9 Reducing Complications and Margin Issues with Nipple-Sparing Mastectomy

Alice P. Chung and Armando E. Giuliano

Introduction

With advancements in reconstructive techniques, breast imaging and genetic testing, there is a rising rate of mastectomy with an increase in demand for improved cosmesis and better quality of life. Nipple-sparing mastectomy (NSM) with immediate reconstruction has become the preferred surgical approach for the treatment of breast cancer or prophylaxis in appropriately selected patients. To master this technique, one must minimize postoperative complications, reduce the need for secondary operations, and provide optimal local control. This chapter addresses complications and margin issues that are associated with NSM, and provides evidence-based recommendations on how to prevent and manage these potential problems.

A.P. Chung, M.D., F.A.C.S. • A.E. Giuliano, M.D., F.A.C.S., F.R.C.S. (Ed.) (✉)
Department of Surgery, Cedars-Sinai Medical Center, 310 N. San Vicente Blvd., Third Fl., Los Angeles, CA 90048, USA
e-mail: alice.chung@cshs.org; giulianoa@cshs.org

Postoperative Complications

Postoperative complications associated with any operation include bleeding, infection, and poor wound healing, but in patients undergoing NSM these complications can ultimately lead to increased cost, patient dissatisfaction, and loss of reconstruction. It is important to recognize these complications early and identify patients who may be at increased risk in advance. As is the case in all operations, careful patient selection is the key to minimizing complications.

There are complications associated with patient factors and those related to surgical technique. Known patient risk factors for postoperative complications include advanced age, positive smoking history, and presence of medical comorbidities, including cardiovascular disease, diabetes, and obesity [1–3]. These factors increase the likelihood of anesthetic or medically related complications as well as wound complications. In NSM wound complications can be further categorized into hematoma, seroma, cellulitis, abscess, necrosis of the nipple–areolar complex (NAC) (partial or complete), skin flap necrosis (requiring or not requiring operative debridement), implant loss, and capsular contracture. The most common complication after NSM with reconstruction has been reported to be wound complications with skin flap and nipple necrosis comprising the majority of wound complications.

J.K. Harness, S.C. Willey (eds.), *Operative Approaches to Nipple-Sparing Mastectomy*,
DOI 10.1007/978-3-319-43259-5_9

Table 9.1 Reported incidences of postoperative complications following mastectomy with or without reconstruction

Complication	Reported incidence (range), %
Pulmonary embolus [4–6]	0–0.2
Cardiac event [6]	<0.1
Deep venous thrombosis [4–7]	0.3–0.7
Pneumonia [6]	0.2
Bleeding [4, 5, 7]	0.4–11.6
Infection (cellulitis) [4, 6, 8]	1.6–2.8
Infection (abscess) [4, 6]	0.1–1.8
Nipple necrosis (partial) [9–12]	0–38
Nipple necrosis (complete) [9, 11–13]	2–17
Skin flap necrosis (minor) [9, 12, 14, 15]	5.2–8
Skin flap necrosis (requiring operative debridement) [9, 14, 16]	0.6–5
Loss of reconstructed breast [1, 2, 9, 10, 16]	0.8–2.8

The reported incidences of the most common complications are listed in Table 9.1.

Skin Flap and Nipple Necrosis

Ischemia of the skin and nipple can lead to skin flap or nipple necrosis. These events place the patient at increased risk for infection, operative intervention, and implant loss and are likely to result in a significant level of patient dissatisfaction [17–19]. Nipple loss due to ischemia is a complication that is unique to NSM, but the factors that increase risk for skin flap necrosis are similar to factors that increase the risk for nipple necrosis. Patient characteristics (i.e., age, ethnicity [20], smoking history [9, 21, 22], history of diabetes [13, 14], BMI [9, 10, 13, 14], breast cup size, prior irradiation, prior breast surgery [9, 11, 14, 23], indication for mastectomy (malignancy versus prophylaxis), location of the NAC [13, 24]), surgical technique (type of mastectomy incision, mastectomy technique [14, 15, 25–28], type of reconstruction [1, 4, 11, 13, 22, 23, 29], volume of expander fill [13, 25, 27], unilateral versus bilateral mastectomy [1, 30], use of prosthetic material [13, 23, 31], concurrent axillary surgery [13]), tumor characteristics (more advanced cancer stage [32], aggressive tumor characteristics [9, 33], use of neoadjuvant chemotherapy [34]), surgeon experience [13] and post-mastectomy radiation have all been implicated as factors that may increase risk of ischemia to the nipple.

There are conflicting results among retrospective studies that have assessed patient age as a potential risk factor for complications following NSM and skin sparing mastectomy. Some studies have found that older age is associated with higher rates of necrotic complications [2], while others have determined that young age is a predictor of complications, and still others have found no association between patient age and complication rates [9, 20, 21, 35]. It is unclear from the current literature whether age alone is a significant risk factor for necrotic complications following NSM.

Ethnicity has been shown to be associated with incidence of wound complications. De Blacam and colleagues assessed over 10,000 patients who underwent mastectomy and found that Asian and Pacific Islanders had lower rates of wound infection compared to other races [20]. Akinyemiju et al. studied over 71,000 women treated for breast cancer and found African-American race to be associated with a higher rate of postsurgical complications [36]. The study included wound complications, infections, urinary, pulmonary, gastrointestinal, or cardiovascular complications. Butler et al. compared postoperative morbidity of 138 African-American women to 654 Caucasian women treated with mastectomy and free-flap autologous reconstruction and found no difference in either major or minor postsurgical complications [37]. Studies on how ethnicity impacts complications specifically in NSM are limited.

Multiple studies on risk factors in NSM have found smoking to be a significant risk factor for nipple necrosis [3, 10, 13, 14, 20–22]. Gould et al. evaluated nipple necrosis in 233 cases of NSM and found that smokers had a nipple necrosis rate of 44 % compared to 15 % in non-smokers. Fischer and colleagues identified over 9300 patients treated with mastectomy and immediate tissue expander reconstruction and identified active smoking as a highly significant risk factor for implant or expander loss [1, 2]. In Colwell et al.'s evaluation of complications after NSM, smoking was found not only to be a risk factor for nipple necrosis but was also associated with having multiple postoperative complications, including infection, hematoma, and implant loss. Smoking compromises the arterial supply to tissues, and the nipple and mastectomy flaps are particularly vulnerable because of the diminished blood supply caused by removal of the breast, as well as the large dead space underlying the wound. Patients who smoke should be counseled that they are at increased risk for postoperative complications and smoking cessation prior to surgery should be encouraged.

There are a number of physiologic factors that contribute to deficient wound healing in patients with diabetes, including impaired growth factor production, angiogenic response, macrophage function, collagen accumulation, and fibroblast migration and proliferation [38]. Because of these factors, diabetes has been postulated to be a risk factor for nipple necrosis. De Blacam et al. conducted a prospective study of over 10,000 patients undergoing mastectomy and found that diabetes was a significant independent risk factor for wound complications, namely infection [20]. Matsen and colleagues evaluated risk factors for skin flap necrosis in over 600 patients undergoing mastectomy with immediate reconstruction and found that diabetes was not a significant risk factor for mild necrosis [14]. On univariate analysis, diabetes was associated with moderate and severe necrosis, but this finding did not persist on multivariate analysis. Gould et al. compared the rates of nipple necrosis in patients with comorbidities versus those who did not have comorbidities and found that patients with diabetes or hypertension had a much higher rate of nipple necrosis than those who did not have either medical condition (58 % vs. 16 %, p –0.09) [13]. Diabetes may more likely be a significant risk for nipple necrosis when combined with other risk factors.

Obesity is another patient characteristic that has been associated with necrotic complications after NSM. De Blacam prospectively studied over 26,000 patients treated with breast cancer surgery and found BMI > 25 kg/m^2 to be the strongest predictor of wound complications when compared to multiple other comorbidities (i.e., smoking, diabetes, hypertension, heart failure, steroid use, chemotherapy, or radiation therapy) [20]. Fischer et al. studied over 15,000 cases of breast reconstruction and found an incidence of obesity of 27 %. The authors found that progressively higher BMIs were associated with higher rates of complications, including wound complications and loss of reconstruction [39]. Among studies of NSM, high BMI was strongly associated with skin and nipple necrosis [10, 13, 14].

Breast cup size is an important factor because it is associated with the length of the mastectomy flaps. The larger the breast cup size, the longer the flap and the higher the risk of ischemia to the skin flaps and NAC [9, 13, 14, 23, 40]. Gould and colleagues found that patients with a C cup breast size or larger had a 34 % risk of nipple necrosis, whereas those with A–B cup sizes only had 6 % risk of nipple necrosis [13]. The authors attribute this finding to longer distance between the nipple and surrounding blood supply from the chest wall, potential for decreased vascular perfusion to the skin envelope during dissection, and increased manipulation of the skin envelope. Wang et al. compared rates of necrosis in patients who had NSM with tissue expander reconstruction with breast size greater than 352 g (n = 115) to those with breast size less than 352 g (n = 109) [40]. They found that the larger sized group had an 8.1 % higher rate of superficial nipple necrosis, but found no difference between the groups with respect to necrosis requiring operative intervention. Based on these studies, larger breast size alone should not be a contraindication to NSM. However, when combined with additional risk factors, counseling regarding increased risk may be warranted in patients with larger breast size.

Women with significant ptosis are considered poor candidates for NSM due to excessive skin flap length and risk of ischemia [24]. In addition, there is the perception that the NAC cannot be reliably repositioned on a breast mound after mastectomy. Therefore, they are considered better candidates for skin-sparing mastectomy with subsequent nipple reconstruction. Gould et al.

evaluated risk factors among 113 patients undergoing NSM and did not find an association between ptosis and risk of nipple necrosis [13]. However, the authors did not report the number of patients with ptosis in the study. Chidester and colleagues report successful free nipple grafting as a technique for sparing the NAC in a small series of five patients with significant ptosis undergoing mastectomy. They reported no nipple losses and only one patient who had partial nipple loss [24]. Doren et al. performed free nipple grafting on a slightly larger series of patients undergoing mastectomy ($n=36$) and reported no complete nipple losses with an average graft take of 94 %, which are similar rates seen with reduction mammoplasties [41]. DellaCroce et al. published a series of 116 NSM cases performed in patients with grade 2–3 ptosis who had immediate autologous tissue flap reconstruction followed by delayed mastopexy [42]. The autologous flap provides vascular ingrowth to support perfusion to the NAC despite the complete incisional interruption during mastopexy. The authors reported a 7.7 % rate of wound dehiscence, 3.4 % rate of skin flap necrosis with no cases of NAC necrosis, demonstrating that mastopexy after NSM in patients with severe ptosis is possible.

Prior irradiation is considered a significant risk factor for ischemia following mastectomy. Multiple studies evaluating NSM in patients who have received prior radiation therapy or post-mastectomy radiation therapy demonstrate that irradiated patients have a higher risk of postoperative complications [43–47]. One of the largest recent series was published by Sbitany and colleagues who compared outcomes of NSM in 727 non-irradiated breasts, 63 previously irradiated breasts, and 113 breasts that were irradiated after NSM [45]. Any radiation was associated with a 21 % increased rate of infection requiring antibiotics, and a 19 % increased rate of expander loss. Radiation prior to NSM was associated with a higher rate of wound breakdown. All groups had a similar rate of nipple or areolar necrosis. Tang and colleagues studied a similar number of patients that were divided into three cohorts (816 with no radiation, 67 with prior radiation, and 97 who had post-mastectomy radiation) [47]. They also found that radiation before or after NSM increased overall complications (10, 22, and 18 % for the respective cohorts), but they found a higher rate of nipple loss in the radiated breasts, though infrequent (1, 4, 4 %, respectively). Other complications reported included malposition of the NAC (17–28 %), capsular contracture (12–17 %) and reconstruction failure (3–8 %). Despite the higher rate of complications, the rate of nipple retention and reconstruction retention remained high in patients treated with radiation.

History of prior breast surgery may increase the risk of wound complications in NSM due to existing scars that may compromise the blood supply to the NAC. In Matsen's prospective study of skin flap necrosis in 606 mastectomies with reconstruction, the authors found history of prior breast reduction to be strongly associated with increased rates of necrosis [14]. Dent and colleagues reviewed their series of 398 NSM cases where 41 patients had prior cosmetic breast surgery, including reduction mammoplasty, augmentation, and mastopexy [48]. The authors performed NSM with implant-based reconstruction using the inframammary fold incision with an average time interval of 8 years between the time of the cosmetic surgery and NSM. Patients with prior breast surgery had higher rates of mastectomy flap ischemia and hematoma compared to those who had never had prior cosmetic surgery, and among those who had prior breast surgery, single stage reconstruction was associated with higher rates of full-thickness ischemia. The authors concluded that patients with history of prior cosmetic breast surgery should be cautiously considered for NSM with implant-based reconstruction, especially in the setting of single stage reconstruction.

The indications for mastectomy have been evaluated as potential risk factors for complications following NSM. Those who receive NSM for the treatment of malignancy have *not* been found to have a higher rate of complications when compared to patients having NSM for risk reduction [12, 49] Among patients treated with NSM or skin-sparing mastectomy for risk reduction, Gould et al. found a significantly higher rate of overall complications in patients who had

NSM compared to those having skin-sparing mastectomy [13], but the addition of axillary surgery did not affect the rates of complications in either group. In Lee's study of 130 patients undergoing NSM with reconstruction, among those who had tissue expander reconstruction, higher degree of axillary intervention was correlated with higher rates of wound complications, specifically skin flap necrosis [29].

A number of studies have identified incision type as a predictor of skin flap or nipple necrosis [9, 10, 21, 22, 49, 50]. The most common types of incisions in NSM include radial, periareolar, inframammary, mastopexy, and transareolar. Endara et al. conducted a review of 48 studies on NSM with 11 of the studies reporting complication rates according to incision type [11]. The combined nipple necrosis rate in procedures where a radial incision was used was 8.8 %. This rate was similar to 9 % with the inframammary incision and increased to 17 % with the peri-areolar incision. The mastopexy incision was associated with the lowest rate of nipple necrosis (5 %). Transareolar incision resulted in an unacceptably high rate of nipple necrosis (82 % in 11 procedures), and is not recommended. Among patients treated with post-mastectomy radiation, Peled and colleagues found a higher rate of incision breakdown with the inframammary incision compared to other incision types (21 % versus 10 %) [50]. In addition, the authors found that when inframammary incision breakdown occurred, a higher rate of implant loss was observed. This suggests that the inframammary incision should be used with more caution in patients planning to receive post mastectomy radiation.

Technique of mastectomy has been investigated as a factor for increased rates of skin flap necrosis. There are conflicting reports regarding the association of the tumescent mastectomy technique with skin flap or nipple necrosis. Among several series of risk factor analyses for NSM, Mlodinow et al. and Chun et al. found tumescent technique to be associated with skin flap necrosis, while Khavanin et al. and Matsen et al. did not find a correlation between tumescent technique and necrosis [14, 15, 25, 27]. Seth and colleagues compared outcomes in 333 patients who had mastectomy with tumescent technique to 565 patients who had mastectomy without tumescence. The authors found that the total complication rate was significantly higher in the tumescence group (23 %) compared to the non-tumescence group (18 %), with higher rates of operative complications, non-operative complications, and major skin flap necrosis in the tumescence group [26]. Abbott and colleagues compared complication rates in 70 mastectomy cases performed with tumescent technique to 64 cases performed with electrocautery [28]. and the authors did not observe a significant difference in complication rates between the two groups. The tumescent technique can be safely utilized in NSM, but perhaps caution should be used with this technique in patients with multiple risk factors for complications.

The use of reconstruction adds complexity to the mastectomy and one would expect an increase in the incidence of postoperative complications. Fischer and colleagues compared complication rates in 30,440 women treated with mastectomy without reconstruction to 12,383 women who had mastectomy with tissue expander reconstruction and found that reconstruction did not confer increased risk in medical, wound, or overall 30-day morbidity [4]. Kim et al. compared complication rates in 70 patients who had NSM with autologous reconstruction to 60 patients treated with NSM and tissue expander reconstruction and found that the autologous reconstruction group had a significantly lower rate of complications (10 % versus 23 %) after adjusting for factors such as age, body mass index, breast size, and tumor factors [29]. The authors hypothesize that higher rates of necrotic complications in tissue expander reconstruction may be due to the dead space beneath the mastectomy flap which is more reliably obliterated in autologous reconstruction. The fluid in the dead space can interfere with revascularization of the skin flaps, thereby increasing the risk of necrosis. In a systematic review of 48 studies of NSM performed by Endara et al., 45 % of cases were two stage tissue expander reconstruction with nipple necrosis rate of 4.5 %, 41 % of cases were single stage direct implant reconstruction with a 4 % nipple necrosis rate, and 14 % were autologous tissue reconstruction cases which had a nipple necrosis rate of 17 % [11]. The authors did not attempt to explain the difference in nipple necrosis rates observed; however, there were only two studies of autologous reconstruction included in the pooled analysis, one study had a 23 % rate of nipple necrosis and the other study only had 2 % with nipple necrosis. In a risk analysis of necrotic complications following 170 NSM in which 37 % of NSM cases had autologous reconstruction, Garwood et al., identified autologous reconstruction as an independent risk factor for necrosis [22]. The data appears to be somewhat conflicting with regards to whether type of reconstruction increases rates of necrotic complications and is limited by small numbers of patients and presence of multiple confounders.

Volume of tissue expander fill can affect the blood supply to skin flaps. Therefore, higher fill volumes should be associated with higher rates of skin flap and nipple necrosis. Mlodinow and colleagues reviewed over 1560 mastectomies with tissue expander reconstruction cases and found that 8.6 % experienced skin flap necrosis [15]. Regression analysis identified high intraoperative tissue expander fill volume (>67 % of total expander volume) to be strongly correlated with skin flap necrosis. Lee et al. assessed complication rates in 130 patients who had NSM, 60 of whom had tissue expander reconstruction, and did not find expander fill volume to impact rate of complications [29]. The mean percentage of volume fill was only 34 %, which is much lower than observed in Mlodinow's study.

The use of prosthetic or biological material, such as acellular dermal matrix, for coverage of tissue expanders or implants has increased over the last decade. Several investigators have evaluated the impact of its use on postoperative complications. Peled et al. conducted a prospective study of 450 cases in 288 patients who had NSM with or without placement of acellular dermal matrix [31]. They found that acellular dermal matrix reduced the incidence of major complications, including infection, unplanned reoperation, and implant loss. In a risk analysis performed by Gould et al., use of biomaterials was not associated with a significant difference in rate of nipple necrosis [13]. Dent et al. reviewed risk factors for NAC ischemia in 318 NSM cases and found use of acellular dermal matrix to be significantly associated with ischemia of the NAC [23]. While the impact of biomaterials on the rate of nipple necrosis is unclear, proponents feel there may be a reduction in the rate of more significant complications that warrant its use in breast reconstruction.

Use of methylene blue dye has been associated with skin necrosis in surgical patients. Lee et al. reported six cases of skin necrosis associated with use of methylene blue dye in patients undergoing mastectomy and sentinel node biopsy followed by immediate implant-based breast reconstruction [51]. Reyes and colleagues reported two cases of severe necrotic complications of methylene blue use in breast surgery that required multiple surgical debridements and negatively impacted the cosmetic outcome in both cases [52]. In patients undergoing sentinel node biopsy at the time of NSM, lymphatic mapping with either Isosulfan Blue or radioisotope should be strongly considered. Methylene blue should always be diluted to avoid necrosis.

The incidence of contralateral prophylactic mastectomy (CPM) has increased dramatically in the last decade, with reported rates increasing by 150 % in the last decade [53]. The addition of CPM has increased the potential for more surgical complications. Osman and colleagues compared complication rates in 3722 patients who had unilateral mastectomy to 497 patients treated with bilateral mastectomy for breast cancer treatment [30]. The authors found a significantly higher rate of postoperative complications in the bilateral mastectomy group (5.8 %) compared to the unilateral group (2.9 %) at 30 days. Wound complications were the most common complication in both groups. Type of reconstruction was not reported in this study. Silva et al. identified over 20,000 patients from the National Surgery Quality Improvement database who had either unilateral mastectomy ($n = 13{,}268$) or bilateral mastectomy ($n = 7233$) with reconstruction [54]. The authors found that bilateral mastectomy was associated with longer hospital stays, higher rates of transfusion, reoperation, and wound disruptions. There was no difference between the unilateral and bilateral mastectomy groups in terms of medical complications. Sharpe and colleagues reviewed the National Cancer Database, which included 315,278 patients who had unilateral mastectomy, 75,437 patients who had bilateral mastectomy, and 97, 301 had reconstruction [55]. They reported no difference in 30-day mortality or readmission rates between unilateral and bilateral mastectomy groups but found significant delays to surgical and adjuvant therapy with bilateral mastectomy, regardless of whether reconstruction was performed. There has not been any such comparison specifically in NSM reported in the literature.

NSM was initially introduced for selective use in early breast cancer due to concerns regarding oncologic safety. The majority of early studies did not identify an association between tumor characteristics and overall complication rates [22, 35, 56]. Lohsiriwat et al. evaluated the effect of tumor features on the rate of nipple necrosis in 934 NSM performed for breast cancer with the only exclusion criteria being NAC involvement by imaging or a positive retroareolar margin identified by intraoperative frozen section [33]. They found no association of clinicopathologic features, including tumor size, nodal status, histology, tumor grade, presence of extensive in situ component, lymphovascular invasion, tumor receptor status, and Ki67, with nipple necrosis. Burdge et al. performed skin sparing mastectomy or NSM on 60 patients with locally advanced disease who had post-mastectomy radiation [57]. They report a wound and necrosis complication rate of 16.7 % and implant loss in 5 % which is comparable to reports in patients with earlier stage disease. Santoro and colleagues performed 186 NSM in patients with breast cancer; 51 had neoadjuvant chemotherapy [58]. The authors found no correlation between use of neoadjuvant chemotherapy and overall complication rate or nipple necrosis rate. It appears that NSM can be performed in patients with larger, more aggressive tumors with complication rates comparable to those with earlier stage disease even after chemotherapy.

In summary, there are multiple factors that contribute to skin and nipple necrosis, and higher risks are associated with cases where multiple risk factors are present. Despite the relatively moderate incidence of wound complications associated with NSM, skin or nipple necrosis rarely leads to loss of reconstruction. Careful selection of patients is warranted for successful execution of NSM and caution must be exercised in high risk cases.

Techniques for Prevention of Nipple Necrosis

A number of techniques have been proposed to prevent nipple necrosis in high risk patients. Jensen and colleagues reported successful NSM in 20 high risk patients who were treated with a surgical delay procedure in an effort to maximize viability of the NAC [59]. The authors propose that creation of a surgical wound stimulates the body to improve blood supply to the wounded tissue. They selected patients who had breast ptosis, prior breast scars, or active smoking history who desired NSM. The patients were initially taken to the operating room for elevation of skin flaps directly beneath the NAC and surrounding breast tissue. Approximately 4–5 cm of surrounding breast tissue was undermined, and a biopsy of the nipple ducts was performed at this time. The incision was closed without removal of any breast tissue other than the sub-areolar biopsy. Definitive NSM with immediate reconstruction was then performed 7–21 days later. In two patients, the sub-areolar biopsy was positive for malignancy requiring subsequent removal of the NAC at the time of mastectomy. Of the remaining patients, all had survival of the NAC following NSM. This technique may increase surgical options for patients at high risk for nipple necrosis following NSM. Figure 9.1 shows an example of a patient who was at increased risk for nipple necrosis due to history of prior periareolar incision. The surgical delay procedure was performed and she was able to retain her native nipple–areolar complex despite experiencing an initial period of ischemic change in the

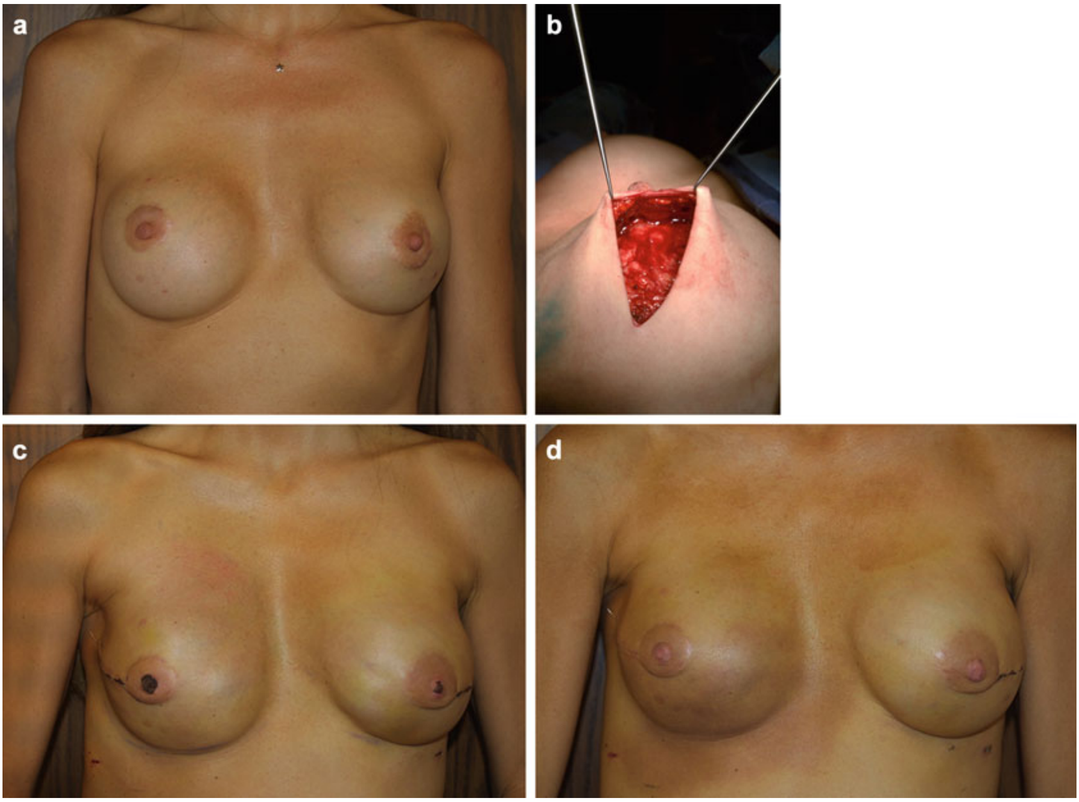

Fig. 9.1 (**a**) Patients with pre-existing periareolar scars are at high risk for nipple necrosis after nipple-sparing mastectomy because once the breast is removed, the entire blood supply to the remaining nipple–areolar complex must come from surrounding skin. Skin perfusion is known to be limited by surgical scars. (**b**) A surgical delay procedure works by stimulating blood supply to increase in tissues which will remain attached during and after the planned mastectomy. This delay procedure preserves all blood supply which might come from the surrounding skin (maintaining 360° skin perfusion) and separates the nipple–areolar complex from the underlying breast. Over the next 7–14 days, blood supply to the nipple from the surrounding skin improves. (**c**) Following mastectomy, the patient is seen to have sustained partial thickness injury to the nipples bilaterally but not full thickness nipple loss. (**d**) Two weeks following mastectomy and placement of breast implants, bilateral survival of the nipple–areolar complexes is evident

nipple. Figure 9.2 demonstrates the use of the surgical delay in a patient with severe ptosis who initially had nipple ischemia but ultimately was able to preserve her nipple–areolar complex.

Swistel and colleagues describe the use of preoperative Doppler ultrasound of the internal mammary artery perforators as a procedure to improve viability of the NAC in NSM with implant-based reconstruction [60]. Prior to NSM, location of the internal mammary artery perforators was identified by Doppler ultrasound and marked on the patient. During the NSM, the perforators corresponding to the Doppler mapping were then identified and spared. The authors compared outcomes of 97 NSM in which the internal mammary artery perforators were mapped to 97 NSM that did not have the vessels mapped by Doppler. The application of the Doppler mapping added an average of 4 min to the NSM procedure. There was no significant difference in wound complications between the two groups. The authors concluded that Doppler ultrasound may be a useful, inexpensive adjunct to improve NAC viability in NSM, but that their study was underpowered to draw any correlative conclusions about the various factors that may contribute to rates of skin or nipple necrosis.

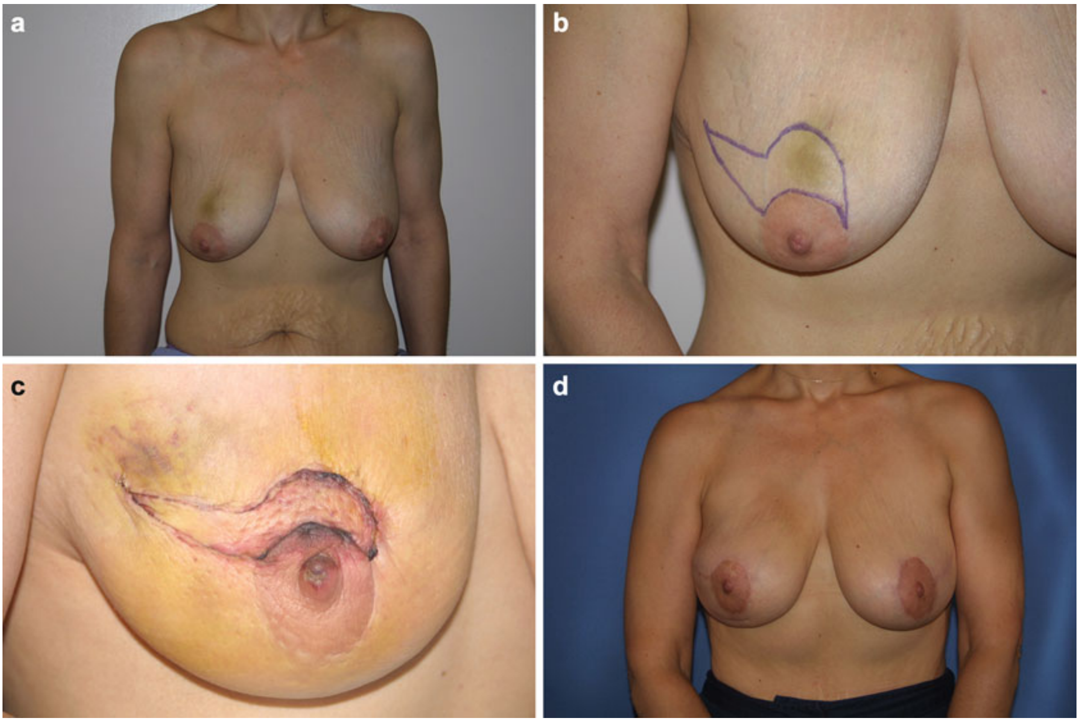

Fig. 9.2 (**a**) Patients with breast ptosis who are active smokers are generally considered to be poor candidates for nipple-sparing mastectomy. The distance from the suprasternal notch to the nipples in this patient was 27 cm. (**b**) A "hemi-batwing" incision is used to elevate the nipple–areolar complex off from the underlying breast. Undermining of the breast skin is done for 4 or 5 cm around the skin island so as to "delay" the nipple–areolar complex and the surrounding skin. (**c**) Undermining of the nipple–areolar complex and surrounding skin has resulted in signs of injury to the tissue but not in loss of the tissue. Improvement in blood supply which occurs as this tissue heals demonstrates the "delay phenomenon." (**d**) The patient is seen following a right mastectomy and free flap breast reconstruction with complete survival of the nipple–areolar complex. The left nipple–areolar complex was elevated using a "hemi-batwing" breast reduction. Thus, patients with breast ptosis who are active cigarette smokers can benefit from nipple-sparing mastectomy using the technique of the surgical delay

Intraoperative perfusion mapping using laser-assisted indocyanine green imaging has been reported as an effective method of defining vascular perfusion of the mastectomy skin to predict necrosis in breast reconstruction cases [61]. This technology has been successfully used intraoperatively to identify areas of poor vascular perfusion in time to make intraoperative decisions that may minimize complications in the postoperative period [62, 63]. It has not been shown to be cost-effective for use in all cases of mastectomy with reconstruction but perhaps may be reserved for cases where patients may be at increased risk of skin flap necrosis [64].

Once ischemia of the skin flap or nipple is identified postoperatively, there are techniques that may inhibit progression of ischemia and enhance survival of the skin or nipple. Nitroglycerin ointment is a topical vasodilator that increases local blood flow to the skin by relaxing the smooth muscle walls of the subcutaneous arteries and veins. Gdalevitch et al. conducted a randomized controlled trial evaluating the impact of topical nitroglycerin on skin flap necrosis in patients treated with mastectomy and reconstruction [65]. The target accrual was 400 patients, but the trial was stopped early due to proof of efficacy following the initial interim analysis. One hundred and sixty-five patients were randomized to receive either a single dose of 45 mg of topical Nitroglycerin or placebo at the time of placing the surgical dressing. With minimum follow-up of 27 days, there was a significant absolute difference in mastectomy flap necrosis rate of 18.5 %, with a rate of 15 % in the group that received Nitroglycerin compared to 34 % in the group that received the placebo. The application of a single postoperative dose of Nitroglycerin decreased the incidence of flap necrosis by 50 % and is a simple, cost-effective, efficacious method of reducing skin flap necrosis in patients undergoing mastectomy with immediate reconstruction.

Hyperbaric oxygen therapy has been shown to successfully salvage mastectomy skin flap necrosis in several case reports [66–68]. By using a closed chamber with increased atmospheric pressure and oxygen concentration, the partial pressure of oxygen in tissues can be increased. Patients may require multiple treatments to mitigate the consequences of ischemia of the skin or NAC, but the treatments are minimally invasive and well tolerated. Further research is needed to determine the role of hyperbaric oxygen in the treatment of skin flap ischemia, but it is currently an option that may have benefit in cases where skin or NAC viability is threatened.

The literature to support use of these more novel techniques remains limited at this time. As the use of NSM continues to increase, more data on methods of minimizing or preventing nipple and skin flap necrosis are likely to be obtained. We currently must rely on preoperative risk assessment and judicious patient selection to minimize wound complications of NSM.

Margin Issues in Nipple-Sparing Mastectomy

Positive margins following mastectomy have been reported to range from 5 to 12 %, and close or positive margin status after mastectomy has been associated with increased risk of local recurrence even in early node-negative breast cancer [69–71]. Margin involvement following mastectomy is an indication for either reoperation or radiation therapy, both of which can lead to significant patient dissatisfaction. Retroareolar margin involvement typically warrants removal of the NAC. When there is a positive margin in a location other than the retroareolar tissue after mastectomy, identifying the exact location on the skin flap where the margin is involved can be challenging. If re-excision is not possible, radiation therapy may be necessary. In the remaining section of this chapter, techniques of minimizing positive margins as well as management of positive margins will be discussed.

Prediction of nipple involvement would allow selection of patients for NSM with lower risk of positive retroareolar margins that may require subsequent NAC removal. Brachtel and colleagues studied occult nipple involvement in 316 mastectomy specimens, and found 21 % with occult nipple involvement [72]. Tumor factors that were strongly associated with occult nipple involvement on multivariable analysis included Her2 amplification, larger tumor size, and shorter tumor–nipple distance. Zhang et al. pooled data from 27 studies of NSM that investigated the risk factors for occult nipple involvement [73]. Significant predictors of nipple involvement included tumor–nipple distance ≤2.5 cm, nodal involvement, stage 3 or 4 disease, tumor size >5 cm, ER-negative status, PR-negative status, Her2-positive status, and DCIS as compared to invasive primary tumor. Several studies have suggested using preoperative breast imaging to predict nipple involvement [74–76]. Karamchandani et al. found that suspicious enhancement on MRI or suspicious findings on mammography within 20 mm of the nipple was predictive of nipple involvement in 85 % of cases. Ponzone and colleagues correlated imaging findings with pathologic findings in 112 NSM cases and found that the combination of intraoperative assessment of the retroareolar margin plus tumor to nipple distance on MRI yielded specificity and accuracy rates of predicting nipple involvement of 96.2 and 84.1 %, respectively.

Intraoperative frozen section analysis of the retroareolar tissue at the time of NSM is a reliable means of determining whether the NAC can be preserved. A positive intraoperative report allows immediate removal of the NAC, sparing the patient from a second operation to remove the NAC. In Brachtel's evaluation of occult nipple involvement in 316 mastectomy specimens, the authors found that a positive retroareolar margin correlated with occult involvement of the nipple papillae and distal nipple structures with a sensitivity of 0.8 and a negative-predictive value of 0.96 [72]. Duarte et al. compared accuracy, sensitivity, and specificity rates of frozen section, imprint cytology, and permanent histology in the evaluation of sub-nipple tissue for 68 NSM cases [77]. The authors found that the accuracy rates of frozen section and permanent histology were very similar and were better at predicting occult nipple involvement than imprint cytology (Table 9.2). False-negative rates in retroareolar biopsies have been attributed to incomplete excision of tissue beneath the nipple base as well as to underestimation by frozen section analysis of the retroareolar tissue fragments. The tissue frequently becomes distorted during frozen section causing difficulty in accurately assessing the margins. Piato and colleagues proposed a technique of frozen section analysis of retroareolar tissue that was reported to have an increased accuracy rate for prediction of occult nipple involvement [78]. The authors suggest using sharp dissection and cold bistoury for tissue dissection to avoid artifacts that can be caused by cautery. They excised 1.5 cm diameter of tissue below the nipple base, and had 4 μm histologic sections cut at 200 μm intervals. The false-negative rate of the frozen section analysis was only 1.3 % (Table 9.3).

Table 9.2 Comparison of frozen section, cytology, and permanent histology of sub-nipple tissue in predicting occult nipple involvement

	Frozen section (%)	Imprint cytology (%)	Permanent histology (%)
Accuracy	87	77	87
Sensitivity	50	38	63
Specificity	92	82	90
Negative predictive value	44	21	46
Positive predictive value	93	91	95

From Duarte GM, Tomazini MV, Oliveira A et al. Accuracy of frozen section, imprint cytology, and permanent histology of sub-nipple tissue for predicting occult nipple involvement in patients with breast carcinoma. Breast Cancer Res Treat 2015; 153: 557–563 with permission

Local recurrences following NSM have been reported to range from 0.6 to 6 % with follow-up ranging from 13 months to 5 years [22, 79, 82, 85, 86]. Kneubil and colleagues evaluated risk factors of locoregional recurrence in patients who had false-negative frozen section or close margins of retroareolar specimens [82]. The 5-year cumulative rates of locoregional recurrence and NAC recurrence were 11.2 and 2.4 %. Locoregional recurrence rates were highest in patients whose retroareolar biopsies contained atypia. In situ carcinoma as the primary tumor was a significant predictor of NAC recurrence. Lohsiriwat and colleagues analyzed 861 cases of NSM treated with electron beam intraoperative radiotherapy [87]. With mean follow-up of 50 months, 36 patients (4.2 %) presented with local recurrences, among which seven (0.8 %) presented with Paget's disease of the nipple. Treatment of the Paget's recurrences consisted of excision of the NAC, and one patient with significant invasive disease received external beam radiation following NAC removal. After 47.4 months of additional follow-up, none of those with Paget's recurrences developed local or distant recurrence and all were alive at date of last contact. Significant predictors of Paget's recurrences included DCIS as primary tumor, invasive tumor with extensive intraductal component, negative hormone receptors, overexpression of Her2, and high tumor grade.

Management of positive margins after NSM includes re-excision, radiation, or no further treatment. Amara and colleagues performed 1176

Table 9.3 Comparison of false-negative rates of frozen section analysis of retroareolar biopsy

Reference	No. of patients	False-negative	%
Crowe et al. [79]	37	6	16.2
Benediktsson et al. [80]	205	3	1.5
Luo et al. [81]	52	8	15.4
Kneubil et al. [82]	948	88	9.3
Alperovitch et al. [83]	219	9	4.1
Eisenberg et al. [84]	325	9	2.8
Piato et al. [78]	158	2	1.3

NSM in 751 patients and identified nipple involvement in 2.7 % of cases [88]. Eleven (34 %) were treated with removal of the NAC, five (6 %) had radiation without removal of NAC, and eight (25 %) had no further treatment. With mean follow-up of 31.3 months, there were no recurrences in the preserved NAC. Camp et al. found 22 out of 438 (5 %) patients who had NSM with positive retro-areolar biopsies [89]. Management included excision of the nipple in eight patients and removal of the NAC in nine patients. Only 4/17 excised nipples had residual malignancy. The authors suggest that removal of the nipple or NAC may not be necessary in all cases of retroareolar involvement. Becker and Billington report a case of a patient who had NSM with a positive retroareolar margin who strongly desired preservation of the nipple skin [90]. The authors performed re-excision of the glandular tissue with preservation of the overlying nipple skin via direct vertical incision of the NAC to minimize disruption of the blood supply to the nipple. The base of the NAC was excised leaving only skin, and a drain and platelet-rich plasma were left in the subcutaneous pocket prior to wound closure. The authors reported successful nipple preservation with no necrosis.

Post-mastectomy radiation is another means of managing positive margins after mastectomy. Agarwal and Agarwal evaluated the Surveillance, Epidemiology, and End Results database from 2006 to 2010 and found that patients who had NSM ($n = 470$) were more likely to receive post-mastectomy radiation therapy compared to those who had mastectomy without preservation of the NAC ($n = 112, 347$) [91]. The authors did not have data regarding margin status; therefore, it is unclear if NSM cases had radiation for treatment of positive margins or merely for concern for leaving ductal tissue behind. Gomez and colleagues conducted a literature review of 30 studies of NSM with nipple involvement and found a paucity of data regarding the role of radiation therapy following NSM [92]. The authors reported rates of nipple recurrence in patients who did not receive post-NSM radiation to range from 0 to 12 %, compared to rates of 0 to 2 % for those who did receive post-NSM radiation, with a pooled review estimating a rate of nipple recurrence of 0.9 % in 2314 patients. Petit et al. evaluated over 1000 patients who had NSM with perioperative radiation therapy [86]. The authors report relapse rate of 1.4 %, although the low recurrence rate may be due to selection of low risk patients. Seventy-nine patients were found to have retroareolar involvement but there were no nipple recurrences, suggesting that radiation played a role in control of microscopic disease.

In summary, close or positive retro-areolar margins in NSM may be avoided by careful selection of patients. Close or positive margins are associated with increased risk of local recurrence and may be managed with re-operation or post-mastectomy radiation, although the benefit of radiation therapy in NSM remains unclear. More research is needed to identify whether there may be subgroups of patients with close or positive margins who can be managed expectantly.

Conclusion

NSM is associated with low rates of morbidity and mortality. Nipple and flap necrosis is a feared complication that rarely leads to harmful consequences if identified early and managed appropriately. Positive retro-areolar margins after NSM can be avoided by appropriate patient selection and use of intraoperative frozen section analysis. Local recurrence rates following NSM are low.

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