Chapter 3

Oncological Aspects of Nipple Sparing Mastectomy

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Introduction

Nipple sparing or total skin sparing mastectomy evolved through two different pathways. The subcutaneous mastectomy was first described by Freeman in 1962 [1]. It differed from the nipple sparing mastectomy (NSM) performed today by the thickness of the skin flaps and the presence of retroareolar tissue. It was popularized by Woods at the Mayo Clinic for the treatment of women at high risk of developing breast cancer [2]. Hartmann et al. first demonstrated the safety of prophylactic subcutaneous mastectomy in a cohort of 575 women at moderate to high risk of developing breast cancer [3]. Seven patients (1.2%) developed breast cancer and only one case occurred in the nipple-areolar complex (NAC) (0.2%) after a median follow-up of 14 years. A subgroup of 23 of these patients carried the BRCA gene mutation with none of these developing cancers in the retained nipple [4].

In the 1990's, the emergence of skin sparing mastectomy (SSM) facilitated immediate breast reconstruction technique and outcomes by allowing for retention of the native skin envelope and the inframammary fold [5]. The oncological safety of SSM was confirmed after large clinical experience and became the standard of care in early stage breast cancer when immediate reconstruction was performed [6]. Going one step further, nipple preservation during mastectomy represents the latest development in the ongoing patient- and surgeon-driven progression

in breast conservation to improve reconstructive cosmesis (Figure 1).Studies have shown that NSM reduces the feeling of mutilation, improves cosmesis, and has higher psychosocial and sexual wellbeing compared to SSM and nipple reconstruction [7,8].

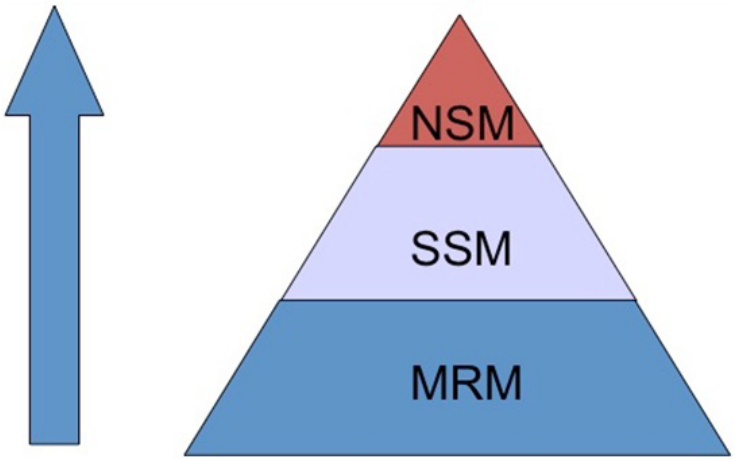

Figure 1: Surgical Conservatism in Breast Cancer: Natural Evolution? MRM: Modified Radical Mastectomy; SSM: Skin Sparing Mastectomy; NSM: Nipple Sparing Mastectomy

Dissatisfaction with conventional methods of nipple reconstruction after mastectomy and increase in incidence of prophylactic mastectomy in high-risk patients of younger age also contribute to growing interest in NSM. Other touted advantages include superior symmetry, potential maintained sensation, and possible single-step immediate reconstruction. Nevertheless, restricted indication, difficult exposure, nipple ischemia risk, and unproven oncologic safety represent current limitations.

Occult NAC Involvement

While gross NAC involvement is an obvious contraindication to NSM, occult disease has been observed in 10-24% of mastectomy specimens[9-14].Predictors of occult NAC invasion include tumor proximity, tumor size, axillary lymph node involvement and HER-2 amplification (Table 1). The wide range of percentages illustrates the heterogeneity of patient selection and histological analysis in existing literature. Nonetheless, out of the collective experience emerge guidelines generally used in selection of patients for NSM: small, early cancers (stage 0 or 1) with tumor location in excess of 2 cm from the nipple. With these more stringent criteria, the reported incidence of NAC involvement after NSM is 3-8% [15-18].

With the increasing popularity of breast magnetic resonance imaging (MRI), its potential to precisely depict tumor size and relative location has led to its use in the preoperative workup for NSM candidates. However, the superiority of MRI to clinical evaluation in this setting is not clear. Steen et al evaluated 77 breasts, of which 23% had tumor involving or within 1 cm. of the NAC [19]. The sensitivity of detecting histopathologically confirmed NAC disease was not higher with MRI (56%) as compared with that attained with clinical assessment alone (61%). However, MRI-measured tumor size (>2cm) and distance from tumor edge to NAC (<2cm) correlated with risk of NAC involvement. Although tumor-to-NAC distances

as short as 1cm on MRI has been proposed an adequate threshold for NSM, many centers now consider NSM in all patients without clinical or imaging evidence of direct nipple involvement [16,18,20,21].

Table 1: Recent published analyses of occult nipple involvement in breast cancer patients.

Authors	Year	Number of Mastectomies	Percent NAC Involvement	Independent Predictors of NAC Involvement
Rusby et al. [12]	2008	130	24.6%	Tumor size Distance from nipple
Brachtel et al. [10]	2009	232	21%	Her-2 amplification Tumor size Tumor-nipple distance
Gulben et al. [11]	2009	387	14.6%	Tumor location Node positivity Lymphovascular invasion
Weidong et al. [14]	2011	2323	10.7%	Increased tumor size Tumor-nipple distance Central tumor location Node positivity Lymphovascular invasion Her-2 amplification Multicentric/multifocal disease
Wang et al. [36]	2012	766	7%	Tumor in all four quadrants Tumor >5cm Grade 3 or higher Her-2 amplification

The retroareolar tissue just deep to the NAC skin is thought to be an indicator of NAC carcinoma involvement, as contiguous tumor spread occurs with direct extension from the retroareolar tissue into the terminal ducts and papillae. In Brachtel et al.'s analysis of 45 cases of carcinoma involving nipples, the retroareolar tissue likewise contained disease in 36 cases [10]. Nine cases with negative retroareolar tissue had nipple involvement, while eight cases with positive retroareolar tissue had no nipple involvement. Use of the retroareolar margin to reflect nipple disease yielded a sensitivity of 0.8 and negative predictive value of 0.96 [10].Simmons et al. analyzed nipple and areolar involvement with cancer after SSM [22]. The authors found that 10.6% of patients were found to have malignant nipple involvement but only 0.9% was found to have involvement of the areola. These findings predated the work of Brachtel et al. but supports areolar preservation in cases of nipple involvement.

Many institutions routinely perform frozen section analysis of the nipple margin at the time of NSM[17,23-25]. This potentially could reduce the number of surgeries required. Intraoperative frozen section has high specificity but only modest sensitivity. Sampling errors, processing artifact, and interpretation difficulties are limiting factors. Distinguishing atypical hyperplasia from ductal carcinoma in situ can be very difficult even on permanent section analysis. In cases of positive nipple involvement, it has the potential to reduce the number of operations. That being said, it can be very anxiety provoking for a woman to undergo general anesthesia not knowing whether she is going to have her nipple removed or not.

Accordingly intraoperative determination of NAC salvageability via frozen section analysis of the retroareolar tissue is often performed. Kneubil et al reported the outcomes of 88 patients (of 948 total NSMs) who had false negative frozen section analysis of the nipple base and 10 patients who had close surgical nipple margins [26]. The overall false negative rate of frozen section analysis of nipple margin was 9.2%. Ninety-three patients (94.9%) received intraoperative radiotherapy. The 5-year cumulative incidence of NAC recurrence was 2.4% (2/98). Both cases were non-invasive recurrences[26]. In their analysis of 52 NSM cases, Luo et al found that frozen section yielded 10% positive results (13or 25% positive on permanent sections)[27]. The overall false negative rate of frozen section was 15%. The sensitivity and specificity of intraoperative frozen section were 38% and 100%.

Alperovich et al. described the use of intraoperative frozen section in 307 NSMs [28]. Twelve cases (3.9%) were found to be positive on permanent section analysis, five had a false negative frozen section. The sensitivity and specificity were 0.58 and 1.

Management of Occult Nipple Involvement

There is no consensus and limited data on the management of occult nipple involvement. Camp et al. reviewed 22 cases of positive subareolar / nipple margins

after NSM [29]. The histology was DCIS in 18 cases and invasive lobular carcinoma 4. Surgical management was performed in 17 cases: nipple removal 8 and NAC removal in 9. Residual DCIS was found in 4 cases (24%), none occurring in the areolar skin.Alperovich et al. described surgical excision of the nipple or NAC in 20 patients after positive subareolar biopsies. Six patients (30%) of resected specimens had abnormal residual pathology.

Amara et al. reviewed 1176 cases NSM managed by nipple coring without use of frozen section analysis [15]. The authors found that 32 cases (2.7%) had involvement of the NAC or nipple on permanent histology, including invasive carcinoma in 56% and DCIS 44%. Management included repeat excision of nipple tissue 11 (34%), radiation 5 (16%), complete NAC removal 8 (25%), and no further treatment 8 (25%). For the nine nipple margin re-excisions performed, scar or fibrous tissue was found in five and benign breast tissue in four. The authors noted that their management of involved nipple tissue margins had evolved over years. The end of the review reserved removal of the NAC reserved for extensive tumor involvement of the subareolar margin and nipple specimen.

Tang et al. reported positive nipple margins in 46 of 1,326 NSMs, 43 (6.7%) of these being performed for cancer[18]. Their method of pathological examination was similar to that of Amara et al. Thirty-nine of the patients had surgical excision including NAC excision 19 and nip-

ple excision only in 20. In twenty-eight cases (72%), no residual malignancy was found. The pathology of residual disease was DCIS 8, invasive lobular cancer 2, and invasive ductal cancer 1. Analysis found that positive nipple margin was associated with larger mean invasive tumor size (2.3cm. vs. 1.6cm., p=0.007). The authors noted that the incidence of positive nipple margins for therapeutic NSM decreased from 11% in 2007-2011 to 5.4% in 2012-2104 ($p<0.05$). At a 36-month median follow-up, there were no recurrences in the NAC. They have adopted a policy similar to that of Amara et al., excising only the nipple papilla in cases of positive nipple margins. Removal of the nipple only preserves the areola and facilitates implant preservation and improves the cosmesis of future nipple reconstruction.

Postmastectomy radiation therapy is a reasonable option for involved nipple margin for patients requiring radiation for other indications. The use of a single dose of intraoperative radiation to the NAC during NSM was described by Petit et al. [30]. In the Milan experience by Lohsiriwat et al, recurrence within the NAC was observed in 11 cases (1.3%) [31]. Seven patients (0.8%) developed Paget's disease at a mean of 32 months from NSM. Treated with nipple excision, all of these patients remained disease free at mean follow-up of 47.4 months.

NAC Recurrence and Breast Cancer Survival[MH]

Local recurrence rates following NSM mirror those after skin sparing mastectomies with NAC sacrifice. The incidence of specific NAC recurrence after therapeutic NSM is very low (Table 2). Kim et al. reviewed 152 cases of therapeutic NSM and immediate reconstruction with a median follow-up of 60 months [32]. Two patients (1.3%) developed NAC recurrence and were treated with local excision. They remained free of disease at last follow-up

Table 2: Recent Published Studies of Therapeutic NSM and NAC Recurrence.

Authors	Year	Number of Therapeutic NSM	Follow-Up (months)	NAC Recurrence (%)
Petit et al. [37]	2005	579	Median 41	0
Sachini et al. [38]	2006	68	Median 24.6	0
Paepke et al. [39]	2008	94	Median 34	0
Gerber [40]	2009	60	Mean 101	1.7
Babiera and Simmons [41]	2010	53	Median 15	0
Kim et al. [32]	2010	152	Median 60	1.3
Jensen et al. [23]	2011	77	Mean 60.2	0
Peled et al. [42]	2012	152	Median 45	0
Lohsiriwat et al.[31]*	2012	861	Median 50	1.3
Sakurai et al.[33]	2013	788	Median 78	3.7
Shimo et al. [34]	2016	425	Median 46.8	2.3

NAC: Nipple-Areolar Complex.
*Received intraoperative radiotherapy

Sakurai et al. published their experience with 788 therapeutic NSMs, which were compared to a cohort of 144 patients who were treated with conventional mastectomies [33]. The two groups were similar in disease stage

and tumor size. None received adjuvant radiation. In the NSM group, NAC recurrence was observed in 3.7%. At five and ten years, disease-free survival was 86% and 83%, compared with 83% and 80% in the conventional mastectomy group. The median follow-up for this study was 78 months. The authors also make the interesting comment that recurrence at the NAC was associated with more favorable overall survival than skin envelope recurrence (Figure 2)[33]. This observation may reflect the distinction of nipple recurrence from other local recurrence patterns as a function of surgical conservatism versus tumor biology.

Shimo et al. reviewed 425 therapeutic NSMs in 413 patients[34]. NAC recurrence occurred in 2.3% (10 cases) a median of 26.5 months after surgery. The mode of presentation was crusty nipple lesion in 5, bloody nipple discharge in 4, and surveillance ultrasound 1. Three patients developed systemic metastases after NAC recurrence. NAC recurrence was associated with increase incidence of distant metastases and decrease in survival.

A recent Cochrane analysis of the use of NSM in the treatment of cancer was performed on 11 cohort studies of 6502 patients as of September 2014 [35]. It was not possible to conclude whether or not local recurrence or survival was similar to traditional and skin sparing mastectomy.

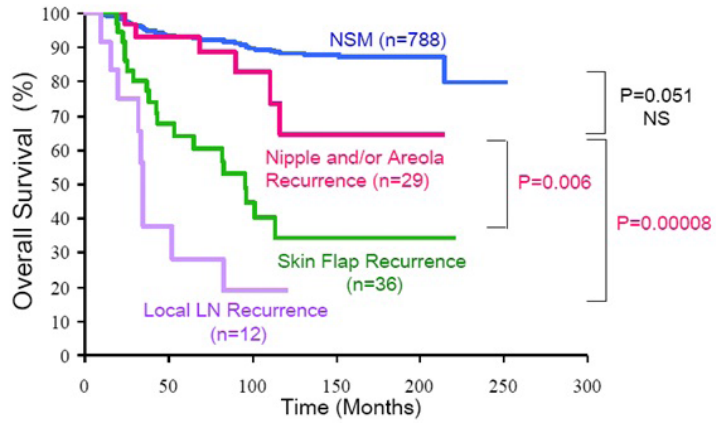

Figure 2: Kaplan-Meier analysis of overall survival of NSM stratified by site of first recurrence. With permission from:Sakurai T, Zhang N, Suzuma T, Umemura T, Yoshimura G, et al., Long-term follow-up of nipple-sparing mastectomy without radiotherapy: a single center study at a Japanese institution. Med Oncol. 2013;30: 481.

Conclusions

The incidence of occult NAC involvement after therapeutic nipple sparing mastectomy is very low (3-8%). Tumor size and distance from the NAC are predictors of occult involvement. Many centers now consider NSM in all patients without clinical or imaging of direct nipple involvement.

The use of frozen section analysis of nipple margins is hindered by modest sensitivity, sampling errors, processing artifact, and interpretation difficulties. Careful sampling of the retroareolar tissue and excision of the nipple

ducts within the papilla submitted for permanent histology allows more accurate pathologic assessment.

The surgical treatment of nipple involvement is dependent of the careful pathological sampling. Unless there is involvement of the retroareolar tissue, re-excision of the nipple margin or nipple papilla excision can be performed. The majority of positive re-excisions are ductal carcinoma in situ. Radiation therapy is an option for occult nipple involvement if other tumor characteristics warrant its use.

The incidence of NAC recurrence after therapeutic NSM is low. Studies of oncological safety are hindered by short follow-up and variations in indications and surgical technique. A recent Cochrane analysis could not conclude whether or not local recurrence or survival was similar to traditional and skin sparing mastectomy.

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