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Review

Delay techniques for nipple-sparing mastectomy: A systematic review

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KEYWORDS
Nipple—areola complex-sparing mastectomy;
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Summary *Background:* Rare but serious complications of nipple-sparing mastectomy (NSM) include necrosis of the nipple—areolar complex (NAC) and mastectomy skin flaps. NAC and mastectomy flap delay procedures are novel techniques designed to avoid these complications and may be combined with retroareolar biopsy as a first-stage procedure. We performed a systematic review of the literature to evaluate various techniques for NAC and mastectomy flap delay.
Methods: PubMed and Cochrane databases were searched from January 1975 through April 15, 2016. The following search terms were used for both titles and key words: 'nipple sparing mastectomy' AND ('delay' OR 'stage' OR 'staged'). Two independent reviewers determined the study eligibility, only accepting studies involving patients who underwent a delay procedure prior to NSM and studies with objective results including specific outcomes of NAC and mastectomy flap necrosis.
Results: The literature search yielded 242 studies, of which five studies met the inclusion criteria, with a total of 101 patients. Various techniques for NSM delay have been described, all of which involve undermining the nipple and surrounding mastectomy skin to some degree. Partial NAC necrosis was reported in a total of 9 patients (8.9%). Mastectomy flap necrosis was reported in a total of 8 patients (7.9%). Three of five studies reported positive retroareolar biopsy findings in a total of 7 patients (6.9%).
Conclusions: Delay procedures for NSM have a good safety profile and may be considered in patients at risk for NAC or mastectomy flap necrosis, such as patients with pre-existing breast scars, active smoking, prior radiation, or ptosis. These procedures have the added benefit of allowing a retroareolar biopsy to be sent for permanent sections prior to mastectomy, allowing the surgical team to plan for the removal of the NAC at the time of mastectomy if indicated and eliminating the risk of a false-negative result on frozen section analysis.
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Contents

Background . . . 237
Methods . . . 237
Results . . . 237
Discussion . . . 238
Delay techniques . . . 238
Location of incisions . . . 240
Retroareolar biopsy . . . 240
Techniques in patients with nipple ptosis . . . 241
Conclusion . . . 241
Conflict of interest . . . 242
Sources of funding . . . 242
References . . . 242

Background

Nipple-sparing mastectomy (NSM) combines the skin-sparing mastectomy technique with preservation of the nipple—areolar complex (NAC). NSM is becoming increasingly more common as it provides a superior cosmetic result and has a good safety profile compared with traditional mastectomy. The procedure is associated with acceptably low local recurrence rates of 3—6% at 5 years, which is consistent with traditional mastectomy outcomes.[1,2]

One of the serious complications of NSM is partial necrosis of the NAC or the mastectomy skin flaps, which may be significant if the prosthesis lies directly beneath the skin flaps. Resultant prosthesis or allograft exposure may require additional surgical procedures, including device removal. Risk for NAC necrosis following NSM has been reported between 7% and 17%.[3—6] Characteristics that place patients at higher risk for NAC necrosis include nipple ptosis, high BMI, history of active smoking, and periareolar scars from previous surgery.[7,8] NAC and mastectomy flap delay procedures have been recently introduced as techniques that may reduce the risk of NAC or mastectomy skin flap necrosis, particularly in these high-risk patients.

Performing a delay procedure prior to NSM also allows the breast surgeon to send a retroareolar biopsy for examination by permanent section before the mastectomy. Intraoperative frozen section examination of retroareolar tissue is considered a critical diagnostic step in determining the eligibility for NSM. However, frozen-section analysis of retroareolar tissue is not as accurate as the analysis of permanent sections. The frozen section examined at the time of intraoperative examination cannot reveal as many features as the paraffin-embedded specimens on permanent pathology because of deeper cuts and the ability to use additional stains such as E-cadherin immunohistochemical analysis.[9] Frozen section examination of retroareolar tissue is highly specific (96—99%)[10,11] but has a wider range of reported sensitivities (as low as 66%).[10] The chance of a false-negative result on frozen section has been reported to be as high as 15.4% in patients undergoing NSM.[12] In patients with a false-negative result, the risk of locoregional recurrence is reported to be 11.2% at 5 years, which is higher than that with traditional mastectomy.[9] If performed as a first-stage procedure prior to NSM, delay procedures have the added benefit of reducing the risk of a false-negative result on frozen section. We performed a systematic review of the literature to evaluate various techniques for NAC and mastectomy skin flap delay.

Methods

PubMed and Cochrane databases were thoroughly searched by the authors from January 1975 through April 15, 2016. In addition, bibliographies of each relevant citation were reviewed for additional sources. The following search terms were used for both titles and key words: 'nipple sparing mastectomy' AND ('delay' OR 'stage' OR 'staged'). The initial PubMed search yielded 236 studies. The Cochrane database search yielded five studies. Two independent reviewers evaluated the titles and abstracts of all 242 studies without language restrictions and subsequently included or excluded studies based on the inclusion and exclusion criteria.

The authors included studies that were published in scientific journals, involved patients who underwent a delay procedure prior to NSM, and reported objective results including specific outcomes of skin flap and NAC necrosis. All types of reconstructive techniques were included. The authors excluded studies that were focused on procedures unrelated to NSM with delay, studies with fewer than 5 patients, and literature reviews.

Manuscripts of abstracts that met the criteria were reviewed as a second stage. In case of disagreement between the authors, a third senior author made the decision about whether the study should be included or excluded. After revising the list on the basis of our criteria, three studies were selected. The search algorithm is shown in Figure 1.

Results

The electronic literature search yielded 242 studies, 237 of which were excluded on the basis of our criteria. The final pool was comprised five retrospective studies with a total of 101 patients (Table 1). Delay techniques were evaluated

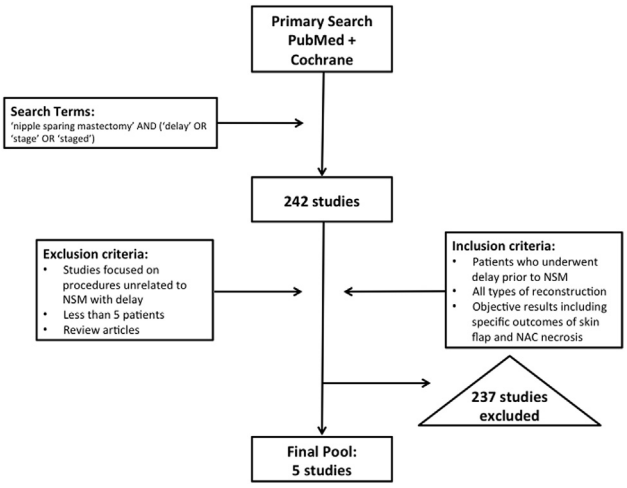

Figure 1 Search algorithm.

and compared, focusing on the location of delay and NSM incisions, degree of undermining, and special techniques used in patients with nipple ptosis. The primary outcomes used to compare studies were the reported rate of NAC and skin flap necrosis and any reported positive retroareolar biopsy results requiring removal of the nipple at the time of NSM.

Delay procedures were performed between 1 and 6 weeks prior to definitive NSM, using a variety of incisions and undermining techniques. None of the patients in these studies developed total NAC necrosis. Partial NAC necrosis was reported in a total of 9 patients, with an overall complication rate of 8.9%. Mastectomy skin flap necrosis was reported in a total of 8 patients, with an overall complication rate of 7.9%. Three of the five studies reported positive retroareolar biopsy findings in a total of 7 patients (6.9%).

Discussion

Delay techniques

Most delay techniques involve undermining the nipple and surrounding mastectomy skin to some degree. The techniques, patient characteristics, and results described in the five included studies are summarized below.

Palmieri et al. was the first to introduce the two-stage concept of delayed NSM in 2005. The first stage was performed on an outpatient basis using tumescent anesthesia. Laparoscopic instrumentation was used to undermine the NAC and surrounding skin, with the goal of detaching the NAC and surrounding mastectomy skin flaps from the underlying parenchyma and severing any vascular connections coming from this tissue. The second stage was performed 3 weeks later, in which the NSM was completed by creating a vertical or lateral incision and placing a textured silicone implant in the submuscular plane. They reported the development of partial NAC necrosis in only one out of a total of 18 patients (5.5%) and was attributed to thermal injury during the learning stages of the procedure.[13]

Jensen et al. described a technique for NSM delay that was applied to 20 patients classified as high-risk for NAC necrosis, determined by the presence of pre-existing breast scars, a history of active smoking, or significant nipple ptosis. In the first stage, dissection was performed beneath the NAC with transection of ducts connecting the breast gland to the nipple, and approximately 4—5 cm of surrounding mastectomy skin was undermined in all directions. This was performed through either a pre-existing scar or a vertical or lateral incision. In addition, a retroareolar biopsy was obtained at the time of this delay procedure, with excision of the NAC at the time of mastectomy if the biopsy was positive. They reported no NAC necrosis and reported a positive biopsy in 2 patients (10%) who then required the resection of the NAC at the time of mastectomy.[7]

Martinez et al. described a similar technique for surgical delay in 20 patients, and 13 of these patients underwent immediate reconstruction with a deep inferior epigastric perforator flap after NSM. The first stage involved an inframammary fold (IMF) incision, undermining of the NAC and mastectomy skin 5 cm medially and laterally and 2 cm superiorly, placement of a silicone sheet between the skin and breast tissue, and placement of a 15-French Blake drain in the inferior pocket. Retroareolar biopsy was performed at this stage. They reported no NAC necrosis, and 1 patient required debridement for mastectomy skin flap necrosis (5.0%). Two patients underwent nipple resection at the time of mastectomy based on positive retroareolar biopsy results (10%).[14]

Bertoni et al. recently reported the results of combining surgical delay with indocyanine green (IC-GREEN, ICG; Pulsion Medical Systems SE, Germany)-based intraoperative angiography for 28 high-risk patients undergoing NSM. Their technique was applied to patients with ptosis, BMI $\geq$30, prior breast surgery, prior radiation, and active smokers. The first stage, performed 3—6 weeks prior to NSM, included baseline imaging performed prior to NAC devascularization using ICG and the SPY Elite system (Novadaq Inc.). Using a periareolar incision, the NAC and approximately 5 cm of the surrounding skin were divided from the underlying breast tissue in the subcutaneous plane, and a retroareolar biopsy was obtained during the same procedure. The location of the periareolar incision was planned based on the arterial inflow pattern to the NAC to avoid transection of critical vascular inflow. During the second stage, NAC perfusion was again assessed with ICG-SPY, and the NSM was completed by a vertical or lateral incision, which was again based on the arterial inflow pattern. They reported partial NAC necrosis in only 2 patients (7.1%) and positive retroareolar biopsy results in 3 patients (10.7%), leading to NAC removal at the time of mastectomy.[8]

Delay procedures in patients with nipple ptosis may combine delay with a mastopexy or reduction mammoplasty as a first-stage procedure. Spear et al. (2011) described a two-staged approach for patients with nipple ptosis using mastopexy, with nipple repositioning and skin envelope reduction (with or without a small parenchymal resection) as a first-stage procedure. A Wise pattern or vertical approach was used, with both approaches involving circumareolar incisions. The authors emphasize that de-epithelialization with preservation of periareolar dermis is critical to first-stage mastopexy to maintain adequate NAC

Table 1 Summary of the included articles.

Author and year of publication	Number of patients	Delay technique	Indications for delay	Time between stages	Outcomes
Palmieri et al., 2005	18	First stage: Dissection beneath NAC and periareolar skin with local tumescent anesthesia and laparoscopic instrumentation Second stage: NSM (via vertical or lateral incision), retroareolar biopsy, and reconstruction with permanent implant	All patients who meet criteria for NSM	3 weeks	Partial NAC necrosis due to thermal injury in one patient (5.5%)
Spear et al., 2011	15	First stage: Wise-pattern or vertical mastopexy +/− reduction mammoplasty Second stage: NSM (via vertical limb of mastopexy or IMF incision), retroareolar biopsy, and reconstruction with TE (13) or permanent implant (2)	Patients who meet criteria for NSM with grade 2 or 3 nipple ptosis, in whom preservation of the NAC is important	3—4 weeks (minimum)	Partial NAC necrosis in 6/43 breasts (13.9%); Mastectomy skin flap necrosis requiring operative debridement in 7/43 breasts (16.3%) with one expander explantation for infection related to skin flap necrosis (active smoker)
Jensen et al., 2012	20	First stage: Dissection beneath NAC and 4—5 cm of surrounding mastectomy skin and retroareolar biopsy (through a pre-existing scar, vertical incision from NAC toward IMF, or lateral incision) Second stage: NSM and reconstruction with TE (13), latissimus flap + implant (4), free TRAM flap (1), or permanent implant (2)	Patients with nipple ptosis (NAC below the IMF and suprasternal notch to nipple distance of 26 cm or more), pre-existing breast scars, and history of active cigarette smoking	1—3 weeks	No NAC necrosis (0%); Positive retroareolar biopsies in 2 patients (10%)
Martinez et al., 2015	20	First stage: Dissection beneath NAC and mastectomy skin to 5 cm medial and lateral and 2 cm superiorly (via IMF incision), placement of a silicone sheet between skin and breast tissue, insertion of 15-French Blake drain at inferior pocket, and retroareolar biopsy Second stage: NSM and reconstruction with DIEP flap (13), permanent implant (5), or TE (2)	All patients who meet criteria for NSM	2—3 weeks	No NAC necrosis (0%); Mastectomy skin flap necrosis requiring operative debridement in one patient (5.0%); Positive retroareolar biopsies in 2 patients (10%)
Bertoni et al., 2016	28	First stage: Dissection beneath NAC and 5 cm of surrounding mastectomy skin and retroareolar biopsy using intraoperative imaging of NAC perfusion (ICG-SPY) to guide incision placement Second stage: NSM and reconstruction with autologous tissue transfer (5), TE (20), or permanent implant (2)	Patients with NAC or glandular ptosis, BMI $\geq$ 30, prior breast surgery, prior radiation, or active smokers	3—6 weeks	Partial NAC necrosis in 2 patients (7.1%); Positive retroareolar biopsy results in 3 patients (10.7%)

NAC (nipple areolar complex); NSM (nipple-sparing mastectomy), IMF (inframammary fold), TE (tissue expander), DIEP (deep inferior epigastric perforator), ICG-SPY (indocyanine green based intraoperative imaging using the SPY Elite system (Novodaq Inc.).

perfusion, particularly superiorly from the 9 o'clock to 3 o'clock positions. If parenchyma was excised, it was done through a central inferior wedge, leaving the superior dermis intact. In addition, only small parenchymal reductions were performed, typically with weights less than 100 g per breast. The second-stage NSM was performed a minimum of 3—4 weeks later, with a longer delay in patients undergoing adjuvant chemotherapy. The average time between stages was 3.4 months. The vertical limb of the mastopexy or an IMF incision was used for the second stage to avoid disrupting periareolar tissue. The overall complication rate was 20%, with 13.9% partial NAC necrosis and 16.3% skin flap necrosis requiring operative debridement. One patient who was an active smoker required expander explantation for infection related to skin flap necrosis.[15]

Location of incisions

Particular attention is paid to planning the location of incisions for NSM because of concerns over preserving NAC perfusion. In the first stage of NSM delay, incisions are usually placed within the planned NSM incision. Most authors agree that radial, lateral, vertical, and IMF incisions (Figure 2) are safer than periareolar incisions in terms of preserving blood supply to the NAC.[16,17] This is consistent with cadaveric and imaging studies, which suggest that the dominant blood supply to the NAC originates from superomedial source vessels off the internal mammary artery.[18,19] Additional blood supply through the branches of the lateral thoracic artery pass through deep breast tissue before ascending toward the NAC; however, these vessels would be divided during mastectomy.[20] Thus, it is important to preserve as much of the periareolar dermis as possible, particularly medially. Increased necrosis rates with NSM have been observed when using periareolar incisions involving more than 30% of the NAC without a delay procedure.[16,21,22]

Placement of incisions also depends on preoperative breast size. Although the IMF incision is aesthetically well hidden and preserves NAC perfusion, it may not provide adequate access to the upper quadrant of the breast in patients with large breasts.[17,23,24] Radial incisions starting at the lateral aspect of the NAC with a curved extension toward the axilla is the preferred incision for easiest access to the upper quadrant of the breast and axilla while still preserving NAC blood supply.[16,17] Options for patients with smaller breasts include an IMF incision or a vertical incision from the NAC extending inferiorly toward the IMF.[7,15]

In patients with previous breast scars, most authors prefer to place the incision within the previous scar, such as in the vertical limb of a mastopexy or reduction mammoplasty scar.[7,13] Performing NSM in patients with previous periareolar scars has been found to be safe with a low risk of NAC necrosis as long as the periareolar scars are avoided when making new incisions for the mastectomy. Special attention should be directed at maintaining blood supply through the periareolar scar tissue.[7] Vaughn et al. achieved 100% NAC survival after NSM in 11 patients with prior circumareolar incisions using an IMF incision for mastectomy in all cases.[25]

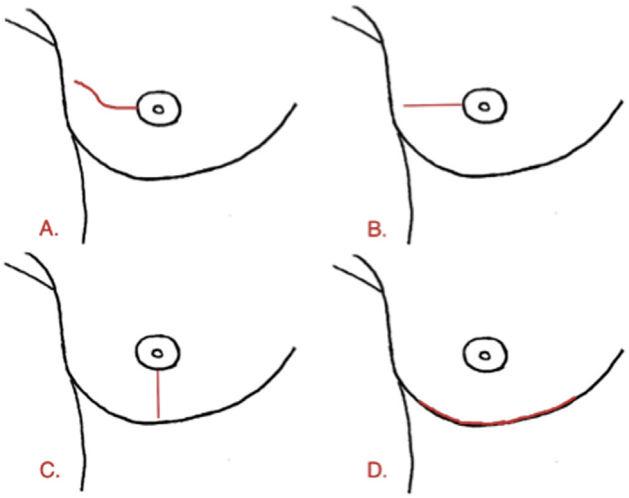

Figure 2 Preferred nipple-sparing mastectomy incisions. A. Radiolateral, B. Radial, C. Vertical, D. Inframammary.

Intraoperative imaging using ICG-SPY has become a commonly used adjunct in NSM, both in the assessment of NAC and mastectomy flap perfusion and in planning incision placement.[26] Bertoni et al. were the first to report the combining of this technology with a delay procedure in high-risk patients.[8] The authors examined NAC arterial inflow and classified patients into four groups according to the perfusion pattern and used this pattern to plan periareolar incisions for delay and mastectomy procedures. Patients with NAC perfusion coming predominantly through the underlying breast tissue, as opposed to from the surrounding skin, were found to be at higher risk for ischemic complications including epidermolysis and NAC necrosis.

Retroareolar biopsy

Delay prior to NSM provides the opportunity to send a retroareolar biopsy for permanent sections instead of sending frozen sections intraoperatively at the time of mastectomy. Three of the studies in our final pool reported sending retroareolar biopsies during the delay procedure, with positive biopsy results in as high as 10% of the patients in these studies. Because a positive retroareolar biopsy result requires the removal of the nipple at the time of NSM, this is valuable information to obtain prior to mastectomy. Knowing that the NAC needs to be sacrificed ahead of time allows the surgical team to contemplate an alternative technique for the mastectomy and reconstruction and prepare the patient appropriately.

An unexpected positive retroareolar frozen section can create some difficult choices for the plastic surgeon. If the incision used for the NSM is located away from the NAC, such as an IMF incision, a positive biopsy would be an extremely unfortunate intraoperative finding. Excision of the NAC at this time would require a second incision and may create a situation that increases the risk of mastectomy skin flap necrosis, particularly in cases of thin mastectomy skin flaps. In this case, the plastic surgeon may not be able to continue with the reconstruction that was originally planned.

In addition, permanent section analysis is more sensitive than frozen section analysis and eliminates the risk of a false-negative result, which would require an additional surgery to excise the NAC at a later date.[10] Furthermore, patients who are potential candidates for NSM but have questionable preoperative imaging on mammography may be assessed for suitability for NSM with the preoperative biopsy.

Techniques in patients with nipple ptosis

Patients with nipple ptosis who are otherwise candidates for NSM present a challenge to the reconstructive surgeon. Although once thought to be a contraindication to NSM, patients with ptosis are more recently being considered candidates for NSM using special techniques or staged procedures. Although most authors recognize that patients with severe ptosis are not candidates for NSM,[15,27] patients with moderate ptosis may be eligible. However, it is difficult to achieve a good cosmetic result in these patients without performing a mastopexy. Because mastopexy usually involves a circumareolar incision, this can be severely detrimental to nipple perfusion. In addition, patients with nipple ptosis are at increased risk for skin flap or NAC necrosis because they have long thin mastectomy skin flaps.[15] It should be noted that this discussion specifically pertains to ptosis of the nipple. Glandular ptosis without nipple ptosis, or pseudoptosis, is much less problematic regarding the preservation of NAC perfusion and can often be handled with a vertical or Wise pattern incision during NSM. Two of the five studies in the final pool reported the results of performing delay in patients with nipple ptosis.[7,15]

Woods first described performing NSM with simultaneous mastopexy for patients with ptosis in 1987 using either a donut or vertical skin excision pattern[28] and reported the results of using their technique in 33 patients.[29] When a donut mastopexy was performed, the periareolar skin was de-epithelialized with preservation of the dermis, and an IMF incision was used for the mastectomy. When a vertical mastopexy was performed, the skin inferior and superior to the nipple was de-epithelialized and inferior medial and lateral skin triangles were excised to create access for the mastectomy, effectively creating a Wise pattern skin excision. The authors reported wound complications in 18% of patients, including 3% rate of partial nipple loss and 6% rate of total nipple loss.

Rivolin et al. performed simultaneous periareolar mastopexy and NSM in 22 patients with mild-to-moderate ptosis using a radial lateral extension from the edge of the de-epithelialized periareolar skin for the mastectomy. They describe using extreme care in de-epithelializing the periareolar skin, avoiding any tears in the dermis to preserve blood supply to the NAC. There was a trend toward higher rates of partial and total NAC necrosis in this group compared to that in the traditional NSM group (18.2% vs. 2.9%), although the difference did not reach statistical significance.[27]

Spear et al. (2011) was first to introduce the concept of a two-staged approach for patients with ptosis, described above.[15] In the first-stage mastopexy, they used circumareolar incisions but emphasized maintaining periareolar dermis and performing only small parenchymal reductions when needed. Similar to other authors, the periareolar scars were avoided in the second-stage mastectomy, with incision placement in the vertical limb of the mastopexy or within the IMF. With no reports of total NAC necrosis, their rate of partial NAC necrosis of 13.9% is comparable to the reported risk for NAC necrosis after NSM in the literature.[3–6]

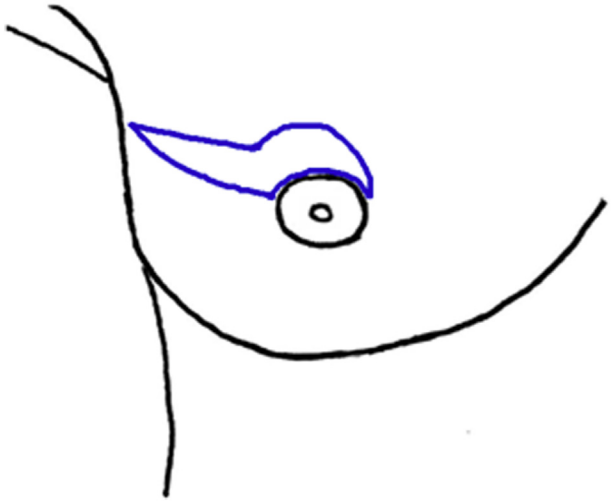

Figure 3 Hemi-batwing incision used for mastopexy with delay in patients with ptosis.

Jensen et al. described a modification of their delay technique in 8 patients with nipple ptosis (defined as nipple location beneath the IMF and sternal notch-to-nipple distance of 26 cm or greater) using a "hemi-batwing" incision. The skin excision pattern traveled halfway around the superior areola with a superolateral radial extension (Figure 3). At the time of delay, the inferior border of this pattern was incised, and the NAC and surrounding skin was undermined, preserving NAC perfusion through the inferior and medial periareolar dermis. This delay procedure allowed the safe removal of superior skin at the time of NSM with nipple elevation to a more normal position, with no reports of NAC necrosis.[7]

The reports of using delay procedures prior to NSM in patients with moderate nipple ptosis confirm that it is safe to perform a mastopexy as a first-stage procedure, with similar rates of NAC necrosis as those reported in the literature. However, the authors agree that careful attention should be paid to preserve the periareolar dermis, particularly superiorly and medially.

Conclusion

Delay procedures prior to NSM have a good safety profile, with complication rates that are comparable to those reported in the literature. The literature on delay procedures for NSM is limited, with only a small number of retrospective studies available. These procedures were designed to reduce the risk of NAC and mastectomy flap necrosis; however, larger retrospective and future prospective studies are needed to provide more support for this

hypothesis. NSM delay procedures may be considered for patients at high risk for NAC and mastectomy flap necrosis, such as patients with pre-existing breast scars, active smoking, prior radiation, or significant nipple ptosis. Future studies examining NSM delay in these high-risk patients would also be useful.

Conflict of interest

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Sources of funding

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