an additional 63 patients (11 %) had carcinoma identified in the NAC on final pathology [21].

Several groups, including ours, have chosen to use the permanent pathologic analysis to guide management of the NAC when tumor involvement is identified. This provides every opportunity to save the nipple skin. The presence of tumor in the NAC complex, as long as it is clear of the margin, is no longer used as an absolute requirement for NAC skin removal in our practice, as well as several other groups that have adopted this strategy. Coopey et al. reported that 24 of 315 (8 %) therapeutic TSSM specimens had a positive subareolar margin [23•]. When margins were positive, they excised to clear margins and/or resected the nipple itself while preserving the areolar skin to improve cosmesis. In a recent review of our experience, we found that 32 of the 626 (5.1 %) therapeutic mastectomy specimens contained invasive or in situ carcinoma within the nipple tissue on final pathologic analysis [15]. We do not routinely perform frozen section analysis of the retroareolar tissue due to low yield and potential false-negative rate. Our treatment algorithm has evolved over time, with our more recent approach being primarily to perform re-excision of the nipple margin in cases of invasive cancer, though we also adapt our approach based on plans for adjuvant radiation and systemic therapy.

Others have used a more conservative approach, excising the entire NAC complex if tumor cells are found in the NAC complex. de Alcantara Filho et al. reported that 11 of 353 (3.1 %) cases undergoing TSSM had involvement of the NAC (which they consider to be the identification of tumor in both frozen section analysis of retroareolar ducts and permanent final pathology), and these were all ultimately managed with resection of the NAC [11].

Outcomes of Prophylactic Total Skin-Sparing Mastectomy

TSSM approaches were first developed to lower the barrier to having prophylactic mastectomy in patients for whom it could be potentially lifesaving, such as gene (BRCA) mutation carriers. As greater numbers of women undergo genetic testing to assess their breast cancer risk, many will consider bilateral mastectomy if they test positive for a deleterious mutation [22•]. The ability to offer the aesthetic benefits of TSSM and immediate breast reconstruction has become increasingly important. Few studies have focused specifically on patients undergoing prophylactic TSSM though many include outcomes of prophylactic TSSM as part of a larger experience.

The incidence of breast cancer after prophylactic TSSM in known mutation carriers or other high-risk patients is between 0 and 0.7 % (Table 2). Coopey et al. assessed outcomes from the Massachusetts General Hospital experience, which included 330 risk-reducing TSSM cases [23•]. None of these patients developed a breast cancer after risk-reducing mastectomy, although they did not describe the follow-up time for this subgroup (overall mean follow-up for therapeutic and prophylactic cases was 22 months). This study also did not include the indications for risk-reducing mastectomy. They recently pooled their data on outcomes in *BRCA1/2* mutation carriers with data from the NorthShore University HealthSystem and reported on 298 cases of risk-reducing TSSM [24•]. Overall mean follow-up for the entire cohort, including therapeutic cases, was 32.6 months (range 1–76 months). During the study period, 1 patient developed a new primary breast cancer, which did not involve the NAC. Spear et al. described 113 TSSM cases for prophylactic indications in their overall series of 162 cases of which 25 % of the patients were *BRCA1/2* mutation carriers [10]. At a mean follow-up of 43 months, none of the patients in their series developed cancer in the breast or preserved NAC skin. We have found similar results when reviewing our experience with TSSM for risk-reducing mastectomy. A comprehensive review of outcomes from 657 TSSM cases included 58 cases done for prophylactic indications [14]. At a median follow-up of 28 months, there were no new breast cancer diagnoses in this subset. In a more recent study specifically focused on outcomes in *BRCA* mutation carriers, we found no new breast cancers in any of the prophylactic cases at a mean follow-up of 51 months [25].

Outcomes After Therapeutic Total Skin-Sparing Mastectomy

The growing literature supporting the oncologic safety of TSSM for therapeutic indications has led to broadening inclusion criteria and increasing use of the technique [16]. The reported risk of locoregional recurrence following therapeutic TSSM is between 0 and 10 % and varies based on selection criteria and breast cancer staging (Table 2). The risk of recurrence in the NAC is between 0 and 3.7 %.

Longer-Term Follow-up

Studies with longer-term follow-up have become more prevalent as centers have started to publish their accumulated experience with TSSM. We recently published our 8-year results with TSSM and immediate reconstruction and found an overall 3 % locoregional recurrence rate at a median follow-up of 29 months and no recurrences within the preserved NAC skin, despite a high-risk population including a significant proportion of patients with locally advanced disease [15]. Stanec

Table 2 Outcomes following TSSM/NSSM for prophylactic and therapeutic indications

Study	Year	Prophylactic cases	Mean follow-up months	Indications	Incidence of new cancers (%)
Spear et al. [6]	2011	113	43	25 % *BRCA1/2+*	0
Warren Peled et al. [10]	2012	245	28	65 % *BRCA 1/2+*	0
Coopey et al. [19]	2013	330	22	–	0
Peled et al. [21]	2014	104	51	50 % *BRCA 1/2+*	0
Yao et al. [20]	2014	298	33	All *BRCA1/2+*	0.7
Study	Year	Therapeutic cases	Mean follow-up months	Tumor stages included	Local-regional recurrence (%)
Jensen et al. [24•]	2011	99	60	0–III	0
Boneti et al. [8]	2011	152	25	0–III	4.6
de Alcantara Filho et al. [7]	2011	157	10	0–III	0
Munhoz et al. [23•]	2013	106	66	–	3.7
Coopey et al. [19]	2013	315	22	–	2.6
Wang et al. [11]	2014	608	29 (median)	0–IV	3
Stanec et al. [22•]	2014	241	63 (median)	0–III	4.1
Yao et al. [20]	2014	51	33	0–III	5.9
Poruk et al. [26]	2014	105	26	0–IV	1.6
Sakurai et al. [25]	2013	788	87 (median)	0–IV	8.2
Fortunato et al. [27]	2013	97	26 (median)	I–III	1
Burdge et al. [28]	2013	39	25	IIB–III	10.3

et al. evaluated outcomes from their 15-year experience of "skin and nipple-areola complex sparing mastectomy" with a median follow-up of 63 months (range 1–180 months) [26]. They found a 4.1 % local recurrence rate in 241 cases, with a 1.2 % rate of recurrence within the preserved NAC. Although they describe excising "part of the tissue beneath [the] NAC," their technique may be more similar to NSM, not including the complete resection of all ductal tissues, which could account for the 1.2 % incidence of NAC recurrence. Munhoz et al. evaluated 106 patients with breast cancer treated with TSSM with a mean follow-up of 65.6 months (range 6–130 months) [27]. They found locoregional recurrences in 4 (3.7 %) patients and none involved the spared NAC. In another study with longer follow-up, Jensen et al. reported outcomes in 99 attempted therapeutic TSSM cases, with no recurrences seen at a mean follow-up of 60.2 months in patients who were able to achieve successful preservation of the NAC based on negative subareolar biopsy results [28].

One outlier with regard to local recurrence was a recently published study of TSSM outcomes in Japanese women that compared oncologic outcomes from 788 patients who underwent TSSM to 144 patients who underwent simple mastectomy [29]. The majority (70 %) of patients in the TSSM group had early-stage breast cancer, compared to 51 % in the simple mastectomy group. However, the rates of recurrence at a median follow-up of 87 months were similar, 8.2 % in the TSSM group and 7.6 % in the simple mastectomy group (p=0.81). Although their technique fits the TSSM technique with complete resection of all nipple tissues, including all ductal tissues, they report a 3.7 % rate of recurrence within the NAC, which is much higher than what has been reported in other studies. This may be related to the fact that although 40 % of their patients had stage IIB or III disease, where postmastectomy radiation therapy would likely have been indicated, none of the patients in their study received radiation, regardless of tumor size or nodal status. They also describe leaving thick (>1 cm) mastectomy skin flaps in areas away from the primary tumor, which may end up leaving some breast tissue behind, particularly in a population of Japanese women who will likely have minimal subcutaneous tissue.

Additional Studies with Limited Follow-up

Coopey et al. assessed outcomes from 315 cases of therapeutic TSSM [23•]. At a mean follow-up of 22 months, the locoregional recurrence rate was 2.6 % in patients who had TSSM performed prior to 2012. They report that no patients who underwent TSSM in 2012 have developed a local recurrence, although the follow-up for this subset is certainly more limited. All recurrences occurred in genetic mutation carriers (2 patients with p53 mutations, 2 patients with *BRCA1* mutations) but none involved the NAC. In a smaller study with similar follow-up, Boneti et al. reported outcomes from 152 TSSM cases at a mean follow-up of 25.3 months, with a local-regional recurrence rate of 4.6 %, none of which occurred in the NAC [12]. de Alcantara Filho et al. published outcomes from the Memorial Sloan-Kettering Cancer Center experience in 2011, which included 157 therapeutic TSSM cases [11]. They had no recurrences at a limited mean follow-up time of 10.4 months.

Outcomes After Therapeutic Resections in BRCA Mutation Carriers

Yao et al. evaluated a subset of 51 patients who were known *BRCA1/2* mutation carriers and underwent therapeutic TSSM [24•]. They reported 3 (5.9 %) locoregional recurrences after NSM, which included one simultaneous local and distant recurrence at 11 months following mastectomy and two axillary recurrences. There were no recurrences in the NAC. Overall mean follow-up for the entire cohort (including patients undergoing risk-reducing NSM) was 32.6 months. Our experience with performing TSSM for therapeutic indications in BRCA1/2 mutation carriers demonstrated no recurrences at a mean follow-up of 37 months [25].

Locally Advanced Breast Cancer

As the indications for TSSM expand, a growing number of reports have included a significant number of patients with more advanced disease. Poruk et al. recently reviewed their outcomes following 105 patients who underwent TSSM and found a 1.6 % local recurrence rate at a mean follow-up of 25.8 months, with no recurrences in the NAC [30]. Their study included a significant percentage (40 %) of patients with locally advanced breast cancer. Another similar study of 97 TSSM cases that included 22 % of patients with locally advanced breast cancer reported one local recurrence away from the NAC at a median follow-up of 26 months [31]. Burdge et al. focused a recent study on a subset of their patients who had locally advanced disease and underwent TSSM or skin-sparing mastectomy [32]. Of the 39 TSSM patients, 10.3 % developed a locoregional recurrence at a mean follow-up of 25.3 months; none of the recurrences occurred in the preserved NAC. In our clinical experience with TSSM, the cumulative incidence of locoregional recurrence at 5 years was 4.5 % for the 170 cases of stage II cancer and 6.9 % for 76 cases of stage III cancer [15]. There were no recurrences that occurred within the NAC.

Conclusions

Longer-term follow-up studies of patients undergoing TSSM have now been published, and we are now able to evaluate the oncologic risk of breast cancer and locoregional recurrence with preservation of the NAC skin. When TSSM is performed for prophylactic indications, the incidence of breast cancer ranges between 0 and 0.7 %. When TSSM is performed for therapeutic indications, the risk of locoregional recurrence ranges between 0 and 10 % in properly selected patients with the appropriate use of neoadjuvant and adjuvant therapy. Recurrences in the NAC following mastectomy are extremely uncommon. The analysis of the nipple tissue resected during these procedures demonstrates low rates of tumor involvement, highlighting the importance of appropriate patient selection based on tumor location. There does not appear to be an increased risk of cancer development in the NAC for risk-reducing procedures for recurrence in therapeutic procedures. While longer-term follow-up is ongoing, the results to date suggest that we can anticipate that the TSSM results will mirror those of skin-sparing mastectomy and support the inclusion of TSSM as a standard approach for mastectomy when performed in appropriately selected candidates.

Compliance with Ethics Guidelines

Conflict of Interest Anne Warren Peled, Frederick Wang, and Laura J. Esserman declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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