

## **Mastectomy Skin Flap Necrosis : Challenges and Solutions**

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## **Abstract**

*Introduction:* Mastectomy skin flap necrosis (MSFN) has a reported incidence in the literature of between 5 - 30%. It is often a significant and under-appreciated problem. The aim of this paper is to review the associated challenges and possible solutions.

*Methods:* A Medline search was performed using the search term "mastectomy skin flap necrosis". Titles and abstracts from peer-reviewed publications were screened for relevance.

*Results:* MSFN is a common complication and may be partial or full thickness. Predictive patient risk factors include smoking, diabetes, obesity, radiotherapy, previous scars and severe medical co-morbidity. MSFN leads to a number of challenges including wound management problems, delays to adjuvant therapy, aesthetic compromise, implant extrusion, patient distress and financial loss. Careful pre-operative planning and meticulous surgical technique may reduce the incidence of MSFN. A number of intra-operative techniques are available to try and predict skin flaps at risk of MSFN. MSFN may be managed operatively or non-operatively. Early intervention may reduce the morbidity of MSFN in selected cases. Topical nitroglycerin ointment may be beneficial in reducing MSFN following immediate reconstruction, but the evidence base is still limited.

*Conclusions:* MSFN can result in considerable challenges for the patient and the healthcare service. This paper discusses the management options for this problem.

## **INTRODUCTION**

Mastectomy remains a common procedure, and is performed on approximately half of women with symptomatic breast cancer and a quarter of those with screen-detected breast cancer in the United Kingdom (UK) (1). However, mastectomy skin flap necrosis (MSFN) (see Figure 1) occurs more commonly than appreciated, with reports in the literature ranging between 5 to 30% (2-10).

The recent UK National Mastectomy and Breast Reconstruction Audit (NMBRA) reported an overall incidence of approximately 5% (2). This national audit described outcomes in over 18,000 women undergoing mastectomy with or without reconstruction between 1 January 2008 and 31 March 2009 in the United Kingdom. In response to questionnaires collected 3 months after surgery, 4 per cent of women in the mastectomy alone group reported that the 'breast skin turned dark and died', whereas 6.1 per cent reported this complication in the immediate reconstruction group and 5.5 per cent in the delayed reconstruction group. Other series report even higher rates of MSFN for mastectomy with immediate reconstruction, ranging from 7 to 30% (3-10). Numerous factors may contribute to this high rate, including an increasing rate of immediate reconstruction using skin-sparing mastectomy (SSM) and nipple-sparing mastectomy (NSM) techniques (with the preservation of more skin / longer skin flaps) and a move towards more direct-to-implant reconstructions (11). Whilst SSM preserves the native breast skin envelope to optimise aesthetic outcomes, immediate reconstruction has been shown to

be associated with a higher complication rate than delayed procedures, of which a common early complication is MSFN (12-15).

MSFN ensues when the blood supply to the skin flaps is insufficient to meet their metabolic needs. It is therefore important to understand how blood is supplied to the breast and the overlying skin. Blood is supplied to the breast via perforating branches from the axillary artery, the internal thoracic artery and the second to fourth anterior intercostal arteries (16,17). Perforating cutaneous arterial and arteriolar branches deliver blood to the overlying breast skin, linking to form a continuous plexus. This plexus is best developed subdermally and on the undersurface of the subcutaneous fat (17). Interestingly, these subcutaneous vessels are found at a deeper level in breasts with a thicker layer of subcutaneous fat (18).

There are inconsistencies in the literature as to precisely what is meant by MSFN. Fortunately, a validated scoring system to assess the severity of MSFN has recently been described by the Mayo clinic, called the SKin Ischaemia and Necrosis score (SKIN score) (19). A SKIN score is given based on the depth and area of skin necrosis visible, and this correlates strongly with the need for reoperation. Depth is assessed with a four point letter score, with "A" being no evidence of MSFN through to "D" being full thickness skin flap necrosis. A four point numerical score is given for surface area of the deepest necrosis, with "1" being assigned for 0% surface area through to "4" for >30% of breast skin (or nipple areolar complex in cases of NSM). This simplified scoring system should allow a more accurate and

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reproducible description and quantification of MSFN and facilitate comparisons between future studies.

MSFN and wound breakdown leads to a number of challenges. These are summarized in Figure 3, and include immediate and long-term wound management problems, delays to adjuvant therapy, and aesthetic compromise (particularly to a breast reconstruction) through scarring and distortion. If implants or expanders are used, there is a risk of infection and extrusion. Also, the psychological morbidity to the patient from the resultant anxiety and distress from these complications should not be under-estimated. Strikingly, women who lose their implant have high rates of undergoing no further reconstruction (20).

The aim of this paper is to review the challenges of MSFN, along with possible solutions to this problem.

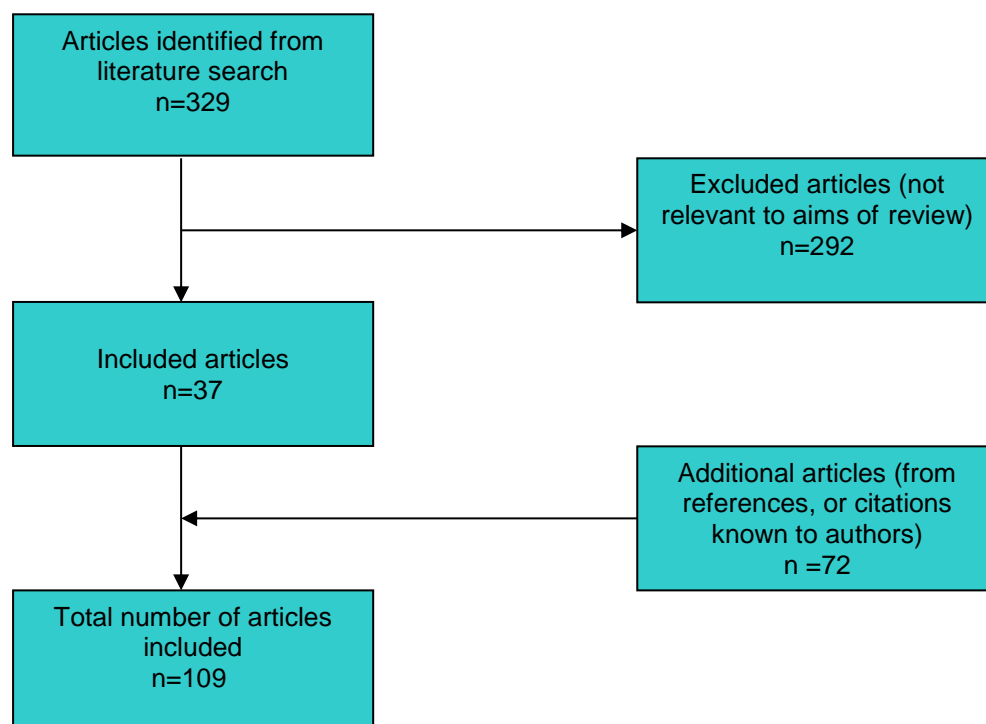
**Figure 1** Photograph showing T junction mastectomy skin flap necrosis post skin- reducing mastectomy and dermal sling assisted implant reconstruction. The dermal sling provided a vascularized bed, protecting the implant beneath and facilitating formation of healthy granulation tissue, permitting healing by secondary intention.



## METHODS

A Medline search was performed in March 2016 using the search term “mastectomy skin flap necrosis” (see Figure 2). Abstracts were screened for relevance to the aims of the review. All directly relevant primary studies were included and referenced. Articles not relevant to the aims of the review were excluded, as were abstracts and reports from meetings not included in peer-reviewed publications. Additional potentially important references known to the authors, or cited within relevant papers, were also investigated. Only articles published in English were included.

**Figure 2** Flow diagram showing selection of articles for review



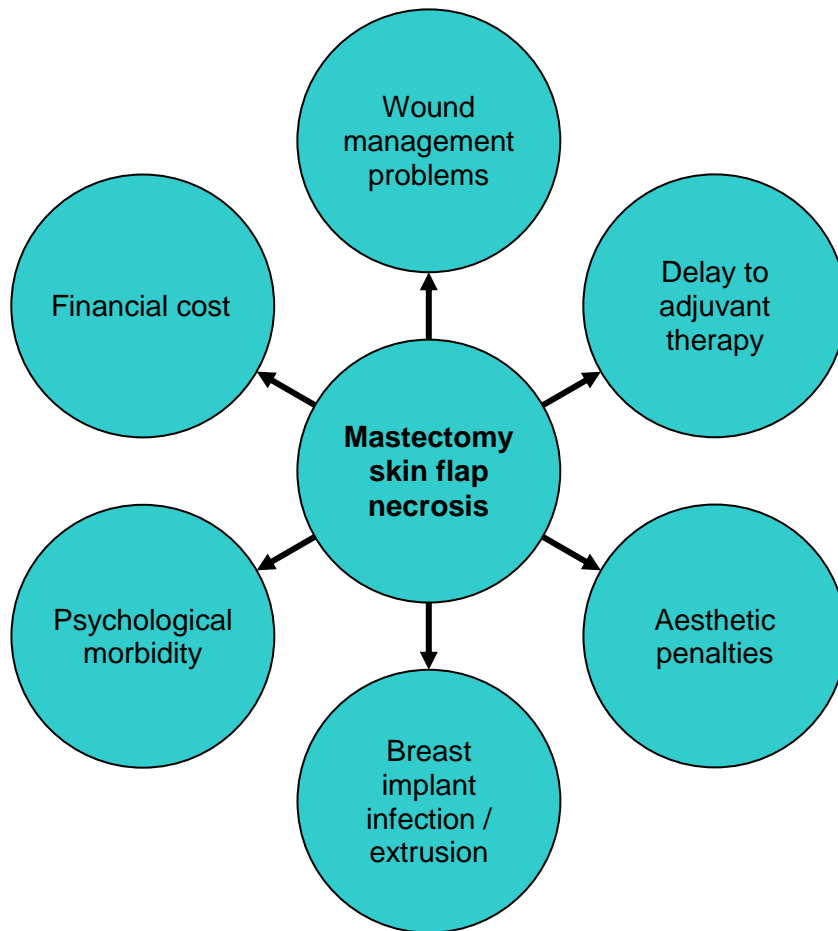
## **RESULTS**

The search identified 329 papers (see figure 2). Only articles published in English were included. 292 articles were excluded, as they were not relevant to the aims of the review. Abstracts or reports from meetings not included in peer-reviewed publications were also not included. 72 additional potentially important articles known to the authors, or cited within relevant papers, were included giving a total of 109 articles used for the review. The results of this MSFN review are presented under the following headings: challenges, prediction, detection, avoidance, and solutions.

### **Challenges**

MSFN and wound breakdown produce a range of challenges, including but not limited to immediate and long-term wound management problems, delays to adjuvant therapy, aesthetic penalties through scarring and distortion, risk of infection and implant extrusion, psychological morbidity to the patient (through anxiety and distress), and increased financial expenditure. These are illustrated in Figure 3 and outlined in more detail below.





**Figure 3** Potential consequences of mastectomy skin flap necrosis

MSFN may present as partial or full thickness necrosis. One of the difficulties in reviewing the literature is the inconsistencies in the definition of MSFN, as superficial wound breakdown may be managed very differently (with local wound care, for example) than full thickness necrosis (which may require surgical debridement). Management options for MSFN are discussed further later, but whichever option is chosen, there is oncological importance to start adjuvant chemotherapy or radiotherapy as soon as clinically possible. This is

commensurate with NICE guidance to start adjuvant therapy within 31 days of completion of surgery (NICE guideline CG80 section 1.6.8) and the European Society of Medical Oncology guidelines indicating that treatment should ideally start within 2 to 6 weeks of surgery. Several papers have shown that SSM and NSM do not lead to significant delays to the start of adjuvant therapy, even when re-operation for skin flap complications is required (21,22). However, oncologists may be understandably reluctant to administer chemotherapy or radiotherapy during compromised or delayed wound healing. More light may be shed upon the possibility of delay to adjuvant therapy following immediate breast reconstruction, when the results from the national UK Immediate Breast Reconstruction and Adjuvant therapy Audit (iBRA-2) are published (<http://ibrastudy.com/iBRA2.php>).

Scarring and distortion from MSFN can and will lead to aesthetic penalty, whether that is a thicker, wider or distorted scar following a simple mastectomy without reconstruction, through to distortion of the skin envelope in SSM or NSM, or even implant extrusion in implant-based reconstruction. Implant-based reconstruction accounts for approximately a third of all breast reconstructions in the UK (2) and around three quarters of all reconstructions in the United States (23). Complications can occur in up to 40% of cases (24) and 40% of patients may require revisional surgery (25). Over the last decade, implant-based reconstruction techniques have evolved from traditional two-stage procedures through to a single stage procedure. Two stage procedures involve initial placement of an expander (often with total submuscular coverage in a subpectoral pocket) followed by a second

procedure to replace this with a definitive implant. Single stage procedures involve the placement of a definitive implant usually in a subpectoral pocket, with either a dermal sling or a biological or synthetic mesh to provide infero-lateral implant coverage (26,27). Immediate implant-based breast reconstruction is now usually combined with a SSM or NSM technique. However, there is still relatively little high-quality evidence comparing the benefits and complication rates of these new procedures and so the UK Implant Breast Reconstruction evaluation study (iBRA) is currently prospectively investigating and evaluating these outcomes (<http://ibrastudy.com/Home.php>).

Patients experiencing visible necrosis of the skin, wound breakdown or discharge, may encounter psychological morbidity such as anxiety and depression, with a decline in their quality of life. MSFN has been shown to negatively impact on patient satisfaction and quality of life (28). Combined with the challenges of receiving a breast cancer diagnosis, recovering from surgery, and adapting to changes in the appearance and feel of one's own body following mastectomy, the subsequent additional burden of MSFN can be particularly difficult during the very challenging and vulnerable post-operative period (29-31). Support from the patient's Breast Care Nurse Specialist can be particularly valuable, alongside that from their surgeon and General Practitioner.

The prolonged wound management with skin flap necrosis, including outpatient appointments, dressings and equipment, or possibly repeat

admission and surgery if indicated, all produce an additional financial burden on healthcare resources (32). A retrospective study from Baltimore in the United States suggests MSFN results in a 50% increase in the cost of inpatient charges within 30 days of mastectomy and tissue expander reconstruction (33). At a time when healthcare systems around the world are under pressure for increased efficiency savings, with the UK's National Health Service no exception to this (34), it is important to consider techniques for anticipating and avoiding MSFN.

### **Prediction**

Skin flap viability may be influenced by both patient and surgical factors. If mastectomy skin flap perfusion with sufficient oxygenated haemoglobin is compromised, necrosis may ensue.

### **Patient risk factors for skin flap necrosis**

Patient risk factors include smoking (14,35-43), age (14,37,38,44,45), hypertension (14,45), previous scars (40), radiotherapy (13,15,21,35,40,42,44,46), diabetes (21), obesity (13,14,21,35,38,40,42-45,47-52), increased breast volume (38,48,53) and severe co-morbidities (54-57).

Smoking impairs wound healing and significantly increases the risk of MSFN following reconstruction (55). The purported mechanism of action of smoking on MSFN may be via nicotine (a known vasoconstrictor), reduced oxygenation of haemoglobin (via carbon monoxide binding) and increased platelet

aggregation (36,58-60).

There is certainly evidence that smoking cessation prior to surgery reduces post-operative complications, as shown in a systematic review and meta-analysis (61). This review examined a range of post-operative complications with different types of surgery and found that the longer the cessation the better, with each week of cessation increasing the magnitude of effect by 19%. However, it is unclear specifically how much smoking cessation is required to reduce MSFN, and this may not always be achievable in the often short time between diagnosis and surgery. Results from an experimental rat model investigating the duration of smoking cessation and its impact on skin survival with random pattern flaps suggests that 4 weeks of pre-operative smoking cessation is required for significant decreases in skin flap necrosis rates (62).

Whilst electronic cigarettes, or “vaping”, do not contain tobacco constituents, they still contain variable amounts of their primary constituent nicotine. Nicotine is known to cause vasoconstriction and inhibition of endothelial-dependent vasodilatation, and so skin flaps with a fragile blood supply may still be placed at risk in patients substituting electronic cigarettes for traditional cigarettes (63).

Previous breast conserving surgery (wide local excision and radiotherapy) may increase the incidence of MSFN, presumably mediated in part by the effects of previous chest wall radiotherapy (64).

Advancing age alone does not appear to be a risk factor for surgical complications following microvascular breast reconstruction (including MSFN) according to a retrospective series from Los Angeles (65). Moreover, it is specifically an increased number of medical co-morbidities and a poorer ASA (American Society of Anaesthesiologists) grade that are predictive of surgical complications. Therefore, the overall health status of the patient seems more predictive of surgical complications than age alone.

Diabetes Mellitus is generally considered a risk factor for vascular complications, owing to a range of vascular abnormalities that can develop, including altered blood viscosity, abnormalities in intimal repair, and abnormalities in endothelial cell, red cell and platelet function. A retrospective review from the MD Anderson centre reported 893 free TRAM (Transverse Rectus Abdominis Myocutaneous) flap reconstructions and found no difference in flap complications in diabetic patients, providing euglycaemia was maintained (66). Specifically, there was no significant difference in terms of the MSFN rate for subgroups with IDDM (Insulin Dependent Diabetes Mellitus) (9.8%), NIDDM (Non Insulin Dependent Diabetes Mellitus) (5.3%) and the non-diabetic group (7.7%). However, only patients with euglycaemia were included in this series, which may limit the broader application of these interesting findings to every diabetic patient being considered for mastectomy.

A large retrospective review of 718 patients undergoing mastectomy and immediate breast reconstruction in British Columbia looked for factors

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associated with MSFN (42). The overall rate of MSFN was 12.9% in this series with a number of patient and surgical risk factors identified as predictors of MSFN. BMI >30, smoking and pre-operative radiation were independent predictors of MSFN. Surgical factors included a longer duration of surgery and Wise pattern mastectomy incision. There was no difference in MSFN rate between immediate autologous versus implant based reconstruction methods in this series.

Mlodinow et al looked for factors predicting MSFN following immediate tissue expander breast reconstruction in their institution (37). 1566 mastectomies were reviewed, with a MSFN rate of 8.6%. Regression analysis revealed smoking status, increased age, tumescent mastectomy technique and high intra-operative expander fill volumes (>66.67%) to be associated with an increased risk of MSFN.

A retrospective review from Harvard of all immediate microsurgical breast reconstructions at a single centre investigated risk factors predictive of MSFN (67). The MSFN rate in this large series of 746 reconstructions was 13.4%. Univariate analysis revealed a significantly higher incidence of MSFN with a higher mastectomy weight ( $p < 0.001$ ), higher autologous flap weight ( $p < 0.001$ ), and in patients with a higher body mass index ( $p = 0.002$ ) and diabetes mellitus ( $p = 0.021$ ). Multivariate analysis showed significant associations between MSFN and both increasing mastectomy weight (OR 1.348 per quartile increase,  $p = 0.009$ ) and diabetes (OR 2.356,  $p = 0.011$ ). Possible explanations for the increased MSFN rate with larger mastectomy

weights could be the larger skin flap surface area with the larger breast volume, or perhaps increased skin tension on the flaps following reconstruction. These predictors may be particularly helpful in pre-operative counseling and procedure selection.

The majority of the literature investigating risk factors for MSFN is limited to retrospective series, with inconsistencies in the definition of MSFN and patient selection. However, Matsen et al have recently published a prospective study to address these limitations (68). This prospective study measured MSFN rates (scoring it mild, moderate or severe) and measured pre, peri and post-operative variables to look for associated factors, with 8 weeks of follow up. 606 consecutive mastectomies (SSM = 84%, NSM = 16%) with immediate reconstruction (implant or expander based = 94%, autologous = 6%) were performed. 85 (14%) underwent some form of MSFN. 46 (8%) were mild, 6 (1%) moderate and 31 (5%) severe. The median size of the necrotic tissue, reported as the largest single dimension, was 3cm (range 0-24cm), 9cm (range 1.5-15cm) and 8cm (range 0.5-26cm) respectively. 25 of the severe necrosis cases were not healed by 8 weeks following surgery. Nine breasts underwent debridement in theatre and four implants were lost. Univariate analysis for *any* MSFN showed smoking, history of breast augmentation, NSM and time from incision to specimen removal to be significant. In multivariate analysis, nipple sparing, time from incision to specimen removal, sharp dissection and previous breast reduction were significant for any necrosis. NSM was associated with higher rates of MSFN for every severity. In those with moderate or severe MSFN, univariate analysis showed BMI, diabetes,



NSM, specimen size and expander size to be significant. Multivariate analysis showed NSM and specimen size to be significant. Interestingly, the majority of MSFN was mild in this prospective study (the degree of necrosis being difficult to measure and quantify in retrospective studies), and so did not delay adjuvant therapy. Moderate and severe necrosis were less common, and return to theatre and implant loss rates were less than 2% in these groups. This may be due to their policy of full muscle coverage for expander-based reconstructions.

*Surgical technique and skin flap viability*

Surgical factors increasing the risk of MSFN include higher mastectomy weight (43,48), incision type (47,69-72) including the Wise pattern mastectomy incision (48), decreased mastectomy skin flap thickness (73), volume of tissue expander fill (45), and perhaps the mastectomy technique itself, such as the use of tumescence (37,44,45,47).

Lee et al performed a review of the rate of mastectomy flap complications for NSM and reconstruction at their institution (11). They found higher rates of mastectomy flap complications, including mastectomy flap necrosis and nipple loss, in implant-based techniques rather than autologous. This initially seems somewhat surprising, as one might have expected the autologous group to have more risk factors for MSFN, such as a longer operative time, and perhaps this technique is selected more often in women with larger more ptotic breasts, who may also tend to have a higher BMI. However, the patient and procedure related characteristics were reportedly similar between the

groups in this review. Whatever the true explanation for the differences observed in mastectomy flap complications between groups, this is an interesting finding in light of the trend towards increased numbers of implant-based reconstructions now being performed.

The determinants of optimum mastectomy flap thickness have previously been reviewed (73). A balance must be obtained during mastectomy between achieving clear resection margins, whilst not making the flaps so thin that they risk flap necrosis. This is achieved through careful adherence to the oncoplastic plane between the subcutaneous fat and the breast parenchyma. Subcutaneous tissue thickness can be extremely variable and does not correlate with Body Mass Index, patient age or the thickness in the other breast (74). The oncoplastic plane may be difficult to identify in some patients, and may be absent up to 44% of patients (75). However, once identified, close adherence to it is crucial to achieving both an oncologically sound SSM whilst preserving the blood supply to the skin. Along with meticulous surgical technique, a good knowledge of the blood supply to the skin and nipple of the breast may help to avoid MSFN in SSM and NSM (76).

Neoadjuvant therapy may help downsize tumours that are close to the skin, or adjuvant chest wall radiotherapy may be utilized for close resection margins, which might help avoid the need for overly thin skin flaps. MSFN rates close to 17% have been reported with flaps 4-5mm thick (77), whereas others have achieved rates of less than 5% with thicker 10mm flaps (78,79), suggesting that thicker flaps may reduce rates of MSFN. However, these reports are only

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case series, and not randomized controlled trial evidence, and the measurement methods for thickness are not standardized and are therefore difficult to reproduce.

There are of course various operator technical factors which may reduce the chances of MSFN, such as careful tissue handling (especially whilst raising the mastectomy flaps), avoiding tension during closure (especially important with Wise pattern incisions) and respecting the oncoplastic plane of dissection for mastectomy flaps, so they are not fashioned overly thin.

Whilst preservation of more breast skin during mastectomy (as in SSM or NSM) may improve the aesthetic results of breast reconstruction, MSFN rates remain high with this technique (80). NSM is a significant predictor of MSFN, as well as nipple areolar necrosis, and has been associated with higher complication rates in several studies (53,68,69,81).

Higher rates of MSFN have also been reported with the use of Wise pattern skin reducing mastectomy techniques and immediate reconstruction for large breast volumes (82). In this retrospective series, mastectomy weight was significantly associated with skin complications requiring surgery (age-adjusted OR per 100g=1.6; CI 1.1-2.3, p=0.02). This might be expected to some extent, as Wise pattern reduction techniques are inherently at risk of “T junction” necrosis, and larger breasted individuals requiring skin reduction may carry other contributory patient risk factors, such as an elevated BMI for example. As always, minimising skin tension is crucial in avoiding MSFN in

Wise pattern techniques.

Some surgeons inject saline into the subcutaneous plane (often with local anaesthetic and / or adrenaline), to perhaps “hydro-dissect” the breast off the skin flap if performed under pressure, or at least to make the fascial plane thicker and easier to adhere to, whilst also purportedly minimizing blood loss and the use of diathermy. It is argued that the liquid finds the plane of least resistance between the subcutaneous fat and the fat of the glandular breast tissue below. Anecdotally, this approach seems quite popular and effective across different units. However, the literature reports contrasting experiences with tumescence. Two retrospective case series urge caution, reporting this as a risk factor for the development of post-operative skin flap necrosis, whilst two more recent studies (one prospective) did not find tumescence to be a significant factor for MSFN. Chun et al report tumescent mastectomy technique as a significant risk factor for MSFN after mastectomy and immediate reconstruction in a retrospective series of 380 consecutive cases (OR 3.98;  $p < 0.001$ ) (44). Other risk factors in this series included previous irradiation, age and Body Mass Index. Mlodinow et al also report tumescent mastectomy technique to be associated with MSFN in their large series of 1566 immediate tissue expander reconstructions (37). However, these retrospective series do not prove causality. On the other hand, two very recent publications indicate that tumescence is not a significant risk factor for MSFN (10,83). These contrasting findings suggest that other factors may be involved.

It has also been suggested that the use of diathermy rather than scalpel dissection may increase the MSFN rate, presumably via coagulation injury to the adjacent subdermal plexus. However, in a retrospective study of 151 SSMs, there was no significant difference between diathermy or scalpel dissection (48).

Carlson et al have looked at predisposing factors for nipple ischaemia after NSM in a prospective series of 71 NSMs (84). 40 mastectomies were for cancer and 31 were risk reducing (n=45 patients). The majority were expander or implant reconstructions, with only 3 flap-based reconstructions. Partial nipple necrosis occurred in 28.2% of cases and the majority healed uneventfully, with only one case requiring secondary nipple reconstruction. Higher rates of nipple necrosis occurred with periareolar incisions (OR 9.69, CI 1.57 – 59.77, p=0.014) or excision of the ducts from the undersurface of the nipple (OR 10.54, CI 1.88-59.04, p=0.007).

### **Detection**

A number of methods and devices have been employed to assess tissue perfusion intra-operatively in order to try and avoid mastectomy flap necrosis, but none have achieved universal acceptance. Intra-operative devices are often not readily available in all hospitals, and can be expensive or time consuming when compared to traditional methods of clinical evaluation of skin flap perfusion. Therefore, in resource-limited environments, their use may be best reserved for operations at higher risk of MSFN. The various different methods of evaluation have been reviewed and helpfully summarized in

tabulated form, along with supporting references, by Gurtner et al (85). The ideal system would allow accurate identification of the supplying vessels (and their corresponding perfusion zones), accurate assessment of tissue perfusion, and delineation of vulnerable tissue at risk of necrosing. For breast reconstruction, particularly implant-based, the earlier that MSFN is detected, the better. Ideally, areas of non-viable skin or areas of dubious viability would be detected intra-operatively, permitting excision during the mastectomy, before necrosis ensues. For implant-based reconstructions, it may also provide an opportunity to consider choosing a smaller implant, or perhaps choosing an expander in such cases, according to surgeon judgement and preference.

If ischaemic areas are not identified intra-operatively, early post-operative detection may still allow excision and resuturing, and may save an underlying implant from potential infection and extrusion (86).

Clinical evaluation of flap perfusion has been the traditional and most widely used method to assess the adequacy of the remaining blood supply, once the underlying breast has been removed (87). Traditional methods of skin flap viability assessment include assessment of skin colour, capillary refill, skin temperature and dermal bleeding. However, clinical evaluation alone has its limitations (88,89) leading to the development of several technologies that can be used intra-operatively, including handheld Doppler (90), laser Doppler flowmetry (91,92), fluorescein angiography (56,93,94) and indocyanine green angiography (95).

Doppler ultrasound is somewhat limited by being inherently operator dependent, whilst laser Doppler flowmetry may underestimate flap survival and the equipment is large. Fluorescein dye testing has been used to evaluate skin flaps in plastic surgery for many years and may play a role in the evaluation of equivocal mastectomy flap viability, allowing excision of areas with poor perfusion unlikely to survive. The fluorescein dye is injected intravenously and a wood's lamp used to evaluate flap fluorescence. Losken et al studied this in the periareolar skin of 50 SSM flaps (56). Flaps with areas of non fluorescence  $>4\text{cm}^2$  tended not to survive, whilst areas  $<4\text{cm}^2$  typically would survive, except in the irradiated breast. However, fluorescein techniques are limited by the long half-life of the contrast medium, preventing re-evaluation during the intra-operative period and risking false-positives.

Indocyanine green contrast agent has shown some encouraging results in the intra-operative assessment of mastectomy flap perfusion and prediction of subsequent flap necrosis. A large case series from Emory University has looked specifically at indocyanine green angiography in predicting MSFN in a prospective cohort of 118 patients undergoing SSM and breast reconstruction (80). 14 patients experienced postoperative skin flap necrosis. Skin with 25% perfusion or less was not viable 90% of the time, whilst areas with greater than or equal to 45% perfusion survived 98% of the time. This may be a useful adjunct to the prediction and avoidance of MSFN. Intra-operative indocyanine laser perfusion assessment tools, such as the SPY system (LifeCell Corp., Branchburg, NJ) have been used to identify mastectomy skin

flaps at risk of subsequent ischaemia and necrosis (96). Indocyanine green was used to evaluate mastectomy flap perfusion in 39 patients undergoing mastectomy and immediate breast reconstruction with a prosthesis, and this was compared to 52 patients in the pre-SPY era. The post-operative complication rate in this retrospective study was reported as two fold higher in the pre-SPY group, but this did not reach statistical significance ( $p=0.06$ ). However, the number of repeat visits to theatre was significantly higher in the pre-SPY era. Five of the seven patients with complications in the post –SPY group were identified by SPY as having poor flap perfusion, but none were identified with clinical judgement alone. The main limitations of this study were its small size and retrospective non-randomised design, but it still suggests that the SPY system may be able to contribute peri-operatively to the identification of tissue at risk of ischaemia and necrosis. Indocyanine green has also been used to describe specific nipple-areolar complex perfusion patterns and may be a helpful adjunct in evaluating higher risk perfusion patterns in NSM to try and avoid ischaemic complications (97).

Indocyanine green angiography has the advantage of a short half-life and good safety profile. It is also cleared rapidly from tissues facilitating repeat evaluations of tissue perfusion during the same procedure. It may have advantages over clinical evaluation or fluorescein techniques in predicting MSFN (43). However, although this method may aid in predicting necrosis, it only appears cost effective if used selectively for high-risk cases (98). A prospective trial has compared two intra-operative vascular imaging techniques with clinical assessment to assess mastectomy skin flap perfusion



to predict areas of necrosis (43). Laser-assisted indocyanine green dye angiography, fluorescein dye angiography and clinical assessment were all compared to evaluate the skin flaps of 51 tissue expander – implant reconstructions (n=32 patients). 21 cases (41.2%) underwent “all-inclusive necrosis”, of which 6 cases were full thickness, 5 (9.8%) of which required intervention. Unsurprisingly, statistically significant risk factors for necrosis included smoking, obesity, and a breast weight of over 1kg. However, laser-assisted indocyanine green dye angiography and fluorescein dye angiography over-predicted areas of necrosis by 72% and 88% respectively (p=0.002). The laser-assisted indocyanine green dye angiography was a better predictor of MSFN and more specific than fluorescein dye or clinical assessment, but would over predict MSFN without quantitative analysis.

The intra-operative oxygen tension of mastectomy skin flaps can be measured, as reported in a pilot study by Rao et al (99). In this small series of 10 patients undergoing simple mastectomy or SSM, only one patient developed flap necrosis and the authors identified a reduction in skin flap oxygen saturation and flap length as predictors of this. This non-invasive technique requires further evaluation before any recommendations can be made regarding its use in MSFN prediction.

### **Avoidance**

Unfortunately, many patient risk factors are not modifiable in the time scale between diagnosis and surgery. Where patients are assessed as having a high risk of MSFN, performing a simple mastectomy with a delayed

reconstruction may permit both the timely administration of any adjuvant therapy but also more time for modification of any adjustable risk factors prior to reconstruction.

Very large tumours may benefit from downsizing with neoadjuvant therapies prior to surgery in selected suitable patients, which may avoid the need to fashion ever-thinner mastectomy skin flaps to achieve tumour clearance, and thus reduce the chances of MSFN. Consideration ought to be given within the Multi Disciplinary Team (MDT) as to which patients might benefit from neoadjuvant chemotherapy (100) or neoadjuvant endocrine therapy (101,102).

Khavanin et al performed a retrospective review of 966 consecutive patients undergoing SSM or NSM and expander based reconstruction at a single institution in Chicago between 2004 and 2012 (45). They were looking for risk factors for MSFN requiring surgical excision and found that necrosis rates were higher in the high fill cohort than the low fill cohort (10.4% vs 7.1%  $p=0.027$ ). However, multivariate logistic regression did not identify high expander fill volumes as an independent risk factor for MSFN. Interestingly, four risk factors were identified that acted synergistically with high fill volume to increase the risk of MSFN, namely tumescence (Synergy Index (SI)=25.3), followed by hypertension (SI=2.39), obesity (SI=2.28) and age greater than 50 (SI=1.17). Acellular Dermal Matrix (ADM) use was not associated with MSFN in this study. The authors suggest that the epinephrine in the tumescent solution may reduce dermal blood flow sufficient to put the flap at risk of

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necrosis, whilst the small vessel disease associated with the other three risk factors may also decrease mastectomy skin flap perfusion, which then go on to manifest as full thickness necrosis in the setting of high intra-operative fill volumes. This study has significant limitations of course, not least the retrospective nature, being from a single centre, and it only addresses those variables documented in the records, when other factors may be at play. However, despite these limitations, using smaller intra-operative inflation volumes for expanders in higher risk cases may reduce the incidence of significant MSFN.

Interestingly, Gdalevitch et al from the University of British Columbia have recently reported the results of a Randomised Controlled Trial into the effects of applying nitroglycerin ointment (a potent topical vasodilator of both arteries and veins) to mastectomy skin flaps following immediate reconstruction (103). A single application of 45mg of nitroglycerin ointment (2%) was applied to the mastectomy skin flaps at the end of the operation at the time of dressing application, and the dressings left in place for 48 hours. They terminated the study after 165 patients had been recruited (85 to treatment, 80 to placebo), as the interim analysis showed a significant reduction in MSFN in the group receiving the nitroglycerin ointment (15.3% flap necrosis rate) versus placebo (33.8% flap necrosis rate;  $p=0.006$ ). They conclude that application of this vasodilator “is a simple, safe and effective way to help prevent mastectomy skin flap necrosis”. However, the evidence base in support of its widespread use is still somewhat limited as this was only a single study on 165 patients.

## **Treatment**

MSFN can be managed operatively or non-operatively. Operative management firstly necessitates debridement of necrosed tissue, and then several options to deal with the skin loss, including resuturing, replacing skin (with grafting or flaps), conversion to another breast reconstruction (where indicated), or allowing healing by secondary intention. Non-operative options involve allowing the necrosed tissue to shed and subsequent healing by secondary intention, but this requires regular and active wound management entailing numerous dressing changes, often over a prolonged period, whilst this process occurs. Wound management devices, such as vacuum dressings, may aid wound healing, particularly for larger areas of necrosis.

No clearly defined course of action exists, with management often decided on a case-by-case basis, in line with surgeon preference. The risk of further operation in order to expedite wound healing must be weighed up against a protracted course of wound healing, requiring long term dressing care. Some feel that patients at higher risk of MSFN, or with full thickness defects, should be treated more aggressively (9). Patients awaiting the timely administration of adjuvant therapy may benefit from operative management to try and expedite wound healing (104).

## **Non-operative management**

Non-operative management remains the favoured course of action for MSFN following simple mastectomy, or with autologous reconstruction, with skin

grafts reserved for massive skin necrosis (21). Allowing the wound to heal by natural wound contraction and re-epithelialisation may lead to less significant contour defect and avoid the patch appearance of a skin graft (4). The use of hyperbaric oxygen has had successful results within case reports, but has no robust evidence to support its use (105,106).

Non-operative management involves the use of dressings, such as alginates and silver preparations (to reduce bacterial burden) in a dynamic fashion, adapting to wound appearance, improvement and patient preference. Antimicrobials may be required in case of infection, while small areas of eschar may be debrided in the outpatient setting (4,104). Wound management devices, such as vacuum dressings, may facilitate wound healing, particularly where larger areas of necrosis are encountered.

#### Operative management

Consideration of early operative intervention for MSFN is particularly important where there is an underlying implant reconstruction. Partial thickness MSFN with an underlying vascularised dermal sling may be suitable for non-operative management (as demonstrated in Figure 1). However, where an ADM has been used, consideration should be given to early excision of any skin necrosis and resuturing, to try and save the implant from extrusion (86).

Where the risk of MSFN is considered to be very high during mastectomy, other operative management strategies may involve the use of skin banking

(107) or skin grafts, which may either be split or full thickness, using redundant abdominal dog ear tissue, for example (9).

Skin banking is a method of delayed inset of the flap - the autologous tissue is not de-epithelialised at the time of primary reconstruction and is placed into the subcutaneous pocket, providing options where there is questionable viability of skin flaps, should native mastectomy skin necrose (4,107). However, this does commit the patient to a second operation and therefore should perhaps be reserved sparingly for patients with multiple risk factors, where it is considered very likely they will experience skin necrosis.

There has been a report of excising a questionably viable skin flap, thinning it and then replacing it as a full thickness skin graft following radical mastectomy (108). Whilst this was reported in relation to radical mastectomies in the 1970s, it could be theoretically applicable to any graftable bed, but is not widely used.

Rates of NSM are on the increase, but this procedure carries with it the attendant risk of nipple necrosis. This has been extensively reviewed by O'Connell, and may be avoided through a combination of careful surgical technique and a good working knowledge of the skin and nipple vasculature (76). However, when it does occur, it may be treated by excision of the nipple.

The technique of "surgical delay" has been reported to improve nipple-areolar complex (NAC) survival rates (109). This is where the NAC is disconnected

from the tissue beneath a few weeks prior to NSM, allowing the blood supply from the adjacent breast skin to augment, but also allowing confirmation of clear retro-areola margins. If the biopsy proves to be involved, the NAC can then be removed at the subsequent mastectomy. Jenson et al report very good NAC survival rates with this technique.

### **CONCLUSIONS:**

This paper has reviewed the challenges of MSFN, along with possible solutions. In summary, MSFN occurs more frequently than perceived, reported somewhere in the range of 5 – 30% of cases in the literature. MSFN may be partial or full thickness. A SKIN score based on depth and extent correlates with the need for reoperation. Patient risk factors for MSFN include a history of smoking, obesity, diabetes, previous radiotherapy, previous scars and severe medical co-morbidities. Careful pre-operative planning may reduce the chances of MSFN, such as modification of patient risk factors (where feasible), consideration of neoadjuvant therapies, considering the most appropriate type of and timing of reconstruction for that individual's risk profile, for example, perhaps avoiding immediate SSM in very high risk cases. Surgical technique plays an important role in avoiding MSFN, including optimizing mastectomy skin flap thickness and using the oncoplastic plane. A number of intra-operative techniques have been developed to detect areas of skin at risk of MSFN, including clinical evaluation, handheld Doppler devices, laser Doppler, fluorescein angiography and indocyanine green techniques. MSFN leads to a number of challenges, including immediate and long-term wound management problems, delays to adjuvant therapy, aesthetic penalty,

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risk of infection and extrusion of breast implants, psychological morbidity, and an increased financial burden. A recently published RCT has reported that nitroglycerin ointment applied to mastectomy skin flaps following immediate reconstruction may reduce the incidence of MSFN, but the evidence base is still limited. MSFN may be managed operatively or non-operatively, depending on the individual case. Early intervention in selected cases may avoid or reduce some of the possible adverse consequences, such as implant loss.

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The authors declare no conflicts of interest.



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