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## Skin Flap Necrosis After Mastectomy With Reconstruction: A Prospective Study

Cindy B. Matsen, MD<sup>1</sup>, Babak Mehrara, MD<sup>2</sup>, Anne Eaton, MS<sup>3</sup>, Deborah Capko, MD<sup>4</sup>, Anastasia Berg, BS<sup>4</sup>, Michelle Stempel, MPH<sup>4</sup>, Kimberly J. Van Zee, MD<sup>4</sup>, Andrea Pusic, MD<sup>2</sup>, Tari A. King, MD<sup>4</sup>, Hiram S. Cody III, MD<sup>4</sup>, Melissa Pilewskie, MD<sup>4</sup>, Peter Cordeiro, MD<sup>2</sup>, Lisa Sclafani, MD<sup>4</sup>, George Plitas, MD<sup>4</sup>, Mary L. Gemignani, MD<sup>4</sup>, Joseph Disa, MD<sup>2</sup>, Mahmoud El-Tamer, MD<sup>4</sup>, and Monica Morrow, MD<sup>4</sup>

<sup>1</sup>Breast Care Team, Department of Surgery, Huntsman Cancer Institute at the University of Utah, Salt Lake City, UT

<sup>2</sup>Plastic and Reconstructive Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY

<sup>3</sup>Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY

<sup>4</sup>Breast Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY

### Abstract

**Background**—Rates of mastectomy with immediate reconstruction are rising. Skin flap necrosis after this procedure is a recognized complication that can impact cosmetic outcomes and patient satisfaction, and, in worst cases, potentially delay adjuvant therapies. Many retrospective studies of this complication have identified variable event rates and inconsistent associated factors.

**Methods**—We designed a prospective study to capture the rate of skin flap necrosis and pre-, intra-, and post-operative variables with follow-up to 8 weeks post-operatively. Univariate and multivariate analyses were performed for factors associated with skin flap necrosis.

**Results**—Out of 606 consecutive procedures, 85 (14%) had some level of skin flap necrosis: 46 (8%) mild, 6 (1%) moderate, 31 (5%) severe, and 2 (0.3%) uncategorized. On univariate analysis for any necrosis, smoking, history of breast augmentation, nipple-sparing mastectomy, and time from incision to specimen removal were significant. In multivariate models, nipple-sparing, time from incision to specimen removal, sharp dissection, and previous breast reduction were significant for any necrosis. When looking only at moderate or severe necrosis, BMI, diabetes, nipple-sparing mastectomy, specimen size, and expander size were significant on univariate analysis. Nipple-sparing mastectomy and specimen size were significant on multivariate analysis. Nipple-sparing mastectomy was associated with higher rates of necrosis at every level of severity.

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Address correspondence and reprint requests to: Cindy Matsen, MD, Breast Care Team, Department of Surgery, Assistant Professor, Huntsman Cancer Institute at the University of Utah, (T) 801 581 2304, (F) 801 585 3749, cindy.matsen@hsc.utah.edu.

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**Conclusions**—Rates of skin flap necrosis are likely higher than reported in retrospective series. Modifiable technical variables have limited impact on rates of necrosis. Patients with multiple risk factors should be counseled about the risks, especially if they are contemplating nipple-sparing mastectomy.

### Keywords

skin flap necrosis; mastectomy; breast reconstruction

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## INTRODUCTION

Mastectomy is a common procedure which is increasingly chosen by patients for breast cancer management. At present, nearly 40% of women in the United States with breast cancer undergo mastectomy each year, and increasing numbers are opting for immediate reconstruction<sup>1,2</sup>, making the potential complications of the procedure of great clinical interest.

The most recent national data indicate that the choice of procedure is becoming dichotomized, with women choosing either bilateral mastectomies or breast conservation.<sup>1-5</sup> In contrast to lumpectomy, which is an outpatient surgical procedure with very low complication rates, mastectomy with reconstruction generally requires an overnight stay and has higher complication rates. Wound complications, including flap necrosis, are the most common complication and may significantly impact both cosmetic outcomes and costs. Severe flap necrosis may delay adjuvant chemotherapy or radiotherapy. Additionally, an increasing number of women undergoing mastectomy with reconstruction are opting for nipple-sparing procedures. Ischemia of the nipple and areola are common with this procedure, and flap necrosis of this area and the surrounding skin are recognized complications.<sup>6,7</sup> As surgical practice and patient choice continue to evolve, it is important to define risks of potential complications to improve patient selection and counseling during the decision-making process.

Reported rates of skin flap necrosis range from 2%–22% in retrospective studies.<sup>8-15</sup> The literature is inconsistent due to differing definitions of skin flap necrosis and variable patient selection criteria. Studies have shown many factors to be associated with skin flap necrosis including smoking<sup>9,13,14,16</sup>, obesity<sup>8,9,12,14,15,17-19</sup>, incision type<sup>11,20-22</sup>, age<sup>14,16-18</sup>, hypertension<sup>14,18</sup>, tumescence<sup>16-18</sup>, volume of tissue expander fill<sup>17,18</sup>, and larger breasts.<sup>8,23</sup> To address the limitations in the literature, we designed a prospective study to determine the rate of skin flap necrosis after mastectomy with reconstruction and to identify potentially modifiable factors that could improve patient selection and outcomes.

## METHODS

With approval from the Institutional Review Board, the Breast Surgery Service and the Plastic and Reconstructive Surgery Service at Memorial Sloan Kettering Cancer Center developed a list of potentially important patient- and surgeon-level study variables. Pre-, intra-, and post-operative data with follow-up to 8 weeks post-operatively were collected prospectively on all patients undergoing unilateral or bilateral mastectomy and

reconstruction from September 10, 2013 to February 28, 2014. There were no exclusion criteria, and we included patients with prior cancer treatment, neoadjuvant chemotherapy, skin-sparing or nipple-sparing mastectomy, and tissue expander, implant, or autologous tissue reconstruction. All surgeons from both services participated. Intraoperative, pre-precision measurements of flap dimensions were performed as diagrammed in Fig 1. At completion of the mastectomy, the Plastic Surgery team determined if over 5cm of dermis was exposed on the mastectomy flaps. The plastics team also trimmed the skin flaps intraoperatively to facilitate wound closure or when vascular compromise was noted based on visual inspection. The indication for trimming was not captured; indocyanine green imaging was not used in this study.

Skin flap necrosis was defined as mild (no intervention needed, fully healed at 8 weeks), moderate (office debridement, fully healed at 8 weeks), or severe (OR debridement, implant loss, or not fully healed at 8 weeks).

All analyses were done per breast, not per patient. Patient characteristics were summarized using frequency and percentage for categorical variables, and median and range for continuous variables. Factors associated with any necrosis and moderate/severe necrosis were identified using univariate logistic regression models with oncologic surgeon and reconstructive surgeon random effects to account for possible correlation between outcomes from the same surgeon. Factors with  $p < 0.1$  on univariate analysis were candidates for inclusion in the multivariate models, and backward selection until all variables had  $p$ -values of  $< 0.1$  was used to create the final models. Because expander size was only defined in the subgroup with implant/tissue expander reconstruction and width of the skin ellipse was only defined in patients with skin-sparing mastectomy, separate models were built on these subgroups to allow these variables. All statistical analysis was performed in SAS 9.2 (SAS Institute, Cary, NC). Two-sided  $p$ -values  $< 0.05$  were considered significant.

## RESULTS

During the study period, 606 mastectomies were performed in 376 patients; there were 146 unilateral mastectomies and 230 bilateral mastectomies. 279 (46%) were for invasive cancer, 69 (11%) were for DCIS, 1 (0.2%) was for malignant phyllodes tumor, and 257 (42%) were risk-reducing mastectomies.<sup>24</sup> Median patient age was 48 (22–76) years, and the median body mass index (BMI) was 25.3 (16.5–50); 324 (53.5%) procedures were in overweight patients (BMI $>25$ ), and 133 (21.9%) were in obese patients (BMI $>30$ ). Patient and operative characteristics are listed in Table 1.

There were 511 (84%) skin-sparing mastectomies and 95 (16%) nipple-sparing mastectomies included in the study. Tissue expander or implant reconstruction accounted for 567 (94%) of the reconstructive procedures, and the remaining 39 (6%) were autologous tissue reconstruction procedures (10 TRAM, 24 DIEP, 5 latissimus dorsi). Acellular dermal matrix was used in 48 (8.5%) of the expander/implant cases. Of the 230 bilateral procedures (460 breasts), 131 (33% of breasts, data missing for 65 breasts) were performed by two teams of breast surgeons (i.e., a fellow and attending, and two assistants for the case). Twelve breast surgeons and 6 plastic surgeons participated in the study.

### Any skin flap necrosis

Overall, 85 (14%) breasts in 67 patients had some degree of skin flap necrosis: 46 (8%) mild, 6 (1%) moderate, and 31 (5%) severe. Two (0.3%) patients with skin flap necrosis were not categorized because they received follow-up at other institutions. The median size of the necrotic tissue was reported as the largest single dimension and was 3 (0–24) cm, 9 (1.5–15) cm, and 8 (0.5–26) cm, respectively. 25 of the severe necrosis breasts were categorized as such because they were not healed by 8 weeks postoperatively, 9 breasts underwent debridement in the OR, and 4 implants were lost (Table 2).

Smoking (current or in the last 6 months) ( $p=0.05$ ), history of breast augmentation ( $p<0.01$ ), nipple-sparing mastectomy ( $p<0.01$ ), and time from incision to specimen removal ( $p<0.01$ ) were significantly associated with any degree of necrosis by univariate logistic regression analysis. Previous breast reduction, diabetes, sharp dissection, and expander size were not statistically significant, but had  $p$ -values of  $<0.1$  and were included in the multivariate models. Two multivariate models were built. One excluded the expander/implant size variable to allow inclusion of all patients, regardless of reconstruction type. A second model included the expander/implant size variable and only included cases undergoing TE or implant reconstruction. In the first model, nipple-sparing ( $p<0.01$ ), time from incision to specimen removal ( $p<0.01$ ), sharp dissection ( $p<0.01$ ), and smoking ( $p=0.03$ ) were significantly associated with any degree of necrosis (results not shown). In the second model, these factors remained significantly associated with any degree of necrosis, except smoking ( $p=0.08$ ), and previous breast reduction ( $p<0.01$ ) was also associated with necrosis (Table 3). No significant differences in rates of necrosis were found between oncologic or plastic surgeons on either analysis.

### Moderate or severe necrosis

On univariate analysis of factors associated with moderate or severe necrosis, BMI ( $p<0.01$ ), diabetes ( $p<0.01$ ), nipple-sparing mastectomy ( $p<0.01$ ), specimen size ( $p=0.03$ ), and expander size ( $p=0.02$ ) were significant. Width of the skin ellipse was not significant, but had a  $p<0.1$  and was included in the multivariable models.

We first built a multivariate model on the subset of patients who had skin-sparing mastectomy and TE/implant reconstruction that included the expander/implant size and width of skin ellipse variables. Both of these variables were eventually dropped out of the model, which allowed us to include all procedures in the final model. In the final model, only nipple-sparing mastectomy ( $p<0.01$ ) and specimen size ( $p<0.01$ ) were significantly associated with moderate or severe necrosis (Table 4). No significant differences were found between oncologic or plastic surgeons in rates of moderate or severe necrosis.

Nipple-sparing mastectomy was associated with significantly more skin flap necrosis at all levels of severity ( $p<0.01$ ) (Fig 2).

## DISCUSSION

During the study period, the overall rate of skin flap necrosis after mastectomy with reconstruction was 14%. This is higher than many published retrospective reports<sup>11–13</sup>, but

represents a more accurate estimate because prospective data collection allowed us to identify mild necrosis which, by our definition, does not require debridement or a return to the operating room and is unlikely to be well documented in the medical record. We chose to define the degree of necrosis in easily reproducible terms and found that the majority of necrosis was mild, did not delay adjuvant therapy, and likely had little impact on the patient's experience, though we did not specifically measure this.

Moderate and severe necrosis have a much larger impact on patient outcomes and were much less common. Returns to the operating room and implant loss were rare, with each occurring in <2% of patients. This is lower than previously reported rates of 2.7% and 2.5% from our institution.<sup>10</sup> Those studies looked at reconstructive failure out to 6 months after surgery, which likely accounts for the difference. We specifically did not limit our definition of severe necrosis to these events, however, as delayed wound healing without need for return to the operating room can also significantly impact outcomes. If a patient is not healed by 8 weeks postoperatively, this indicates a more severe degree of ischemia and/or wound healing problems, which may be associated with infection, increases the risk of dehiscence, and can potentially delay the receipt of adjuvant therapy.

Though we had very few implants lost, these patients warrant special interest as prior studies have shown that patients who lose their implant have a high rate of foregoing any further reconstruction.<sup>25</sup> The low implant loss rate in our study may be due, in part, to our practice of full muscle coverage whenever possible for TE based reconstruction.

Smoking status has been the most consistent patient level factor to be associated with skin flap necrosis after mastectomy with reconstruction, more than doubling the risk of necrosis in prior studies.<sup>13,14,16</sup> We did not show this factor to be significantly associated with any skin flap necrosis nor moderate to severe necrosis on multivariate analysis. This may be due to our definition of current or past smoking status, which included those who had quit in the last 6 months.

Prior breast-reduction surgery was also significantly associated with any necrosis in our study. This variable has not been examined in prior studies limiting comparisons. The presence of prior incisions on the breast likely results in more ischemia in the dissected flaps, thereby contributing to necrosis.

Breast size measured by cup size<sup>23</sup> and BMI<sup>17,19,26</sup> have previously been shown to be associated with skin flap necrosis. We measured these variables as well as specimen size, and clearly all are highly correlated. On multivariable analysis, only specimen size was found to be associated with moderate to severe necrosis, suggesting that it represents a more specific identification of the reason why cup size and BMI have been significant factors in the past.

Though technical variables had limited impact in our study, there are a few that merit discussion. Tumescence has been shown in prior studies to be associated with skin flap necrosis<sup>16,17</sup>, but this was not a significant factor in our study, consistent with a study by Khavanin et al in 2014.<sup>26</sup> These varying results could be a signal of surgeon or institution variability. In our study, sharp dissection (knife versus cautery) was associated with any

necrosis, but not moderate to severe necrosis, and this has not been previously identified as a risk factor. Time to specimen removal was also a significant risk factor for any necrosis, but not moderate to severe necrosis. This variable, too, has not been identified in prior studies and is likely related to specimen size and surgeon experience. All of the attending surgeons in this study are breast specialists, but time in practice ranged from 1 to more than 20 years, and trainees did participate in the majority of cases. The level of participation varied, and we were not able to capture this variability in our data. It is possible that rates may be even higher in centers with less experienced surgeons.

Nipple-sparing mastectomy was the most significant predictor of skin flap necrosis and has been associated with higher complication rates in multiple studies.<sup>11,23,27</sup> Our study confirms that patients choosing this procedure have a significant risk not only of necrosis of the nipple areolar complex but of skin flap necrosis also. While this may not deter patients from this choice, it does warrant a more extensive conversation to ensure they understand the potential outcomes. Studies on other modifiable variables that may decrease complications for this procedure, such as incision type<sup>11,23,27</sup>, are inconsistent. While the long-term oncologic outcomes for nipple-sparing mastectomy are still not well established, it is clear that the acute complication rates are significantly higher than complication rates in skin-sparing mastectomy. This may be offset with the overall higher satisfaction with outcomes in these patients.<sup>28,29</sup> The level of satisfaction, however, is affected by the occurrence of post-operative complications, including skin flap necrosis, again warranting a frank discussion with patients who choose this procedure. These patients may benefit from nipple-areola delay procedures aiming to improve the blood supply of the nipple areola complex, an approach which merits further investigation.

Identification of patients undergoing nipple-sparing mastectomy with the highest risk of ischemic complications could be useful. A study from Stanford used intraoperative skin perfusion assessment using laser-assisted indocyanine green angiography (SPY Elite) prior to mastectomy to identify patterns of perfusion associated with ischemic complications of the nipple-areolar complex.<sup>30</sup> This technique has also been applied to skin-sparing mastectomy and was found to correlate well with patient outcomes.<sup>31</sup> While this method may help to identify patients at higher risk for necrosis, it is not cost-effective if applied broadly<sup>32</sup>, and we did not use this method in our study. Even with optimal patient selection, the SPY information may not be clinically useful as most surgeons are hesitant to default to primary removal of the nipple-areolar complex even when the SPY results indicate extremely poor perfusion.

Though we collected data on a large number of procedures, some variables are underrepresented. Prior radiation therapy has been studied as a risk factor for skin and wound complications after mastectomy<sup>9,17,19,33,34</sup>, and is underrepresented in our study population, with only 7% of patients having prior radiation. We also have no specific data on traction injury, though flap length, incision size, and time to specimen removal may be surrogates of this. In addition, there are likely other modes of injury that contribute to flap necrosis.

While the rates of skin flap necrosis do vary somewhat by institution and individual, this study provides evidence that the rates of any necrosis are likely higher than reported in many retrospective series. While modifiable technical variables had little impact on rates of clinically significant skin flap necrosis, patients with multiple minor risk factors may be targeted for counseling regarding this risk, especially if they are contemplating nipple-sparing mastectomy. Discussing the potential for wound healing complications is especially important for patients electing risk reducing mastectomy. Studies to evaluate interventions to decrease the incidence of flap necrosis in high-risk patients are warranted.

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**Synopsis**

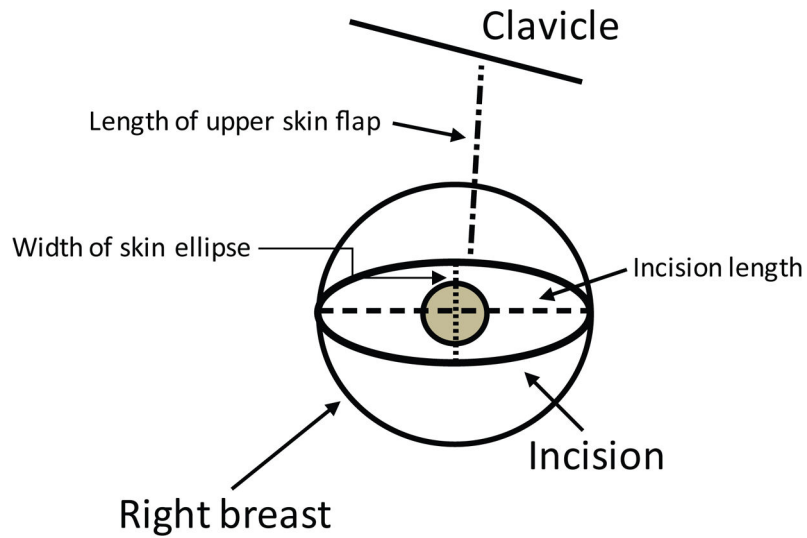
Skin flap necrosis after mastectomy with reconstruction is a recognized complication. Here we identified multiple risk factors, but found little impact of modifiable technical variables. Nipple-sparing mastectomy was associated with higher rates of necrosis at every level of severity.

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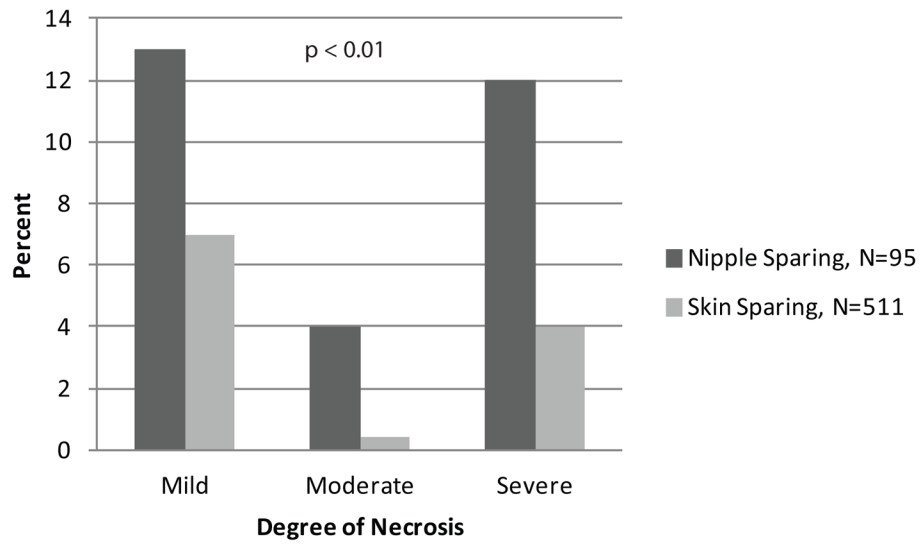
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**Fig 1.**

Diagram of intra-operative pre-incision measurements. Incision length was measured as the horizontal distance between the lateral and medial ends of the incision. Width of skin ellipse was only used for skin-sparing procedures and was measured as the distance between the superior and inferior aspects of the incision. Length of the upper skin flap was measured from the midpoint of the superior incision to the midpoint of the clavicle.



**Fig 2.** Comparison of severity of skin flap necrosis by type of mastectomy, skin sparing (N=509) and nipple-sparing (N=95). Nipple-sparing mastectomy was associated with more severe degrees of necrosis ( $p < 0.01$ ).

**Table 1**

Patient and intraoperative characteristics (all numbers are per breast)

	Characteristic	N (%) or median (range)
<b>Patient characteristics</b>	Age	48 (22–76)
	BMI	25.3 (16.5–50.0)
	Smoking, current or past	238 (39%)
	Hypertension	73 (12%)
	Steroid use	5 (1%)
	Collagen vascular disease	11 (2%)
	Diabetes	22 (4%)
	Bra Size (N=586)	
	A	64 (11%)
	B	186 (32%)
	C	175 (30%)
	D or larger	161 (27%)
<b>Prior treatments or procedures</b>	Neoadjuvant chemo	43 (7%)
	History of RT	44 (7%)
	Prior breast biopsy/lumpectomy	138 (23%)
	Prior breast augmentation	16 (3%)
	Prior breast reduction	14 (2%)
<b>Mastectomy factors</b>	Specimen size (g) (N=520)	547 (74–2428)
	Time to specimen removal (min) (N=532)	43 (13–233)
	Two breast teams (vs one) (N= 524)	131 (25%)
	Sharp dissection (vs cautery)	65 (11%)
	Tumescence	45 (7%)
	Width skin ellipse (excludes nipple sparing) (cm) (N=478)	5 (1–23)
	Length upper skin flap (cm) (N=476)	15 (2–27)
	Length incision (cm) (N=560)	12 (5–47)
	>5cm flap exposed dermis (N= 489)	56 (11%)
	Intraoperative trimming of flap (N=483)	248 (51%)
<b>Axillary procedures</b>	No axillary procedure	216 (36%)
	SLNB only	303 (50%)
	SLNB converted to ALND	45 (8%)
	ALND only	41 (7%)
	Prior SLNB	1 (0)
<b>Reconstructive factors</b>	Expander (vs permanent implant) (N=566)	551 (97%)
	Expander/implant size (excludes autologous flap)(ml)(N=551)	400 (125–750)
	Intraoperative expander fill (ml) (N=551)	180 (30–420)
<b>Cancer characteristics</b>	Invasive carcinoma	279 (46%)
	DCIS	69 (11%)
	LCIS	7 (1%)

Characteristic	N (%) or median (range)
Malignant phyllodes	1 (0)
No cancer found	250 (41%)
Tumor size (cm) (N=361)	1.5 (0.01–9.8)

BMI, body mass index; RT, radiation therapy; SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection; DCIS, ductal carcinoma in situ; LCIS, lobular carcinoma in situ

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**Table 2**

Rates of skin flap necrosis by clinical severity

<b>Degree of Necrosis (N=604)</b>	<b>N (%)</b>
Mild (no intervention, healed at 8 weeks)	46 (8)
Moderate (clinical debridement, healed at 8 weeks)	6 (1)
Severe (operative debridement, implant loss, or not healed at 8 weeks)	31 (5)

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**Table 3**

Factors associated with *any* skin flap necrosis on univariate (UVA) and multivariate (MVA) analyses. Factors with  $p < 0.1$  on UVA were candidates for MVA; backwards selection was used for determine final factors included in MVA. MVA includes patient with TE/implant reconstruction only. N=502 for MVA.

Factor	UVA OR (95% CI)	p-value	MVA OR (95% CI)	p-value
Age (OR per 10-year increase)	0.90 (0.70–1.15)	0.398		
BMI (OR per 1 unit increase)	1.03(0.99–1.07)	0.161		
Cup size C or larger	1.26(0.78–2.04)	0.338		
Smoking, current or past vs none	1.61 (1.01–2.56)	0.045	1.65 (0.95–2.88)	0.077
Hypertension	1.46 (0.77–2.77)	0.247		
History of RT	1.63 (0.75–3.56)	0.218		
Collagen disease	0.69 (0.20–2.37)	0.560		
Neoadjuvant chemo	1.01 (0.41–2.50)	0.983		
Prior breast biopsy/lumpectomy	0.98 (0.56–1.70)	0.940		
Prior breast augmentation	4.16 (1.43–12.04)	0.009	*	
Prior breast reduction	3.14 (0.92–10.71)	0.068	4.33 (1.08–17.41)	0.040
Diabetes	2.60 (0.97–6.99)	0.059	*	
Nipple sparing mastectomy (vs skin sparing)	3.34 (1.88–5.95)	<0.001	5.70 (2.71–11.99)	<0.001
Width skin paddle, excl nipple sparing	1.02 (0.90–1.16)	0.706		
Length upper skin flap	1.08 (0.98–1.19)	0.114		
Length incision	1.00 (0.94–1.05)	0.883		
Specimen size (OR per 100 g increase)	1.05 (0.98–1.12)	0.168		
Time incision to spec removal (OR per 10 minute increase)	1.19 (1.07–1.33)	0.002	1.20 (1.06–1.37)	0.005
Two team vs one team	0.92 (0.51–1.66)	0.777		
Sharp dissection vs cautery	2.20 (0.95–5.05)	0.065	5.94 (2.16–16.34)	<0.001
Tumescence	1.77 (0.78–4.05)	0.174		
Expander vs permanent implant	0.53 (0.14–1.98)	0.349		
>5cm flap exposed dermis	1.58 (0.72–3.45)	0.252		
Expander size, excl. autologous flap (OR per 50 ml increase)	1.12 (0.99–1.26)	0.061	1.15 (1.00–1.32)	0.052
Intraoperative trimming of flap	0.93 (0.55–1.57)	0.786		
Expander fill volume, excludes autologous flap (OR per 100 ml increase)	1.12 (0.85–1.48)	0.412		

\* excluded by backwards selection

UVA, univariate; CI, confidence interval; MVA, multivariable; OR, odds ratio; RT, radiation therapy



**Table 4**

Factors associated with moderate to severe skin flap necrosis on univariate (UVA) and multivariate (MVA) analyses. Factors with p < 0.1 on UVA were candidates for MVA; backwards selection was used for determine final factors included in MVA. N=518 for MVA.

Factor	UVA OR (95% CI)	p-value	MVA OR (95% CI)	p-value
Age (OR per 10-year increase)	0.81 (0.56–1.17)	0.271		
BMI (OR per 1 unit increase)	1.08 (1.02–1.14)	0.009	*	
Cup size C or larger	1.55 (0.76–3.14)	0.224		
Smoking, current or past vs none	1.52 (0.77–2.99)	0.223		
Hypertension	1.05 (0.39–2.83)	0.924		
History of RT	2.08 (0.75–5.77)	0.160		
Collagen disease	1.14 (0.26–5.12)	0.860		
Neoadjuvant chemo	1.28 (0.37–4.45)	0.698		
Prior breast biopsy/lumpectomy	0.80 (0.34–1.89)	0.612		
Prior breast augmentation	1.30 (0.16–10.65)	0.805		
Prior breast reduction	2.83 (0.57–14.06)	0.203		
Diabetes	5.77 (1.86–17.96)	0.003	*	
Nipple sparing (vs skin sparing)	3.99 (1.77–8.99)	<0.001	12.88 (4.32–38.35)	<0.001
Width skin paddle, (excludes nipple sparing)	1.15 (0.99–1.33)	0.073	*	
Length upper skin flap	1.08 (0.94–1.23)	0.291		
Length incision	1.06 (0.98–1.14)	0.135		
Specimen Size (OR per 100 g increase)	1.10 (1.01–1.20)	0.030	1.24 (1.12–1.37)	<0.001
Time incision to spec removal (OR per 10 min increase)	1.08 (0.94–1.24)	0.282		
Two team vs one team	0.91 (0.39–2.11)	0.819		
Sharp dissection vs cautery	0.67 (0.15–3.04)	0.602		
Tumescence	2.29 (0.72–7.26)	0.160		
Expander vs permanent implant	0.76 (0.10–6.10)	0.799		
>5cm Flap exposed dermis	1.43 (0.47–4.37)	0.531		
Expander size (excludes autologous flap) (OR per 50 ml increase)	1.22 (1.03–1.45)	0.024	*	
Intraoperative trimming of flap	1.45 (0.68–3.06)	0.334		
Expander fill volume, excludes autologous flap (OR per 100 ml increase)	1.35 (0.90–2.03)	0.149		

\* excluded by backwards selection

UVA, univariate; OR, odds ratio; CI, confidence interval; MVA, multivariable; BMI, body mass index; RT, radiation therapy;