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Breast

Tumor-to-Nipple Distance in Selecting Patients for Nipple-sparing Mastectomy

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Introduction: Nipple-sparing mastectomy (NSM) is a valid option for carefully selected cases. Oncologic guidelines have not been established, but proximity of the tumor to the nipple, tumor size, lymph node involvement, and neoadjuvant chemotherapy have been suggested as contraindications to nipple preservation. This study describes our experience with NSM in relation to these factors, in particular distance of tumor from the nipple, to help establish evidence-based guidelines for NSM.

Method: All NSM procedures performed at our institution between 2014 and 2018 were reviewed. The tumor-to-nipple distance was measured for each patient using mammography, ultrasound, or magnetic resonance imaging. All patients underwent a frozen section (FS) biopsy of the base of the nipple during surgery, and if cancer was detected, the procedure was converted to a skin-sparing mastectomy. Patients were followed for postoperative complications and cancer recurrence.

Results: Sixty-eight patients (98 breasts) underwent NSM with immediate reconstruction. Fifty-three patients (78%) underwent the procedure for breast cancer. Nipple involvement was detected on FS in 1 patient and on permanent pathology after a negative FS in 1 patient. Forty-three percent of our patients had a tumor-to-nipple distance of ≤2 cm. During a mean follow-up of 32.5 months (±19.4 months), no locoregional recurrences were observed; however, distant metastasis occurred in 3 patients.

Conclusions: When histologic examination from the base of the nipple is negative (either by FS or permanent pathology), NSM can be considered oncologically safe. Lack of nipple involvement by preoperative clinical and imaging assessment and intraoperative FS is sufficient to classify patients as suitable for NSM. *(Plast Reconstr Surg Glob Open 2020;8:e2963; doi: 10.1097/GOX.0000000000002963; Published online 21 July 2020.)*

INTRODUCTION

Nipple-sparing mastectomy (NSM) is a valid option for carefully selected patients with breast cancer and for healthy, high-risk patients undergoing risk-reducing surgery. The uptake of NSM has been facilitated by advances in surgical and reconstructive techniques, as well as recognition that improved systemic therapies have markedly diminished locoregional recurrence rates.[1–3]

Breast reconstruction after NSM yields a superior aesthetic result compared with skin-sparing mastectomy (SSM). NSM is considered feasible both for risk reduction and for treatment of breast cancer[4,5]; however, the indications for NSM for breast cancer are still being debated.

The American Society of Breast Surgeons maintains an ongoing registry of NSM, and in a recent publication,[6] they reported no recurrences in the nipple areola complex (NAC) among 833 cancer cases. In 2009, Spear et al[7] had debated the controversy related to NSM and concluded that provided that certain oncologic and practical criteria are applied, it has the potential to allow less invasive surgery and improve cosmetic outcomes without increased oncologic risk in appropriately selected patients.

Two years later, he published a landmark article,[8] which has since outlined the indications and contraindications

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for NSM. He retrospectively reviewed 162 cases of NSM: 49 for therapeutic indications and 113 for risk reduction. The majority had subareolar biopsies during surgery. In that article, the authors proposed major criteria for NSM. Oncologic criteria included tumor size <3 cm, tumor distance >2 cm from the nipple, clinically negative axillary nodes, and no skin involvement or evidence of inflammatory carcinoma or Paget's disease. Anatomic criteria excluded very large or ptotic breasts and operative criteria included a negative intraoperative frozen section (FS) from the nipple base.

We decided to reexamine the oncologic criteria. The aim of our study was to describe our experience with NSM outside the proposed guidelines.

PATIENTS AND METHODS

All NSM procedures for breast cancer performed between the years 2014 and 2018 at our institution were included in this retrospective study. Patients were offered NSM if the nipple was free of tumors, determined by clinical examination and imaging. Patients with large and ptotic breasts who were not candidates for NSM based on anatomical features were not offered NSM; however, lymph node involvement or planned postmastectomy radiation therapy was not considered a contraindication for NSM. The NSM was carried out by 5 different breast surgeons.

FS biopsy of the tissue at the base of the nipple was performed in all cases, and if cancer was detected, the procedure was converted to SSM. All patients underwent immediate implant-based or autologous reconstruction.

For the purpose of this study, we defined a new parameter: "tumor-to-nipple distance" (TND). TND was determined after reviewing all available preoperative imaging studies by a radiologist and double checked and confirmed by a breast radiologist. The distance was defined as the shortest distance from the mass, calcifications, or enhancement to the base of the nipple as seen on any of the imaging studies (Fig. 1). The imaging modalities used were mammography, ultrasound (US), and magnetic resonance imaging (MRI). We divided the TND into 4 major groups: <1, 1–2, 2–3, and >3 cm.

If neoadjuvant therapy (NAT) was given, image analysis was conducted before and after treatment. Reasons for NAT included large tumors, lymph node involvement, Human Epidermal Growth Factor Receptor 2/Neu (HER2/Neu) positive or triple negative breast cancer, and in cases where the tumor-to-breast size ratio might dictate a large excision with a poor aesthetic result.

Data extracted from medical records included patient demographics, tumor characteristics, lymph node status, surgical risk factors (prior radiation treatment, smoking status, and diabetes), type of NAT, the surgical and reconstructive procedures performed, adjuvant treatment, and postoperative outcomes and complications. Postoperative complications recorded included: infection, wound dehiscence, seroma, skin flap necrosis, nipple–areola complex necrosis, and explantation. Reconstruction was mostly direct to implant with acellular dermal matrix. In selected cases, we performed free flap reconstruction with the deep inferior epigastric perforator flap. Two-staged breast reconstruction was conducted less frequently with insertion of a tissue expander. Follow-up was from the date of surgery to the date of last clinical follow-up. Patients were followed for locoregional recurrence, distant metastases, and death from the disease.

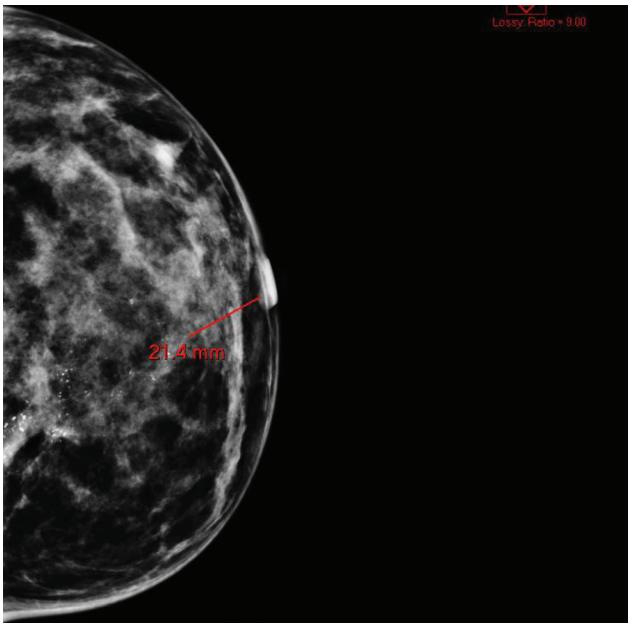

Fig. 1. A mammographic LCC view showing how the measurement was conducted. Note the arrow from the closest detected calcification to the base of the nipple.

RESULTS

Patient Characteristics

We performed 98 nipple-sparing mastectomies in 68 patients over the study period (2014–2018): 43% (42 breasts) for risk reduction and 57% (56 breasts) for breast cancer. Fifty-three patients (78%) underwent the procedure for breast cancer and 15 (22%) for risk reduction. Only the therapeutic cases were analyzed for this report. All patients underwent immediate reconstruction (Table 1). The mean age was 47.6 (±10). Five patients (7%) were known breast cancer gene (BRACA) mutation carriers. Eleven patients (16%) were active smokers (all smokers were requested to stop smoking at least 2 weeks before surgery). Two patients (3%) had diabetes. Six patients (9%) received prior radiation to the operated breast. Twenty-three patients (43%) received NAT. NAT converted 10 patients (43%) to NSM who would otherwise not be considered appropriate. The mean follow-up was 32.5 months (±19.4 months).

Surgical and Reconstructive Procedures

The incisions used for NSM were inframammary fold (N = 23/56 breasts, 41%), lateral radial (N = 29/56 breasts, 52%), and periareolar (N = 4/56 breasts, 7%). Average specimen weight was 412 g (110–1160 g). The majority of the patients (N = 34/53, 64%) had direct to implant reconstruction. Fifteen patients (28%) had deep inferior epigastric perforator flap reconstruction. Four patients

Table 1. Patient Characteristics and Risk Factors, Tumor Characteristics, and Treatments

Patient Characteristics, N = 53 Patients (%)	
Age at diagnosis	47.6 (20–68)
Smoking	11 (20%)
Diabetes mellitus	2 (4%)
BRCA positive, N = 53 patients	5 (9%)
Tumor characteristics, N = 56 Breasts (%)	
Size	1.6 cm (1 mm to 7 cm)
Multifocal	26 (46%)
ER positive	36 (63%)
PR positive	19 (33%)
HER2/Neu positive	7 (12.5%)
Triple negative	6 (10.5%)
Axillary node involvement	15/53 (28%)
Positive FS converted to SSM	2/53 (3.7%)
Treatment, N = 53 (%)	
Prior radiation	6 (11%)
Neoadjuvant chemotherapy	23 (43%)
Adjuvant radiation	23 (43%)
Adjuvant chemotherapy	4 (8%)
Antihormonal therapy	28 (53%)
Biologic treatment	5 (9%)

BRCA, breast cancer gene; ER, estrogen receptor; HER2/Neu, human epidermal growth factor receptor/Neu; PR, pogesterone receptor.

(7%) underwent a staged procedure with tissue expander (Table 4).

Tumor-to-nipple Distance

Of the 53 who were included in this study, 50 patients had imaging studies available for review. Thirty patients had mammography images available. TND was measured on both the mediolateral and the craniocaudal views, and the shorter distance was recorded. Thirty-one patients had MRI and US imaging. Only 12 patients had all the 3 modalities available for review. The mean TND was first calculated per modality (Table 2). TND was divided into 4 groups (Table 3); 6 patients had a TND of <1 cm, and 14 patients had a TND between 1 and 2 cm. Of the 24 patients who received NAT, 7 patients had a complete clinical response and 3 patients showed no response to treatment. The mean TND at the group of <1 cm was 6 mm; the shortest distance documented was 4.3 mm.

Pathologic Characteristics

Tumor size was extracted from the final pathologic report. In cases of multicentric involvement, the largest dimension of the largest tumor was used. If a patient had both invasive and in situ masses, the size of the invasive tumor was used. The mean tumor size was 1.6 cm (1 mm to 7 cm). For the non-neoadjuvant population, mean tumor size was divided into 3 groups: 15 patients had T1 (tumor size of 0–1.9 cm), 10 patients had T2 (tumor size of 2.1–5 cm), and 5 patients had T3 (tumor size of >5 cm). Twenty patients who received neoadjuvant treatment had data regarding tumor size of before and after treatment. The mean tumor size before therapy was 4 cm (1.8–9 cm), and the mean size after treatment was 1 cm (±0.5) according to the pathology report. Twenty-six breasts, presented in 26 patients (49%), had multicentric disease. In 15 cases (28%), there was lymph node involvement. Tumor characteristics are summarized in Table 1. One patient had cancer detected on FS from the nipple base, and the

Table 2. Mean TND per Modality

Imaging Modality	TND (mm)
MMG-CC	38.8 ± 21.3
MMG-MLO	42.7 ± 23.2
MRI	32 ± 21.5
US	35.8 ± 17.7

CC, craniocaudal; MLO, mediolateral; MMG, mammography.

Table 3. TND of 50 Patients Catergorized into 4 Groups

TND			
<1 cm	1–2 cm	2–3 cm	>3 cm
6/50 (12%)	14/50 (28%)	9/50 (18%)	21/50 (42%)

procedure was converted to SSM. Preoperative US measured a TND of 5.3 mm in this patient. One patient had ductal carcinoma in situ at the base of the nipple on final pathology (not detected on FS at the time of surgery). Her TND was 9.5 mm by mammography. Overall NAC involvement in this study was 3.5% (2/56 breasts).

During a mean follow-up of 32.5 months (±19.4 months), no locoregional recurrences were observed. Distant metastasis occurred in 3 patients. One patient developed leptomeningeal metastatic spread 6 months following surgery, and died shortly after. Her TND was 20 mm by US. Another patient had bone metastases 18 months after surgery, and died a year following the diagnosis of metastatic disease. At presentation, her TND was 5 mm per MRI. The third patient developed bone metastases 19 months after surgery. At initial diagnosis, she had a TND of 40 mm by MRI.

Postoperative Complications

Overall, 19 patients (35%) had any postoperative complication. Infection rate was 11%. Nipple-areola complex necrosis occurred in 5 patients (9%) (Table 4).

DISCUSSION

The use of NSM has expanded from risk reducing to therapeutic indications; however, the question whether and when this procedure is oncologically safe is still

Table 4. Surgical Approach and Complications

Incision type	N = 56 Breasts (%)
Inframammary fold	23 (41%)
Radial	29 (52%)
Periareolar	4 (7%)
Method of reconstruction	N = 53 patients (%)
Tissue expander	4 (7%)
Implant	34 (63%)
Free flap (DIEP)	15 (28%)
Complications	N = 53 patients (%)
Total complication rate	19 (35%)
Infection	6 (11%)
Dehiscence	3 (5.5%)
Skin flap necrosis	6 (11%)
Seroma	1 (1.85%)
Explantation	4 (7.4%)
Nipple areola complex necrosis	5 (9%)

DIEP, deep inferior epigastric perforator flap.
Note: some patients had more than one complication. Overall 19 patients had any complication. Some had more than one.

debated. Initial guidelines for NSM were outlined based on the prospective experience of a single institution.[8]

There is an increasing interest in this technique because there is evidence that it provides a better cosmetic outcome and improved quality of life.[9] Our aim in this study is to outline new guidelines for NSM that are being currently used in our institution, mainly based on the TND. We measured the TND on all available imaging modalities and found that 39% of our patients had a TND of <2 cm. According to our institutional practice, we include patients with tumor that is as close as <1 cm to the nipple as long as the nipple is not involved with tumor on FS. We performed intraoperative FS of the nipple base in all cases; however, as long as the nipple base is evaluated separately, it may be done on permanent pathology as well, if FS is not available for any reason.

Overall NAC involvement in this study was 3.5% (2/56 breasts). One patient had her nipple removed within the surgery and the second due to final pathologic diagnosis of ductal carcinoma in situ within the nipple base after a negative FS at the time of surgery.

Mean overall tumor size was 1.6 cm (1 mm to 7 cm). Half of our non-NAT patients had a tumor size of <2 cm (50%), a third of them had tumor size of 2.1–5 cm (33%), and in 17%, tumors were larger than 5 cm at the time of diagnosis. Moreover, almost half of our patients had multicentric cancer (49%), and third had lymph node involvement (28%). The overall complication rate in this series was 35%; however, the infection rate was low (11%). NAC complication rate was 9%, and surgical intervention was indicated in all cases for salvage.

Only 3 patients (6%) had any recurrence, and all recurrences were systemic only. There were no local recurrences in this series.

The safety and practicality of NSM were examined by Jensen et al,[10] who followed 99 patients for 5 years. They observed 3 recurrences with no deaths and therefore concluded that the 5-year recurrence for the procedure is low when NSM margins (both frozen and permanent) are negative. Others have previously published series on NSM suggesting broader guidelines than those proposed in the original study by Spear et al.[8]

Dent et al[11] suggested a TND as small as 1 cm. In their retrospective study, they compared NSM candidates who had a TND of >2 cm to those who had a TND of >1 cm. They found no significant differences in the rates of pathology-confirmed NAC involvement among the groups. Our study included patients who received NAT. Most significantly, we lowered the TND cut-off to 5 mm. In another retrospective study, the TND was challenged to be closer to the nipple than 2 cm. Among 266 cases, no statistically significant difference was reported between a short (<2 cm) and long (>2 cm) TND groups with respect to local recurrence.[12]

de Alcantara Filho et al[13] limited tumor size to <3 cm and TND to >1 cm and excluded patients after NAT. They found that involvement of the NAC was rare (3.1%) and therefore concluded that NSM is suitable when intraoperative FS of the retro areolar tissue is negative. We broadened our guidelines even more and still got a rate of NAC involvement of 3.5%.

Krajewski et al[1] reported on 341 patients, a third of whom fell outside the criteria proposed by Spear et al.[8] They also found that over time, the indications for NSM had been broadened in terms of patient characteristics, tumors >2 cm, lymph node involvement, and prior radiation therapy, without increasing the complication rate. Short-term outcomes were considered excellent; however, follow-up was relatively short.

We decided whether or not nipple preservation was suitable solely based on the TND. Our 3.5% rate of occult nipple involvement is in line with previously reported rates (2.5%–11.9%).[13–15]

Hirohito et al[16] also measured the TND, and considering other factors such as the tumor size, location (central versus peripheral), nipple enhancement by MRI, multicentric/multifocal cancer, and clinical node involvement created an index to help choose appropriate candidates for NSM. According to these criteria, NAC involvement rate was determined to be 3.5% in low-risk, 68.7% in intermediate-risk, and 90% in high-risk specimens. Because we perform FS of the nipple base in all cases, we consider such preoperative stratification unnecessary.

Some[2,17] have suggested that MRI may be helpful in identifying occult NAC involvement, and recommend routine MRI before NSM. We do not perform routine breast MRI preoperatively, and believe that the decision whether to preserve the nipple can be based on any available imaging modality, as long as the base of the nipple is free of tumor on FS followed by permanent pathology. We observed that the smallest TND was detected with MRI; however, we could not confirm this observation because the pathology report cannot specify the TND (as the nipple is not in the specimen).

Multicentricity has been suggested as a risk factor for nipple involvement.[18] The reported rate of occult nipple involvement in multicentric tumors was 29.6% versus 12.4% in solitary tumors ($P < 0.05$).[19–21] We did not confirm this association because 49% of our patients had multicentric disease and none of them had occult nipple involvement.

There are reports in the literature suggesting a higher incidence of nipple involvement in patients with lymph-node metastasis.[22–24] Mallon et al[25] showed in their comprehensive review an overall incidence of nipple involvement of 24.4% compared with 10% in lymph node negative ($P < 0.05$). Our results showed that one patient who had cancer detected on FS had one nodal involvement, whereas the other patient who had nipple involvement had negative nodal status. The other 15 patients who has nodal involvement had nipples free of tumor.

Alsharif et al[26] checked for oncologic outcomes with respect to lymphovascular invasion and nodal status among others, in patients who underwent NSM with immediate breast reconstruction with a TND <2 cm. They concluded that the long-term oncologic outcomes of patients treated with NSM did not significantly differ according to TND when the intraoperative frozen biopsy was negative.

The complication rate in this series (35%) may be partially explained by our high rate of smokers (20%),

prior radiation treatment (XRT) (11%), and alloplastic reconstruction (70%). In a previous publication[27] based on an overlapping dataset, we found that alloplastic reconstruction had a higher complication rate compared with autologous reconstruction.

We included even minor events that were treated conservatively as complications. Moreover, our inclusion criteria for breast reconstruction were very liberal and we tend to operate on obese patients, smokers, and patients who received prior XRT.

In a systematic review by Piper et al,[28] a 9.1% rate of NAC complications was reported, which is similar to the rate in this series (9%). Most of our NAC complications were treated conservatively and did not require surgical intervention.

Nipple ischemia and necrosis may be minimized by preserving major perforating vessels, elevating skin flaps in the plane between the subcutaneous fat and the breast glandular tissue, and the use of incisions that do not devascularize the NAC.[29]

To summarize, literature review suggests strong support of the TND factor, with the minimal favorable distance ranging from 1 to 4 cm. We propose first to exclude nipple involvement by any imaging modality, and performance of a FS biopsy of the nipple base (followed by permanent pathologic evaluation) as the final determinant for nipple preservation, rather than relying on the TND alone. With this approach, the indications for NSM can be expanded to tumors that are located <2 cm from the nipple and even as close as 5 mm. The limitations of this study are its small size and retrospective nature.

CONCLUSIONS

Our results suggest that when clinical examination and preoperative studies do not suggest nipple involvement, and pathologic examination of tissue from the base of the nipple is negative (on FS or permanent histology), NSM can be considered oncologically safe. TND of <2 cm, multicentric cancer, lymph node involvement, or tumor size >3 cm should not be absolute contraindications for NSM. Larger studies and longer follow-up are needed to establish the safety of this approach.

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