Predicting Mastectomy Skin Flap Necrosis with Indocyanine Green Angiography: The Gray Area Defined

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Background: Preservation of breast skin during mastectomy has improved the cosmetic results of breast reconstruction. Unfortunately, the incidence of mastectomy skin flap necrosis remains high using conventional evaluation methods; therefore, accurate prediction of flap viability is an important component of postmastectomy reconstruction.

Methods: The authors studied a prospective cohort of women who underwent skin-sparing mastectomy and breast reconstruction over a 2-year period at Emory University. Mastectomy skin flap perfusion was measured intraoperatively using indocyanine green angiography. Once necrosis matured postoperatively, digital images were taken and superimposed over the intraoperative scan. Perfusion percentages were measured in healthy and nonviable skin.

Results: One hundred eighteen patients were included, and 14 patients (15 breasts) with postoperative skin necrosis and sufficient image data were analyzed. The average woman's age was 49.7 years (range, 28 to 73 years) and the average body mass index was 27.7 (range, 21.2 to 42.2). Skin with 25 percent or less perfusion (perfusion score, ≤25) was not viable 90 percent of the time, and areas with greater than or equal to 45 percent perfusion survived 98 percent of the time. A 33 percent perfusion score had a positive predictive value of removing nonviable skin of 88 percent and a negative predictive value of removing healthy skin of 16 percent.

Conclusions: Indocyanine green angiography is a useful adjunct to assess mastectomy skin flap viability. A gray zone exists between 25 and 45 percent of maximal skin perfusion in which the ultimate viability remains in question. By designating the cutoff perfusion score of 33 percent, the surgeon can expect to more accurately remove nonviable skin. (*Plast. Reconstr. Surg.* 129: 1043, 2012.)

CLINICAL QUESTION/LEVEL OF EVIDENCE: Diagnostic, III.

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DIAGNOSTIC

Preservation of breast skin, the inframammary fold, and now even the nipple-areola complex in women with breast cancer has improved reconstruction aesthetics without compromising oncologic safety.[1–5] However, the incidence of mastectomy skin necrosis is not insignificant, ranging from 10 to 30 percent, and is often difficult to predict.[6–9] Excising skin that may survive or preserving nonviable skin incurs unnecessary morbidity to the patient. Therefore, accurate prediction of flap viability is an important component of postmastectomy reconstruction.

Mastectomy skin flaps are essentially random flaps and rely on perfusion in the subdermal plexus from surrounding chest, axillary, and abdominal vessels. Although most surgeons rely on the clinical assessment of skin flap viability, including color, capillary refill, and dermal edge bleeding, additional measures are often helpful. Adjuvant tools include illumination with a Wood's lamp after fluorescein dye administration, laser Doppler velocimetry, and tissue oxygen saturation measurements.[10,11] These can be difficult to use, have limited sensitivity and/or

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specificity, and have not become routine for mastectomy skin flap assessment.[12,13]

Intraoperative indocyanine green angiography (Spy Imaging; LifeCell Corp., Branchburg, N.J.) has recently been used to assess flap perfusion.[14–17] The lyophilized indocyanine green is injected through a peripheral or central intravenous line. This dye, when excited by the 805-nm laser in the imaging system, emits in fluorescence. The intensity of emission is recorded by a charge-coupled device camera and serves as a function of real-time tissue perfusion. The beneficial use of indocyanine green angiography was recently demonstrated in free and pedicled tissue transfer as an easy way of assessing flap perfusion to aid in surgical decision making.[14,15,17] This technology has also become useful for assessing mastectomy skin flap viability.[16]

Although it is easy to accurately predict mastectomy flap survival in areas of high fluorescence intensity, decision making within the areas of lower intensity (the gray zones) can be more challenging. Improving the specificity of this technique will significantly increase the clinical utility and accuracy. The purpose of this review was to critically assess poorly perfused mastectomy skin flap areas that did not survive postoperatively in an attempt to improve the positive predictive value for skin necrosis.

PATIENTS AND METHODS

One hundred eighteen patients underwent skin-sparing mastectomy and breast reconstruction performed by the senior author (A.L.) at Emory University Hospital between July of 2010 and August of 2011. All mastectomy flaps were evaluated intraoperatively with indocyanine green angiography. The incidence of skin necrosis was 14 percent (n = 17 patients). Fourteen patients (15 breasts) with postoperative skin necrosis and sufficient imaging data to correlate were included in the series.

The 14 women in this cohort were treated by one of three breast surgeons at Emory University. Patients underwent skin-sparing mastectomies with sentinel node biopsies on the cancer side using isosulfan blue. Demographics were queried, including risk factors, reconstructive technique, and flap survival. All of the patients underwent reconstruction immediately after cancer extirpation by means of the following procedures: six tissue expanders (43 percent), six latissimus dorsi/tissue expanders (43 percent), and two transverse rectus abdominis myocutaneous flaps (14 percent). Intraoperative expansion ranged between 200 and 300 cc of saline. Intraoperative decisions were made regarding the need for skin resection based on indocyanine green angiography and clinical assessment. Suspicious tissue was excised when possible.

Skin flap viability was evaluated within the first half-hour after mastectomy with both the indocyanine green angiography imaging system and by clinical examination. Poorly perfused tissue was resected when possible and adjustments were made in expander volume if necessary. After completion of the reconstruction and flap or expander inset, the skin was closed and a final indocyanine green angiogram was obtained. A 5-cc bolus of indocyanine green was injected through the patient's peripheral intravenous line. The Spy Imaging system was positioned over the breast at approximately 20 cm from the skin, and the camera was turned on to record a video of the infusion over a 60-second interval.

Patients were evaluated postoperatively in the clinic to assess skin flap viability. Once necrotic areas had completely matured, digital images were taken with a PowerShot A650 IS (Canon USA, Lake Success, N.Y.). Photographs were taken in the reclined position at approximately 20 cm from the chest to match the images recorded from the indocyanine green angiographic images. The postoperative necrosis images were superimposed onto the intraoperative images, and the areas of ultimate necrosis were outlined (Fig. 1). Twenty data points within the area of necrosis and another 20 data points surrounding the area were sampled randomly using the Spy-Q software (LifeCell Corp.). Patient demographics and comorbidities were compared with necrotic zone scores. Comparisons were made between the outlined area of skin necrosis and the objective flow measurements.

Data were queried using Microsoft Excel (Microsoft Corp., Redmond, Wash.), and statistics were analyzed with StatPlus software (AnalystSoft, Inc., Alexandria, Va.). A Mann-Whitney U test set for a type I error of 5 percent ($\alpha = 0.05$) was used to calculate significance between binary variables, and a Pearson's correlation was used to compare continuous variables.

RESULTS

There were 14 patients and 15 breasts with sufficient data and appropriate postoperative images. The average woman's age was 49.7 years (range, 28 to 73 years) and the average body mass index was 27.7 (range, 21.2 to 42.2). Eleven women were African American (78.5 percent) and the remaining three were Caucasian. Documented comorbidities included tobacco use (n =

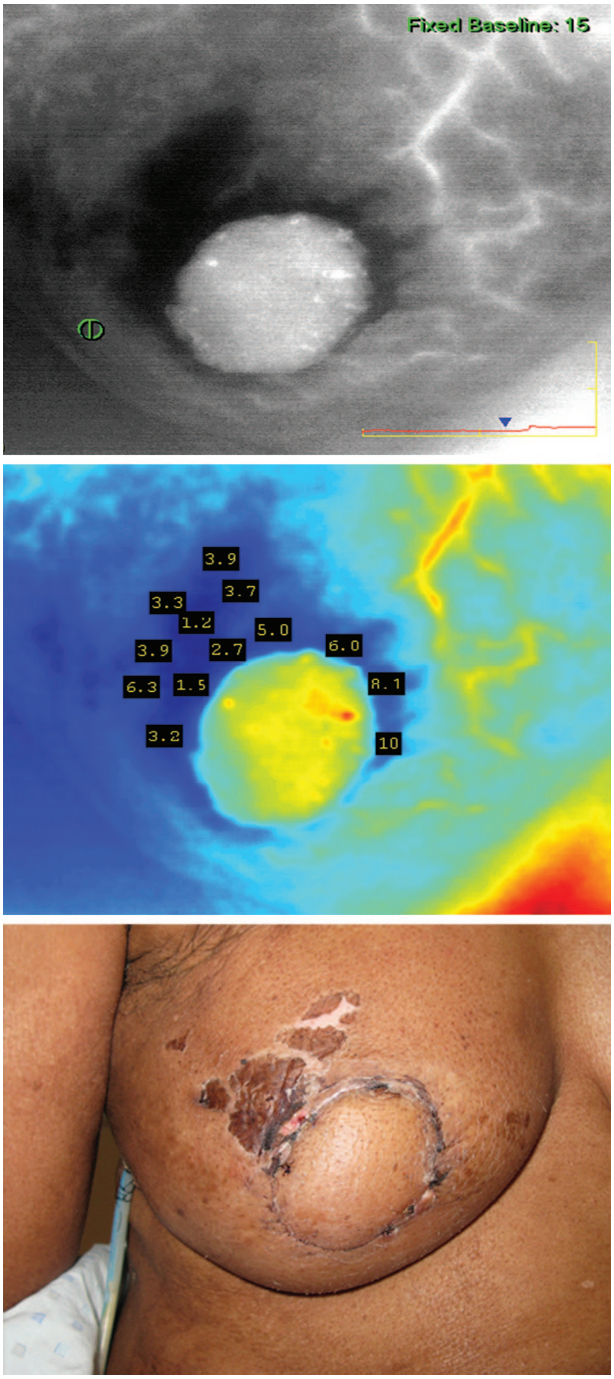

Fig. 1. Study imaging sequence. (*Above*) Intraoperative indocyanine green angiogram. (*Center*) Spy-Q software analysis image. The postoperative breast image with necrosis outline (*below*) was superimposed over the Spy-Q image, and points within the area of necrosis were selected at random (*center*). Twenty data points were also selected in the healthy edges surrounding the necrotic areas (not shown).

3), hypertension ($n = 3$), and prior radiation therapy ($n = 1$). In the case of necrosis, necrotic skin and subcutaneous tissue were excised to viable skin and either treated with conservative wound care or suture approximated in the minor procedure room. None of the tissue expanders required removal, and all 14 women completed their reconstruction successfully.

The average Spy-Q computer-designated percentage perfusion score for the necrotic zone was 24.6 ± 7.11 percent, and the percentage perfusion for the viable surrounding skin was 46.1 ± 12.0 percent. In corollary, the absolute emission scores for necrotic and viable skin were 6.30 and 12.3, respectively. Skin with 25 percent or less perfusion (perfusion score, ≤25 percent) was not viable 90 percent of the time, and areas with greater than or equal to 45 percent perfusion would survive 98 percent of the time. Gaussian distribution curves were created for the skin that necrosed and for the surrounding skin that survived using the Spy-Q emission numbers at the borders (Fig. 2). These normal curves overlap, and they cross at a tissue perfusion of 33 percent of the maximally perfused tissue. The 33 percent perfusion score has a positive predictive value of removing nonviable skin of 88 percent and a negative predictive value of removing healthy skin of 16 percent.

Further analysis of the cohort showed that African Americans had lower perfusion percentages in necrotic skin than did Caucasians (22.9 percent versus 29.3 percent, $p = 0.117$), and nonsmokers had lower percentages than smokers (23.6 percent versus 28.7 percent, $p = 0.243$); however, these values did not reach statistical significance. Patient age and body mass index had no correlation with perfusion percentages ($p = 0.376$ and $p = 0.977$, respectively). The three hypertensive patients had significantly lower perfusion scores in necrotic skin (15.1 percent versus 27.0 percent, $p = 0.015$). Results are listed in Table 1.

DISCUSSION

The importance of accurately predicting mastectomy skin flap viability cannot be overemphasized, because such prediction will significantly reduce postoperative morbidity. Although preservation of native breast skin contributes to the aesthetic outcome of postmastectomy reconstruction, the presence of necrotic skin flaps contributes to delayed healing, complications, and poor outcome. This is even more critical when prosthetic devices are being used for reconstruction. Although the safest option is often to overresect mastectomy skin, this often removes skin that would likely have survived. We have quantified perfusion using indocyanine green angiography and correlated these values with known areas of skin necrosis to determine the pos-

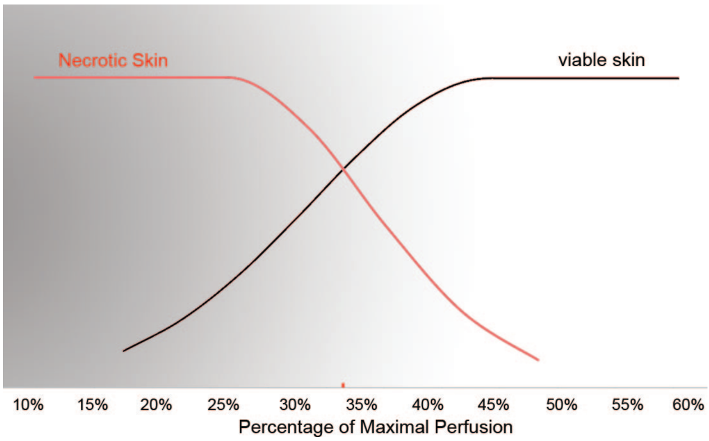

Fig. 2. Intersecting graphs of viable and nonviable skin. Normal Gaussian distributions were created for necrotic and healthy skin. As shown, tissue with less than 25 percent of maximal perfusion was likely to necrose, and tissue with greater than 45 percent will survive. The intersecting point is 33 percent of maximal perfusion.

Table 1. Percentage Perfusion Scores and Patient Demographics

	Necrotic Tissue Perfusion Score (%)	*p*	Viable Tissue Perfusion Score (%)	*p*
Race				
African American	22.9	0.117	44.3	0.531
Caucasian	29.3		48.8	
Hypertension				
Yes	15.1	0.015*	41.7	0.311
No	27.0		48.7	
Smoking status				
Smoker	28.7	0.243	60.0	0.036*
Nonsmoker	23.6		45.1	

*Statistically significant.

itive predictive value to improve the accuracy of this technology.

Clinical examination has long been the most common method used to predict skin flap viability; however, the specificity is reported to be 10 to 30 percent in large series.[18–20] Multiple adjuvant diagnostic tools have been used previously to help predict skin flap necrosis. Losken et al. calculated a negative predictive value of 25 percent when using fluorescein dye to evaluate mastectomy skin flaps.[12] Percutaneous oxygen saturation was evaluated by Rao et al. in 10 patients.[10] One patient (10 percent) experienced flap necrosis, and the authors found that flap length ultimately correlated with nonviability. Sensitivity and specificity were not determined because of the limited sample size. Laser Doppler velocimetry has been studied in both animals and humans, and Perbeck et al. found that laser Doppler velocimetry did not accurately predict skin flap necrosis in all patients who experienced skin slough in their series.[13]

Fluorescence of indocyanine green has become a useful adjuvant to enhance a surgeon's clinical judgment of mastectomy skin flap viability. Newman et al. retrospectively analyzed seven cases of skin flap necrosis and noted a perfusion score of 37 to 45 percent of maximum at the wound edges.[16] This is in agreement with our finding that skin with perfusion of 45 percent or greater had a high likelihood of surviving. Komorowska-Timek and Gurtner recently reported a series of 24 consecutive patients for which the use of Spy angiography decreased their complication rate from 15.1 percent to 4.0 percent.[20] They conclude that further work is needed to define precisely where the threshold of tissue necrosis exists.

Indocyanine green angiography will often provide confirmatory information, especially when skin flaps are thin and appear dusky; however, the true value of this technology is its ability to predict a course that is not suspected clinically. In these situations, it will affect the intraoperative decision-making process and, when acted on appropriately, minimize potential complications. In our series, skin with perfusion less than 25 percent was universally destined for necrosis, a finding that matches a previous animal model of skin flap necrosis and indocyanine green angiography.[21] Moreover, we found that 33 percent of maximal perfusion was an accurate cutoff between likely viable and nonviable skin. The sensitivity of the test at this number is 84.6 percent, with a specificity of 87.5 percent. The ability to objectively analyze perfusion with a specificity of predicting necrosis of 87.5 percent makes indocyanine green angiography a valuable tool. A different perfusion score could be used to increase the specificity but at the expense of removing some skin that would survive.

A patient's age and body mass index did not significantly affect the perfusion score (Table 1). Because indocyanine green angiography interprets skin perfusion by means of the subdermal plexus at roughly 0.5 to 1 cm in depth, the amount of subcutaneous fat should not influence the results. We know that a patient's skin changes with age; however, the decrease in perfusion is global and compensated for by using the percentage of perfusion instead of the absolute fluorescence. Race and smoking status also did not statistically affect the perfusion score; however, there were strong trends that are likely clinically significant. The mean perfusion score of nonviable skin for African Americans was 6 percent lower than for Caucasians. In corollary, the mean perfusion score of ultimately viable skin at the necrotic edge was 4 percent lower. These data suggest that African American skin is able to survive a greater hypoxic insult or that the fluorescence is dampened in a nonlinear relationship (more obstruction at the lower emitting area under insult versus the well-perfused area) by the extra pigment in the dermis. In a related finding, the necrotic skin in smokers required a greater percentage of perfusion to remain viable (5 percent higher). This is not surprising, as nicotine is proven to cause microvessel vasoconstriction and enhance platelet aggregation, thereby inhibiting both wound healing and skin survival under insult.[22–24]

Skin in the patients with hypertension was able to survive at a lower perfusion score. In reviewing the intraoperative anesthesia records of these patients, the systemic mean arterial pressures at the time of indocyanine green angiography were on average 29.2 mmHg lower (73 percent less) than their mean arterial pressure measured in the clinic. We are performing the indocyanine green angiographic imaging at an artificially low perfusion state, one that radically adjusts once the patient is awakened from anesthesia. Therefore, the perfusion cutoff score for hypertensive patients is shifted to the left to approximately 25 percent (from 33 percent).

Of note, we elected to focus on areas of known skin necrosis and critically analyze the data in an attempt to improve reliability using this technique. The Spy-Q analysis software was used to analyze perfusion both as a percentage and as an absolute flow value. The absolute value is a direct measure of the intensity of emittance of the indocyanine green and thus can be dependent on the distance from the camera to the skin, the patient's skin color, and the ambient light in the room. We elected to use the percentage of perfusion compared with a computer-designated best-perfused tissue to control for user variables and other confounders.

There are several limitations to this study, the foremost being the small sample size. The subcategories of race, smoking status, and hypertension are extremely small in numbers, making statistical analysis difficult. There are additional variables that might affect the specificity of indocyanine green angiography, including tumescent solution and isosulfan blue dye, which will need to be examined in future studies. Because there are other factors such as tension or infection that can also contribute to skin necrosis, no study will predict necrosis 100 percent of the time. The goal with any technique is to maximize the specificity to where it is clinically beneficial and to preserve as much of the native breast skin as possible. This study should provide some of the objective data necessary to further improve the accuracy of indocyanine green angiography.

CONCLUSIONS

Intraoperative indocyanine green angiography is a useful adjuvant to enhance a surgeon's clinical judgment of mastectomy skin flap viability. A gray zone exists between 25 and 45 percent of maximal skin perfusion in which the ultimate viability remains in question. By designating the cutoff perfusion score of 33 percent, the surgeon can expect to more accurately remove nonviable skin. Nonsmoking, African American race, and especially hypertension shift this cutoff to the left and should be considered in the clinical decision-making process.

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