Curr Surg Rep (2016) 4:17
DOI 10.1007/s40137-016-0138-1

Nipple-Sparing Mastectomy: To Spare Or Not To Spare?

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Published online: 11 April 2016

Abstract The use of nipple-sparing mastectomy for prophylactic and therapeutic purposes has increased in recent years primarily driven by patient desire for improved esthetics. This article aims to critically review indications, oncologic safety, and recent advances in operative techniques. Current strategies for minimizing complications of nipple-sparing mastectomy are discussed including incision choices, adjunct tactics, and our experience.

Keywords Nipple-sparing mastectomy · Total skin-sparing mastectomy · NAC preservation · Breast cancer · Prophylactic mastectomy · Subcutaneous mastectomy · Local recurrence · Risk reduction · Inframammary · SPY

Introduction

Surgical treatment of breast cancer has evolved significantly in the last several decades concomitant with advances in systemic therapy and diagnostic imaging which have markedly improved cancer outcomes. Nipple-sparing mastectomy (NSM) as both a therapeutic and risk-reducing procedure, with preservation of the skin envelope including the nipple-areola complex (NAC), has seen rapid uptake. A study using Surveillance, Epidemiology, and End Results data reported a 202 % increase in the use of NSM between 2005 and 2009 in the United States [1]. This increase in the performance of NSM is based on patient demand for improved esthetics, but appropriate patient selection and the long-term outcomes in terms of both patient satisfaction and oncologic safety remain undefined. In this article, we review the evolution of NSM and provide our perspective on and approach to this procedure.

Historical Perspective

Subcutaneous mastectomy was first described by Thomas [2] in 1882 followed by Barlett [3] in 1917. With the availability of breast implants in the 1960s, subcutaneous mastectomy with reconstruction became a more common operation [4]. Subcutaneous mastectomy is distinct from contemporary NSM in that in the former a 1–4 cm plate of retroareolar breast parenchyma is intentionally preserved to decrease flap complications and optimize cosmesis. As a result, subcutaneous mastectomy has not been considered by many as an effective cancer operation [5].

The literature regarding the oncologic safety of subcutaneous mastectomy is limited. A survey of plastics surgeons reporting a 0.5 % incidence of recurrence following subcutaneous mastectomy was published in 1975 [6]; however, this methodology provides, at best, low level safety evidence. In the seminal study by Hartmann et al. that demonstrated at least a 90 % risk reduction with prophylactic mastectomy, 90 % of these operations were subcutaneous mastectomy. All seven of the women who developed a breast cancer underwent a subcutaneous mastectomy, but there was no significant difference in the incidence of breast cancer development between women who underwent subcutaneous versus total mastectomy (7 of 575 women vs. 0 of 64 women, $p = 0.38$) and only one

This article is part of the Topical Collection on *Breast Cancer Surgery*.

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cancer developed within the preserved NAC [4]. Benediktsson and Perbeck reported on therapeutic subcutaneous mastectomies employing preservation of a 2-cm diameter, 5-mm thick plate of glandular tissue beneath the nipple to preserve the blood supply of the NAC in 216 cancer patients operated between 1988 and 1994. Local recurrence rates were 28 % at a median of 2.9 years in the 169 patients who did not receive postoperative radiation and 31 % in those under 50 [7]. In general, this approach of deliberate retention of breast parenchyma in either risk reduction or cancer patients has fallen out of favor.

Anatomy (at Risk Tissue with NSM)

The nipple ducts exit at the surface of the nipple in approximately 27 orifices of only which approximately 6 are functional. Since the majority of breast cancers are ductal in origin, many women and physicians have pause for intentionally preserving the NAC and thus a portion of the ductal system. When performing a NSM, the ducts behind the nipple are divided, as there is no anatomic plane between the underlying breast parenchyma and the ductal system, and the ductal network cannot be completely removed without coring out the central nipple ducts. For some patients, it appears counterintuitive to undergo a major operation with the intent of maximally reducing their breast cancer risk and yet purposefully preserve additional ductal tissue. Although even a total mastectomy does not remove 100 % of the breast tissue, retention of additional visible at risk tissue appears undesirable. This concern is potentially greater in patients with a BRCA mutation where every somatic cell carries the deleterious germline mutation. A better understanding of the microscopic anatomy and tissue at risk as well as clinical outcomes have led to greater acceptance.

Both the nipple and areola are covered by keratinizing squamous epithelium, which extends for a short distance down the lactiferous duct [8]. As the duct penetrates deeper into the nipple, there is a transition where the cells lining the duct walls give way to columnar cells. This normally occurs where the squamous epithelium joins the glandular duct epithelium, distal to a dilated segment of the lactiferous duct, referred to as the lactiferous sinus (Fig. 1). This transition from squamous to cuboidal cells was identified between 1.1 and 3.6 mm from the nipple surface in an examination of 11 nipples [9]. The lactiferous ducts extend into the breast through a series of branches, diminishing in caliber from the nipple, eventually to terminate in the terminal duct lobular unit (TDLU) that are embedded in specialized, hormonally responsive stroma concentrated in the central portion of the breast [10]. The majority of breast cancers, as well as most high-risk lesions (ductal and lobular) arise in the TDLU. The TDLU is the tissue at risk to form a primary breast cancer and needs to be removed to prevent future breast cancers. Local recurrence can occur in any of the remaining tissues and does not require TDLUs but is instead the result of residual microscopic cells left behind.

There are no TDLUs in the dermis or epidermis of the NAC, and thus, a NSM performed at this level of dissection would not leave behind tissue at risk. A NSM performed in this manner essentially treats the NAC as a full thickness skin graft and has a higher risk of skin necrosis. Although the majority of TDLUs are concentrated in the deep central portions of the breast, there are TDLUs in the retroareolar tissue. This varies by patient, and the amount of at risk tissue preserved is also dependent on the thickness of the retroareolar tissue left behind. Our group previously performed a complete histologic analysis of 62 NACs from patients with BRCA mutations who underwent mastectomies [11]. TDLUs were identified in the NAC in close proximity to a major lactiferous duct in 24 % of cases but in only 8 % of nipple papilla. TDLUs were identified in the immediate retroareolar tissue in 16 % of specimens. Other series report sparse TDLUs in 9–17 % of nipple specimens, most commonly at the base of the nipple and rarely near the tip or papilla [12, 13]. One novel study assessed the extent of at risk tissue preserved following a SSM. Forty-two patients underwent a SSM, and then immediately at the same procedure, the flaps were resected as part of a standard mastectomy without reconstruction. Residual breast tissue was identified in 60 % of the SSM flaps, and TDLUs were present in 10 %. The prevalence of TDLUs was dependent on skin flap thickness. These data support that the cutaneous portion of the NAC is not at risk for developing new primaries, and a NSM can be a very safe prophylactic procedure compared to a simple mastectomy with little additional at risk tissue preserved and is primarily dependent on retroareolar and skin flap thickness [14].

Patient Selection (Indications/Contraindications)

Nipple-sparing mastectomy is most frequently considered in the setting of risk reduction but is now used increasingly as a therapeutic procedure. Initial indications were fairly restrictive focusing on patients with node-negative primary tumors less than 2 cm, located at least 2 cm from the NAC [15–20] These guidelines were based on known risk factors associated with NAC involvement in total mastectomy specimens. The indications for NSM have expanded, and it is now suggested that there are very few absolute contraindications. These include inflammatory breast cancer, Paget's disease, or direct involvement of nipple with neoplasm or high-risk lesion [21, 22, 23•, 24]. Fortunato et al.

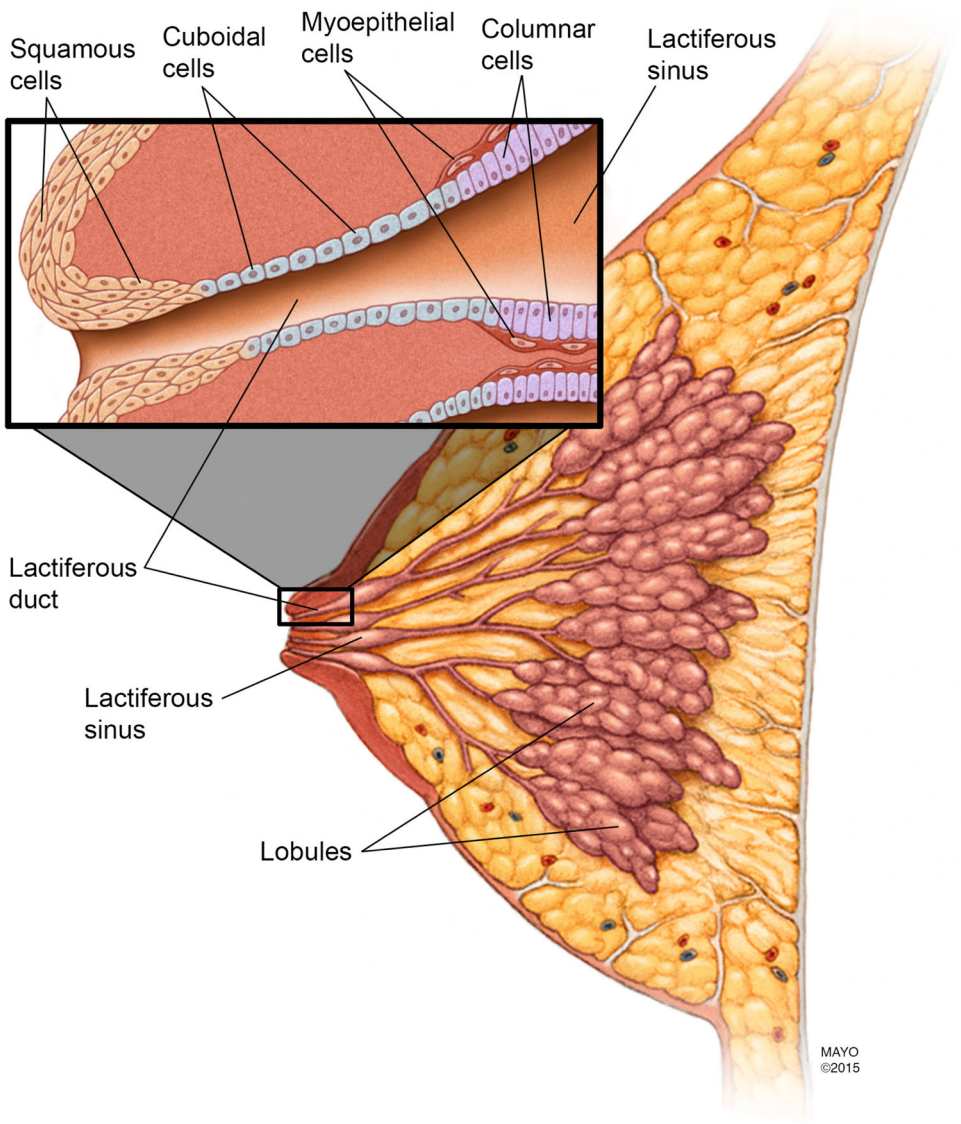

Fig. 1 Lactiferous duct anatomy. Anatomic illustration of ductal system with inset demonstrating magnification view of the cellular transition from the squamous cells at the nipple orifice to the cuboidal cells as they penetrate deeper

challenged tumor size and proximity to the NAC as a contraindication to NSMs [25]. Their patients were offered NSM, including those with multifocal/multicentric cancer and locally advanced disease as long as the distance of the tumor from the NAC was $\geq$ 1 cm. One hundred thirty-eight NSMs were performed in 121 consecutive patients, and there was only one local recurrence, which occurred outside the retained NAC, at median follow-up of 26 months. Another study supported the use of only two independent factors in the preoperative prediction of NAC involvement: (1) identification of clinical NAC abnormalities and (2) the presence of abnormal NAC imaging. The absence of these factors conveyed a low probability of NAC involvement on final pathology. This study noted that these findings were better for excluding NAC involvement than ruling it in. The NAC was involved with cancer 41 % of the time when the tumor was <2 cm from the nipple on preoperative imaging [26].

Peled et al. reported on NSM in 139 patients with Stage IIB and III breast cancer of whom 97 % received chemotherapy and 66 % post-mastectomy radiation. After a mean follow-up of 41 months, seven patients (5 %) had a local recurrence, 21 patients (15.1 %) developed distant recurrence, and three patients (2.2 %) had simultaneous local and distant recurrences. None of the local recurrences involved the NAC [27•]. A retrospective review of 444 patients undergoing NSM at Massachusetts General Hospital included 160 patients who had had a previous breast operation including lumpectomy, augmentation, and reduction mammoplasty [28]. They reported no significant increase in nipple loss, ischemic, or other postoperative complications compared to patients without prior breast

operation, supporting the feasibility of performing NSMs in the previously operated breast. Prior radiation therapy was a significant risk factor for overall complications, flap necrosis, and infections. Similar to most centers, we were initially conservative regarding indications for NSM but, over time, have become less restrictive such that NSM has increased to approximately 40 % of our mastectomy practice of which two-thirds are bilateral. Currently, we perform NSM for cancer patients with larger tumors, those closer to the nipple, patients selected for neoadjuvant chemotherapy, as well as those with node-positive disease. We also are offering NSM to an increasing number of patients with higher body mass index, larger breast size, ptosis, and prior radiation [23, 29].

BRCA 1/2 Carriers (Is It Safe?)

There has been concern regarding the safety of NSM in BRCA mutation carriers. While prophylactic subcutaneous NSM were shown by Hartmann et al. in a large series with long-term follow-up to be a very effective method of risk reduction for high-risk patients, only 26 of these patients were demonstrated to have a BRCA mutation [30]. A contemporary series of NSM in BRCA carriers with an identical study size also demonstrated that this procedure appears to be safe in this patient population (follow-up 37 months) [31]. In a large BRCA cohort, non-NSM prophylactic mastectomy has been shown to be a very effective means of risk reduction in this high-risk population [32]. Yao et al. recently reported on NSM in BRCA1/2 carriers, including 201 patients for risk reduction and 51 for cancer. There were four cancer events reported with a mean follow-up of 32.6 months: three in patients with cancer and one following a risk-reducing procedure. None of these cancers occurred within the NAC [33]. There are several series of BRCA1/2 patients undergoing NSMs for risk reduction and therapeutic indications showing very low rates of subsequent breast cancer development [31, 34, 35]. Jakub et al. presented a multi-institutional study of NSM for prophylaxis in patients at the 2016 American Society of Breast Surgeons (Jakub et al. Multi-Institutional Study of the Oncologic Safety of Prophylactic Nipple Sparing Mastectomy in a BRCA population. American Society of Breast Surgeons, Dallas, Texas, April 2016). No primary cancers developed in 348 patients undergoing 551 prophylactic NSMs with a mean follow-up of 55 months. Although longer-term outcomes of NSM in BRCA1 or 2 carriers are still needed, current data support the short-term oncologic safety of performing NSMs for this patient population.

Surgical Techniques

Incision Choices

Many approaches to NSM have been described and further modifications continue to evolve to meet individual circumstances. The goal of the operation is to remove the breast glandular tissue while retaining the nipple and a viable skin envelope. Appropriate patient selection, incision choice, dissection in the correct plane, minimizing thermal and traction injury, and preserving the dominant perforator vessels are keys to reducing surgical complications following NSM. This is a collaborative effort, and it is critical that the oncologic surgeon and the reconstructive surgeon work in a unified fashion. This includes incision planning for optimal surgical access to the tumor and consideration of cosmetic results based on patient's breast size, degree of ptosis, presence of prior scars, tumor location, and proximity to the skin. The incisions can be broadly divided into inframammary or breast splitting. The more common incisions used for NSM are shown in Fig. 2. Studies comparing incision options have shown that complications are significantly lower with radial incisions compared to periareolar incisions [36, 37]. Although periareolar incisions with lateral extension provide good exposure for both breast surgeon and reconstructive surgeon, there is a direct correlation with the length of the incision around the areola and nipple necrosis. Encircling the areola should be avoided, and incisions surpassing 30 % of the areolar circumference increase the risk of nipple necrosis [38]. Inframammary incisions are becoming increasing popular. This type of incision is most suitable for patients with small, non-ptotic breasts. The vascularity of the skin flap is preserved by the superior and medial perforators, with the dominant perforators typically originating from the intercostal 2nd and 3rd spaces. In larger breasted patients it may be difficult to reach the superior breast parenchyma and the axilla through this incision. The incision can be placed anywhere along the inframammary fold (IMF) and shifting the incision laterally can help with exposure to the upper outer quadrant.

A drawback to the IMF incision becomes apparent if the NAC requires resection due to disease involvement or poor perfusion. When this occurs, resecting the NAC plus having already used an inframammary incision not only prolongs operative time but also compromises the esthetics, especially if the areolar to IMF distance is short. Therefore, if there is high risk of NAC involvement and a nipple-sparing approach is undertaken, a breast-splitting approach is advised, as it allows easy conversion to a SSM. The likelihood of skin involvement also needs to be considered in incision planning as an incision directly over the tumor

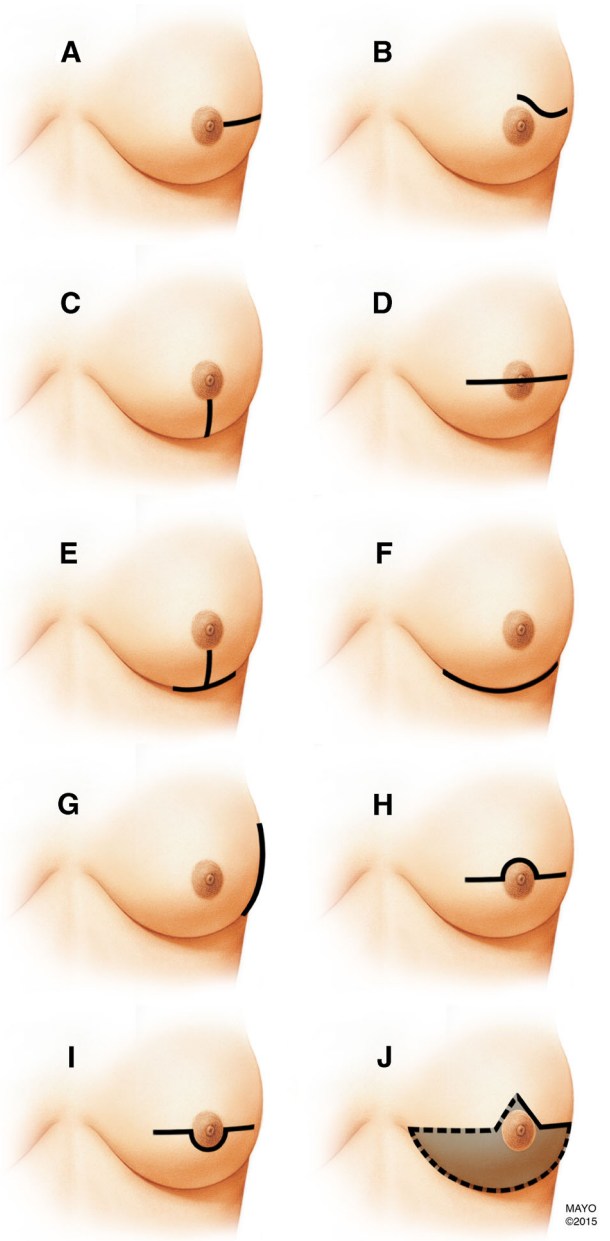

Fig. 2 Nipple-sparing mastectomy incisions. **a** Lateral, **b** modified periareolar, **c** vertical, **d** transareolar transnipple with medial and lateral extensions, **e** anchor or inverted T, **f** IMF, **g** lateral, **h, i** periareolar with medial and lateral extension (superior and inferior), **j** modified Wise pattern with de-epithelialization of the shaded region (used for macromastia)

or including an island of skin may make the most sense. When there is a prior incision, it may be incorporated or completely ignored based on the circumstance. In cases of a failed lumpectomy or excisional biopsy with positive margins, we recommend incorporating this incision in the NSM or excising the scar and dunking it into the cavity to be removed en bloc with the mastectomy specimen (Fig. 3c).

If a periareolar incision is used, one modification is shown in Fig. 3a. Making the incision approximately 2 mm off, the areola minimizes ischemia to the skin edge from a retraction injury. In a two-staged reconstruction procedure, the incision can then be incorporated into the areola border at the time of implant exchange by resecting the small skin bridge between the original NSM incision and the areola border. Breast-splitting incisions should rarely encompass more than 90° of the areola as should making a right angle when transitioning from the areola border to the radial extension. The use of a wavy radial extension allows a larger opening to work through less lateral retraction of the nipple and hides the incision better.

Operative Techniques (Cautery, Scissors, Coring, Intraoperative NAC Pathology)

Intraoperative evaluation of the nipple duct margin by frozen section to confirm tissue behind the NAC is free of disease is advised when performing NSM. Flap thickness is defined by the patient's anatomy as skin flaps should be raised between the subcutaneous fat and breast parenchyma. No such plane exists directly behind the NAC. The tissue behind the NAC is best divided sharply to avoid thermal injury [39]. Some have utilized tumescent solution to better define dissection planes, diminish bleeding, and decrease operative time, but this approach is reported to substantially increase flap necrosis rates when the tumescent is combined with epinephrine [40, 41]. Raising flaps utilizing sharp dissection or cautery are both options. When utilizing sharp dissection, a face lift technique with face lift scissors works well. A headlight and fiberoptic-lighted retractors are particularly useful in this type of incision. Placing the patient in Trendelenburg position can aid visualization when utilizing an IFM incision. Instruments with adequate length should be available such as long DeBakey forceps, cautery extension, and extra-long facelift scissors. We initially used small IMF incisions (6–8 cm) but have increased the length of these incisions over time (11–15 cm) with a concomitant improvement in flap viability, perhaps secondary to less continuous heavy traction on the flap, better visualization, and shorter operative time. The operative team should be cognizant to avoid the skin flap from folding under on itself, such that the skin edge is folded under the retractor, as this will lead to a necrotic skin edge requiring debridement and lowering the NAC as well (Table 1).

The use of intraoperative laser angiography has been reported to decrease flap necrosis rate [42–44] compared with the traditional methods used to evaluate adequate skin perfusion alone, and we have found this useful. Our group is currently attempting to define criteria for selective use, distinguishing a high, intermediate, and low-risk

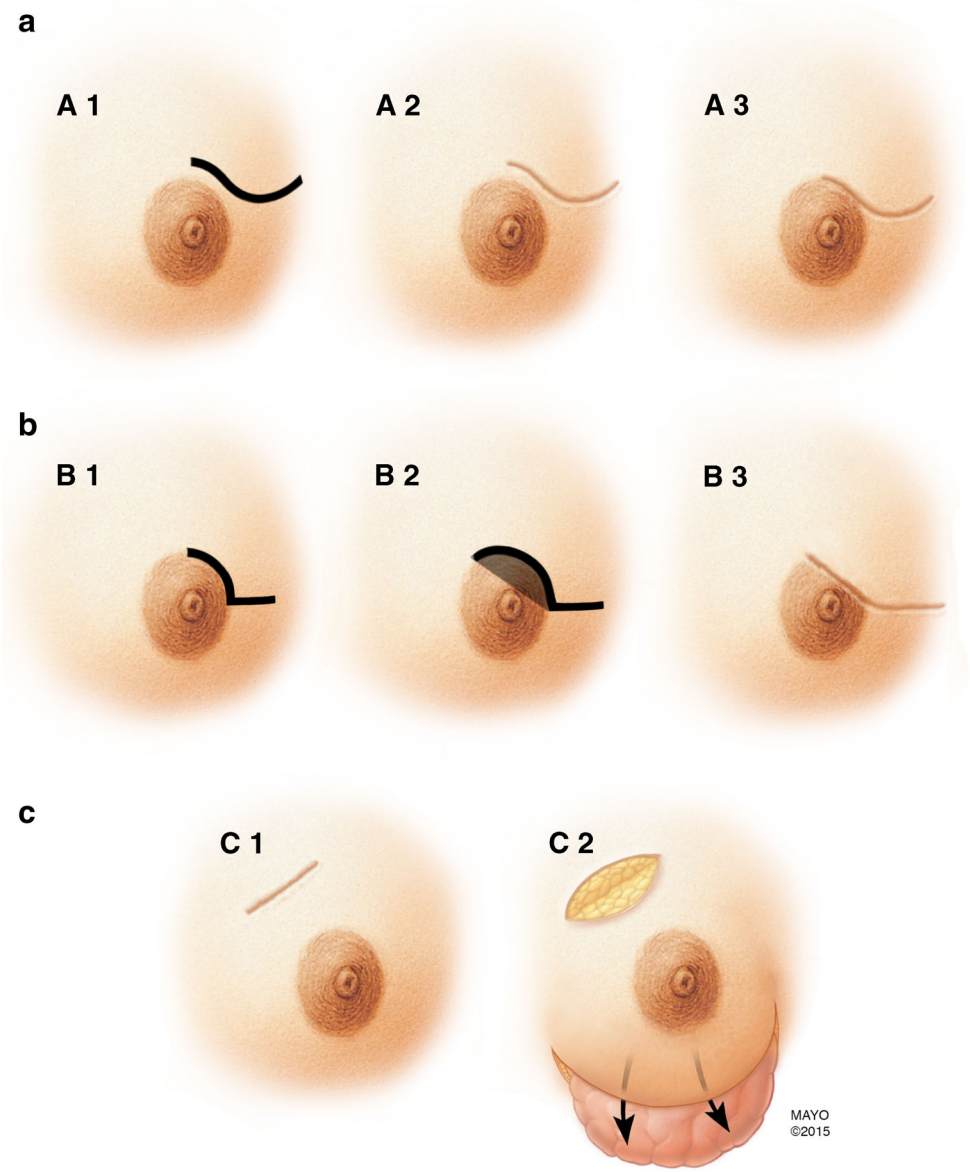

Fig. 3 Incision modifications. **a** Modified periareolar incision (*A1*) incision is 2 mm off the areola border minimizing risk of ischemia to the areolar edge from a retraction injury. In a two-staged reconstruction procedure, the incision is incorporated into the areola border at the time of implant exchange by resecting the small skin bridge (*A2*, *A3*). **b** Periareolar incision where minimal retraction injury requires resection of areolar skin (*B2*), resulting in loss of areolar border (*B3*). **c** Excising prior incision and dunking the scar into the cavity to be removed en bloc with the mastectomy specimen

Table 1 Tips for NSM

Inframammary—do not struggle; make the incision longer
Minimize the extent of or avoid periareolar incisions (<30 % or maximum 90°)
Use a head light and lighted retractors
Consider a cautery tip extension and long instruments
Minimize continuous tension on the flaps from retraction
Use sharp dissection behind the NAC
Avoid thermal injury to flaps
Consider face lift scissors technique
Stand on a mat or sit on a stool
Use Trendelenburg position for inframammary incisions

group. We have also found use of intraoperative laser angiography after expansion, prior to skin closure helpful as the flap may appear viable at the end of the mastectomy, but overexpansion can lead to ischemia. Utilization of the intraoperative laser angiography for incision planning to identify the dominant perforators and base incision planning intraoperatively is a possible opportunity in high-risk cases to further decrease flap necrosis. Mayo Clinic recently reported a retrospective review of 467 breast reconstructions undergoing implant-based reconstruction, comparing complication rates of those who underwent reconstruction prior to the use of intraoperative laser angiography to those who were reconstructed after implementation of intraoperative laser angiography. A subgroup analysis of patients undergoing NSM ($n = 165$) had a 44 % decrease in overall complications from 12.1 % ($n = 1$) to 6.8 % ($n = 5$) ($p = 0.298$) [45].

A randomized controlled trial of nitroglycerin ointment on mastectomy flaps was recently reported by Gdalevitch et al. [46]. Nitroglycerin ointment is a topical vasodilator that increases local blood flow by dilating both arteries and veins. Patients undergoing mastectomy and immediate reconstruction were randomized to either placebo or nitroglycerin ointment (45 mg) applied to the mastectomy skin at the time of surgical dressing. The trial was stopped after the first interim analysis of 165 patients (85 to treatment arm and 80 to placebo group) as nitroglycerin group showed marked reduction in mastectomy flap necrosis (placebo 33.8 %, nitroglycerin 15.3 %, $p = 0.006$) concluding nitroglycerin ointment application is simple and effective way to reduce mastectomy flap necrosis. Further study is needed to define the high-risk patient groups most likely to benefit from this approach.

Outcomes

Postoperative Complications

Nipple or areolar necrosis is a well-described complication of NSM and leads to an increased risk of implant loss. Patients should be informed that in the setting of unilateral breast cancer, a contralateral risk mastectomy essentially doubles the risk of infection, hematoma, and implant loss, and the prophylactic breast is at equal risk of complications as the therapeutic side. Risk factors for flap necrosis include periareolar incision [37], smoking [37, 40], use of tumescent solution [40], increasing age [40], increasing BMI [40], and prior radiation [47, 48].

Oncologic Safety of Therapeutic NSM

Several studies have shown preservation of the NAC with a contemporary NSM is oncologically safe without increased risk of local recurrence in women with sporadic breast cancer [35, 49]. Several studies have reported long-term follow-up demonstrating recurrence rates for NSM is similar to that of mastectomies without preservations of the NAC [35, 50, 51]. In these series, recurrences in the NAC were rare. Sakurai reported long-term follow-up of 788 patients who underwent NSM without radiotherapy. The median follow-up was 78 months with no significant difference in the local recurrence rate between NSM cohort and a mastectomy cohort (8.2 vs. 7.6 %, $p = 0.81$). There was also no significant difference between the two groups in terms of 21-year disease-free survival or the 21-year overall survival [52•] (Table 2).

Our Approach

Our use of NSM has increased over recent years as our indications have become less restrictive. We do not offer NSM to patients who have clinical or radiographic evidence of nipple involvement, Paget's disease, and inflammatory breast cancer or who are current smokers. Patients with prior radiation have an increased risk of complications, but we do not consider this an absolute contraindication to NSM. We utilize both inframammary and breast-splitting incisions. Nipple-sparing mastectomy may be best avoided in patients with extremely large breasts and marked ptosis, although we will sometimes utilize a modified reduction type incision in this population, including de-epithelialization of redundant skin, although this is much more challenging, has a higher risk of complications, and can result in less than ideal NAC location. We selectively utilize intraoperative laser angiography following the mastectomy and after expansion. We do not utilize tumescent solution. We utilize nitropaste selectively and in rare cases use postoperative hyperbaric oxygen. We perform intraoperative frozen section analysis of the nipple margin, and we do not core out the central nipple ducts from the nipple papilla. After NSM, surveillance for local recurrence or new primaries is performed via clinical exam only; we do not offer or recommend mammograms, ultrasounds, or MRIs unless there is a clinical concern. We continue to rigorously evaluate our outcomes as a multidisciplinary team and perform continuous quality review [53].

Table 2 Summary of local recurrence rates in NSM series

Author	Year	NSM (*n*)	SSM (*n*)	NSM LR (%)	SSM LR (%)	Median follow-up (months)
Krajewski et al. [23]	2015	236		1.7		24
Sakurai et al. [52]	2013	788	144	8.2	7.6	78
Peled et al. [38]	2012	657		2		28
Jensen et al. [54]	2011	77		0		60.2[a]
Spear et al. [17]	2011	162		0		30
Boneti et al. [55]	2011	281	227	6	5	25.3
Kim et al. [56]	2010	187		2		60
Petit et al. [57][b]	2009	1001		1.4		19
Garwood et al. [37]	2009	170		0.6		13
Gerber et al. [58]	2009	60	48	11.7	10.4	101
Paepke et al. [22]	2009	96		0		34
Sakamoto et al. [59]	2009	89		0		52
Benediktsson [7][c]	2008	202		25.7		135.6[a]
Crowe et al. [15]	2008	83		4		41
Sacchini et al. [60]	2006	192		0.01		24.6

NSM nipple-sparing mastectomy, *SSM* skin-sparing mastectomy

[a] Follow-up interval was mean (months)

[b] Patients received intraoperative radiation

[c] Included subcutaneous mastectomy

Conclusions

The use of NSM for prophylaxis in high-risk patients and for the treatment of breast cancer has been increasing in recent years due to its superior cosmetic outcome, and the indications have become less restrictive over time. The data to date support the safety of NSM from a preventive standpoint and show local recurrence rates similar to SSM and total mastectomies. The data for use in BRCA patients are thus far supportive but remain somewhat limited. Nipple-sparing mastectomy is associated with increased operative times and a higher complication rate.

Compliance with Ethics Guidelines

Conflict of Interest Drs. Chiba, Jakub, and Hieken declare no conflicts 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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- •• Of major importance

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