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Review

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Mitigating the impact of skin necrosis in reconstruction after nipple-sparing mastectomy

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Abstract

Skin flap necrosis is a common postoperative complication after breast reconstruction, with an incidence of up to 43.4% among patients undergoing nipple-sparing mastectomy. Necrosis can adversely impact aesthetics due to the need to excise nonviable tissue, and increase the risks of infection, implant loss, nipple-areola complex sacrifice and malposition. Patient-specific factors including age, body mass index, and breast size may affect the risk of necrosis. Mastectomy and reconstruction techniques (i.e., choosing between skin- and nipple-sparing mastectomy, and between autologous and alloplastic reconstruction) may also influence necrosis rates. Intraoperative measures such as indocyanine green angiography and autologous skin banking, and the postoperative use of nitroglycerin paste for high-risk patients and warming blankets for autologous reconstruction are methods to help prevent and minimize the morbidity of skin necrosis. Herein, we share our institution's approaches to predicting and mitigating skin necrosis, and methods of optimizing outcomes for breast reconstruction patients.

Keywords: Mastectomy, breast reconstruction, necrosis, autologous flap, implant

INTRODUCTION

Breast cancer is one of the most common forms of neoplasia in women; approximately 1 in 8 will develop it in their lifetime[1]. The number of mastectomies performed each year is rising both as a factor of the growing

incidence of breast cancer and the number of patients seeking prophylactic mastectomies for risk reduction[2,3]. As such, over 137,000 breast reconstructive procedures following mastectomy were performed in the United States in 2020[4]. Roughly 75% of these surgeries involved implant-based, or alloplastic, reconstruction, while the other 25% utilized autologous reconstruction.

The types and incidences of complications following both mastectomy and reconstruction are well-documented. Among the most prevalent of these adverse effects is mastectomy skin flap necrosis, caused by disruption of the vascular supply to the breast. Damage to the subdermal plexus and its deep perforators with subsequent skin necrosis has a documented incidence ranging from 1.4% to 43.4%[5-9]. This wide range is attributed in part to a lack of uniform definition of necrosis; different studies classify necrosis by various criteria, including the intervention needed, the timing of occurrence, the depth of necrosis, or the surface area of tissue involved[6].

Though the framework for determining necrosis may be up for debate, the negative impact is clear: while mild necrosis can be managed with local wound care, moderate to severe skin flap necrosis often requires debridement and reoperation in both alloplastic and autologous reconstructions[8,10,11]. Necrosis can lead to infection and/or implant exposure, ultimately resulting in reconstructive failure[6]. Prior studies have shown that mastectomy skin necrosis greater than 6 cm^2 after autologous reconstruction benefits from operative management due to prolonged healing with conservative care, and that necrosis exceeding 10 cm^2 can lead to severe breast distortion[11,12]. Revision for breast reconstruction is also costly and resource intensive[13,14].

The risk of developing mastectomy skin flap necrosis is influenced by a myriad of factors, including patient demographics and comorbidities, mastectomy technique, and reconstructive pathway. This review paper will detail each of these known risk factors, as well as the intraoperative techniques used to anticipate skin necrosis. We will also review postoperative strategies to prevent skin necrosis. Lastly, we will discuss the future directions of necrosis detection and treatment.

PREOPERATIVE PLANNING

Patient-specific risk factors

A number of both retrospective and prospective studies have identified potential risk factors for developing breast skin necrosis after mastectomy. Independent of both mastectomy technique and reconstruction type, these established determinants include increased body mass index (BMI), older age, diabetes mellitus, and tobacco use[10,12,15-18]. A history of breast irradiation and surgery, including augmentation and reduction, has also been shown to increase the risk of skin necrosis[5,9,17]. Based on our ten-year institutional cohort of 530 patients and 902 breast reconstructions, obesity (BMI > 30 kg/m^2) and hypertension were risk factors across all patients[19].

Increased breast size has also been implicated in skin necrosis, as measured through proxies such as mastectomy specimen weight and volume on mammograms[7,9,20]. However, we have shown that direct anatomic measurement in the preoperative period provides similar predictive power. During the initial consultation, we routinely collect five anatomic breast measurements: nipple-sternal notch distance, nipple-inframammary fold distance, chest width, breast height, and breast circumference [Figure 1]. In our experience, the risk of necrosis increases significantly with a nipple-sternal notch distance > 27 cm, nipple-inframammary fold distance > 8.5 cm, chest width > 15 cm, breast circumference > 29 cm, and breast height > 10.5 cm[21].

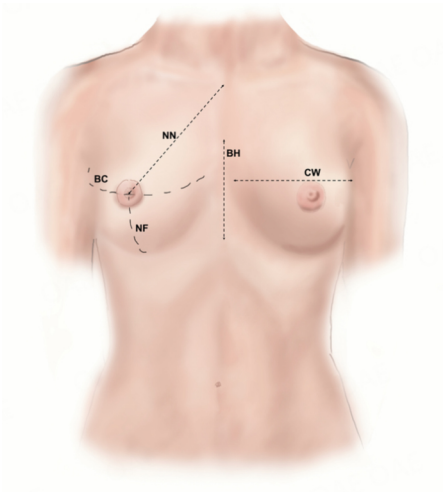

Figure 1. Breast size measurements that our institution takes preoperatively and uses to anticipate the risk of breast skin necrosis after mastectomy. BC: breast circumference; NN: nipple-notch distance; NF: nipple-inframammary fold distance; BH: breast height; CW: chest width.

These measurements not only provide valuable information during reconstruction, such as when selecting tissue expander size or determining DIEP flap dimensions, but they also allow us to calculate breast skin surface area through geometric approximations. In a prior study, we approximated surface area using a cone without its base and a half ellipsoid, and showed that the risk of necrosis increases significantly with surface area > 212 cm^2 on conical estimation and > 308 cm^2 on half ellipsoid estimation[21].

Mastectomy technique

Nipple-sparing mastectomy (NSM) has been shown to lead to psychosocial and sexual well-being compared to skin-sparing mastectomy (SSM)[22]. However, while NSM is oncologically safe, poor vascularity of the nipple-areola complex (NAC) can negatively impact overall results[23]. There is still inconclusive evidence that NSM leads to higher rates of skin necrosis than SSM; Matsen *et al.* and Lee *et al.* demonstrated a significant difference between the two, but Andersen *et al.* and Gould *et al.* found equal rates of skin necrosis[7,17,18,20]. The decision to pursue NSM *vs.* SSM is thus one that must take into account the balance between the risk of complications and quality of life, the comfort level of the breast surgeon performing the procedure, and the risk of skin necrosis at each practitioner's institution as surgical technique will vary.

One of the most significant contributors to breast skin necrosis, particularly in NSM, is the thickness of the mastectomy skin flap. Prior studies have reported that mastectomy skin flaps less than 5-8 millimeters in thickness place patients at increased risk of necrosis[13,15]. Frey *et al.* even introduced an incremental range of ideal flap widths as a function of patient BMI[24]. However, a predetermined thickness can be difficult to implement practically due to benign variations in anatomy; the thickness of breast skin and subcutaneous fat may not correlate with weight or age, and a distinct layer of superficial fascia may be present in only up to 56% of patients[15,25]. As reconstructive surgeons, we rely on our breast surgery colleagues' expertise in determining the appropriate skin flap thickness, treading a fine line between adequate oncologic resection and risking postoperative skin necrosis.

There are several surgical approaches for NSM, notably via inframammary fold (IMF), radial horizontal, radial vertical, and periareolar incisions. Periareolar incisions encompassing more than 30% of the areolar circumference are an independent risk factor for necrosis[26]. In fact, periareolar incisions have been shown

to result in necrosis more than radial horizontal, vertical and IMF incisions[5,15,27]. Carlson *et al.* reported an odds ratio of 9.69 ($P = 0.014$) when studying nipple necrosis after periareolar incision compared to all other incision types. After mastectomy, the branches of the internal mammary and lateral thoracic vessels that normally perfuse the NAC are disrupted; periareolar incisions further damage the subdermal plexus supplying the NAC, resulting in skin necrosis that particularly impacts this region. Our institution, like many others, preferentially uses IMF incisions when possible due to the reduced rates of skin necrosis, improved surgical access to the breast pocket, and aesthetic benefits of concealing the scar below the lower pole of the breast.

Reconstructive options

Patients deciding to pursue either implant-based or autologous reconstruction must consider oncologic treatment regimens, patient comorbidities, aesthetics, and recovery time, among other factors. Though skin necrosis is not the only outcome of interest, it is highly influenced by this choice; Sue *et al.* demonstrated a threefold difference in necrosis rates between autologous flaps and implants (30.4% in flaps, and 10.6% in implants), and Lee *et al.* found a higher rate of necrosis in free flaps compared to pedicled flaps, with an odds ratio of 1.575[18,28]. This increased risk is attributed to the acute stress placed on the breast skin during the microvascular reconstruction, compared to the often-employed two-stage alloplastic technique of slowly inflating tissue expanders (TE) before transitioning to permanent implants. Supporting this theory, higher initial TE fill volumes have been shown to predispose patients to skin necrosis[10,20]. A study by Sue *et al.* found that initial TE volumes greater than 200 mL were associated with an 11.4% risk of necrosis, compared to 5.4% in TEs filled less than 200 mL initially ($P = 0.02$)[10].

Our own study of 902 breasts across 530 patients found a significant difference between breast skin necrosis rates after immediate reconstruction with either DIEP flaps (373 breasts, 26.8% necrosis) or tissue expanders (529 breasts, 15.5% necrosis). However, after controlling for BMI and patient comorbidities, this difference became insignificant[19]. As our DIEP cohort had a significantly higher BMI, mastectomy specimen weight, and prevalence of diabetes, it is possible that these factors, rather than the procedure itself, may be to blame for increased rates of skin necrosis. Higher-BMI patients are better suited for autologous reconstruction than low-BMI patients given the need for sufficient donor tissue, leading to a selection bias that would be difficult to study in a controlled setting. Nevertheless, skin necrosis following autologous reconstruction is easier managed by banking skin during the index operation than in an alloplastic setting which may require a more aesthetically deforming surgery due to the risk of device extrusion and infection[8,28]. The timing of reconstruction can also impact the likelihood of skin necrosis. Though studies have shown that delayed alloplastic reconstruction is associated with reduced rates of necrosis[10], this method subjects all patients to an additional procedure, rather than just those who develop necrosis. These patients differ from those who undergo two-stage DIEP flap reconstruction with skin banking (discussed below) because the additional intermediate operation to place tissue expanders offers no new opportunity to improve cosmesis, as this can be done during the placement of a permanent implant.

We routinely perform delayed DIEP flaps with intermediate, or "babysitter", tissue expanders for patients undergoing post-mastectomy radiation therapy, so as to avoid irradiating the healthy flap. In our study of 344 immediate DIEP flaps and 99 delayed flaps, we found lower rates of skin necrosis in the delayed group compared to the immediate group (2.0% *vs.* 16.0%)[29]. There were no differences in other measured postoperative outcomes. Ultimately, we did not use these findings as an argument to perform delayed DIEP flaps on all patients, as the skin banking technique has provided adequate reconstruction without an additional procedure[13].

INTRAOPERATIVE STRATEGIES

Indocyanine green angiography

Though the incidence of skin flap necrosis is high, there are ways in which surgeons can both anticipate and even mitigate the effects of necrosis intra-operatively. Fluorescent imaging can aid in assessing mastectomy flap skin perfusion in real time, which can help predict the possible extent of skin necrosis[30]. The intra-operative use of fluorescence-guided imaging with indocyanine green (ICG) has been used in clinical practice for over fifty years to assess vascular perfusion. Specialties such as ophthalmology and cardiology have made ICG fluoroscopy a routine part of assessing pertinent vessels, such as retinal and coronary arteries[31]. ICG has multiple benefits in that it is nontoxic to the patient, remains contained within the circulatory system, and is cost-effective[32].

For the past 15 years, ICG fluoroscopy has been implemented to help assess mastectomy flap perfusion intra-operatively to predict skin flap viability[33]. Fluoroscopy can be used during autologous reconstruction to assess the patency of any free-flap microvascular anastomoses and subsequent flap perfusion, both intraoperatively and postoperatively[34]. It can also be particularly beneficial in pre-pectoral implant-based reconstruction where preservation of mastectomy skin is of utmost importance due to the risk of device extrusion.

One prospective study compared intraoperative skin perfusion using ICG-guided imaging to areas of the breast affected by postoperative skin necrosis and found that breast skin with < 25% perfusion intraoperatively was not viable 90% of the time, and areas with > 45% of perfusion on ICG imaging survived 98% of the time[33]. Surgeons can use this intraoperative information to remove any potentially nonviable skin at the time of mastectomy and to guide patient expectations postoperatively. Our imaging protocol calls for an injection of 10 mg of reconstituted dye (or 4 mL of solution) followed by a 20 mL normal saline flush. The imaging device of choice (e.g., Stryker Spy, Medtronic VisionSense) is brought onto the field and run for at least 2 min to allow sufficient time for visualization of contrast media in the mastectomy flaps. The false positive rate of ischemia is almost zero, but areas of delayed or poor perfusion on laser angiography may still be clinically viable. With NSM, excising even a small amount of skin near the incision may lead to nipple malposition and deformity. Therefore, it may be best to take a conservative approach if the area to be excised may lead to deformity. This requires patient handholding and preoperative counseling, as partial skin necrosis will take several weeks to mature and can appear alarming to the uninitiated. In our practice, all patients with potentially compromised skin have a warming blanket and nitroglycerin paste on the mastectomy flaps postoperatively, as discussed below.

Skin banking during autologous reconstruction

While fluorescent imaging using ICG may help predict the occurrence and extent of skin necrosis, skin banking during autologous reconstruction helps address the loss of tissue due to necrosis. Skin loss can significantly alter breast shape, nipple position, and overall breast symmetry[12]. Although skin grafting may mitigate these sequelae, it creates a color and texture mismatch to the bordering native breast skin and can be costly. In cases of skin necrosis in implant-based reconstruction, converting to an autologous reconstruction may be the sole option to address large areas of skin loss.

However, autologous reconstruction affords the surgeon the ability to bank donor skin in the event of skin loss from necrosis or if further resection is needed due to positive margins at the NAC. The use of banked skin to revise an autologous reconstruction has been demonstrated with abdominal flaps (TRAM, DIEP, SEIA) and with transverse myocutaneous gracilis flaps[35,36]. A recent retrospective study from our institution found that managing skin necrosis using banked skin was more cost-effective than using skin grafts with or

without acellular dermal templates when the incidence rate of skin loss exceeding 10 cm^2 surpassed 25.3%[13].

At our institution, DIEP reconstruction is performed in two stages following all NSM approaches: the first involves harvesting the flap and anastomosing it to the internal mammary vessels in a standard fashion. During the first stage, a large elliptical skin paddle is preserved on the flap for both banking and Doppler ultrasound monitoring of vascular patency [Figure 2]. After two weeks (ample time for skin necrosis demarcation and final pathology), we return to the operating room to completely remove the DIEP flap skin - both the banked portion as well as the monitoring paddle - if tumor margins are negative or if there is no skin necrosis. If tumor margins are positive or if there are significant amounts of full-thickness mastectomy skin flap necrosis, the banked skin is used to reconstruct the skin defect due to oncologic re-excision or necrosis. This technique provides a plan to manage necrosis and allows for improved cosmesis. Although a second procedure is not without its risks, such as flap hypoperfusion during induction of general anesthesia, we have not had any instances of flap failure attributed to the second stage banked skin excision in our ten-year experience. Standardizing these methods for all patients undergoing NSM can lead to increased patient satisfaction, cost-effectiveness, and overall stronger reconstructive outcomes. We have found that we use banked skin in 18% of cases: 15% from skin necrosis and 3% from positive margins on final pathology. With NSM, if the skin from the areola cannot be replaced, the circular areola will be excised and closed as an ellipse. Typically, the areola is 20% of the height of the breast and this leads to a profound asymmetry between breasts. The banked skin easily replaces the excised areola and ultimately ends up with a seamless reconstruction following nipple reconstruction and areola tattooing.

POSTOPERATIVE MANAGEMENT

For patients undergoing implant-based reconstruction, intraoperative indocyanine green angiography helps determine the postoperative management strategy. In those with patchy perfusion, significant secondary bruising, or atherosclerotic and vascular comorbidities, topical nitroglycerine is used to increase vasodilation and improve tissue blood flow[37]. In randomized controlled trials, this technique showed efficacy in reducing mastectomy flap necrosis rate[38-40]. At our institution, we use a 2% nitroglycerin ointment when clinical suspicion of potential necrosis is high. It is applied to the entire mastectomy skin flap at the end of the procedure and once more at 12 h postoperatively. As a general principle, nitroglycerin application is discontinued at the time of discharge to avoid systemic hypotension.

We have also explored other modalities of reducing partial- and full-thickness skin flap necrosis in a rodent model. Tacrolimus has been previously shown to increase lymphatic collateral drainage and reduce the incidence of lymphedema and venous congestion[41]. Our study randomized Sprague Dawley rats to receive either topical tacrolimus or placebo daily for one week before and one week after a dorsal skin flap was raised[42,43]. On histological evaluation and image analysis, the tacrolimus group showed significantly increased tissue viability, as well as reduced skin ischemia and full-thickness necrosis. Topical tacrolimus is a possible alternative or auxiliary ointment that may be trialed in high-risk patients, reducing lymphatic congestion and arterial insufficiency to prevent mastectomy skin flap necrosis. Given our promising experience with topical tacrolimus in a rodent model, future studies will examine its application and efficacy in humans, particularly in comparison to our current treatment algorithm with nitroglycerin ointment, as described above.

Aside from topical medications, warming blankets are used at our institution for patients at risk of mastectomy skin flap necrosis. The goal of their use is to attempt to further improve tissue perfusion through heat-induced vasodilation. Other centers have cited the use of space heaters, water-circulation blankets, and heating lamps to have similar effects. These adjunctive tools are widely used in the post-

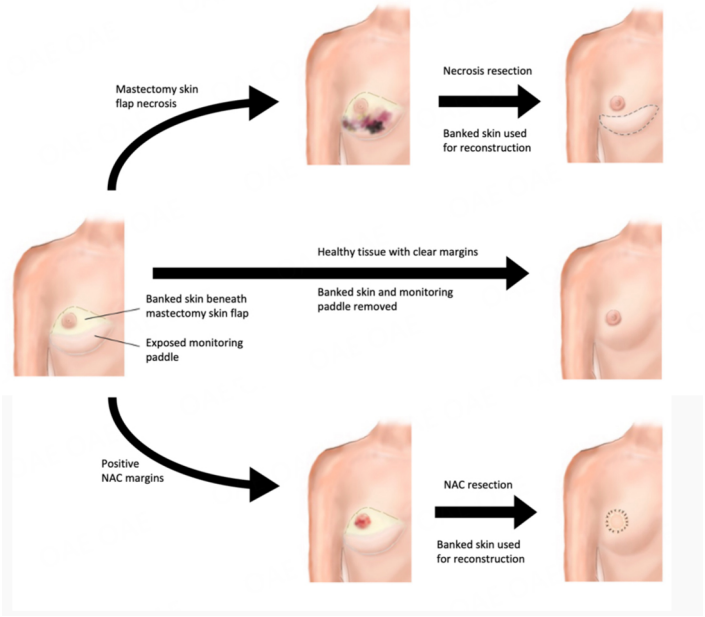

Figure 2. Skin banking during stage 1 of NSM with DIEP flap reconstruction. During stage 2, banked skin can be removed, or used to replace native breast skin in the event of necrosis or additional oncologic resection.

surgical management algorithm for maintaining core body temperature[44]. Heat-induced vasodilation not only improves skin perfusion following both alloplastic and autologous reconstruction, but also helps mitigate microvascular compromise in flap-based reconstructions[19,44]. However, care should be taken, as denervated skin lacks some of the protective vasodilatory effects of normally innervated skin and is therefore at higher risk of suffering thermal burns. Patients should not treat themselves with warming devices after discharge.

CONCLUSION

Skin flap necrosis is a common complication after mastectomy. It is influenced by patient factors such as age, BMI, diabetes, tobacco use, prior surgery, and irradiation. Larger breast size, both in terms of volume and surface area, also increase risk. In the operating room, nipple-sparing mastectomies, thin skin flaps, periareolar incisions, and autologous reconstructions may also promote skin necrosis. However, indocyanine green angiography can assist surgeons with early detection and management of necrosis, and banking skin flaps during autologous reconstruction can provide a cost-effective and aesthetically pleasing option for revision. In the postoperative period, topical nitroglycerin and external warming can improve skin flap perfusion and mitigate the severity of necrosis. In the future, other topical agents such as tacrolimus may be used in similar clinical settings without the systemic effects on blood pressure that limit the use of nitroglycerin. Clearly, while much is known about the risk factors, prevention, and treatment of skin necrosis after mastectomy, more studies must be done to further this field of knowledge and thus improve patient well-being.

DECLARATIONS

Authors' contributions

Made substantial contributions to the design of the study: Black GG, Otterburn DM

Made substantial contributions to manuscript writing: Black GG, Chen Y, Wang ML, Condez K
Made substantial contributions to figure illustration: Chen Y

Availability of data and materials
Not applicable.

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All authors declared that there are no conflicts of interest.

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Not applicable.

Consent for publication
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