

Rapid Communication

Identification of the optimal predictive cutoff value for expanded flap viability using indocyanine green angiography: a prospective study

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Tissue expansion is a frequently used intervention for the reconstruction of large defects. Flap necrosis is one of the most troublesome complications, which may result in post-operative infection, an additional surgical procedure and unsatisfactory aesthetic and functional outcomes in the recipient sites. Therefore, to ensure sufficient perfusion of the expanded flaps, it is necessary to assess the flap perfusion intraoperatively [1].

Traditionally, the assessment of flap perfusion is primarily based on subjective clinical observations of flap color, capillary refill, and pinprick bleeding, which can be misleading. ICGA is a real-time vascular fluorescent imaging technique that uses indocyanine green (ICG) as a contrast agent and near-infrared laser as excitation light. Previous research on the use of ICGA to predict flap necrosis has suggested the predictive fluorescence cutoff values for non-expanded flaps. As for expanded flaps, no cutoff value to predict postoperative necrosis has been identified to date. Consequently, the purpose of this study was to evaluate the predictive value of ICGA on expanded flap viability and to determine the optimal fluorescent cutoff value for intraoperative decision making to prevent postoperative necrosis [2].

A prospective observational study was designed to identify the cutoff value of ICGA to predict expanded flap viability. The study was approved by the Shanghai Ninth People's Hospital Ethics Committee (Approval Number: SH9H-2018-T47-3) and registered on [ClinicalTrials.gov](https://clinicaltrials.gov) (NCT04097665). Patients undergoing expanded flap transplantation performed by the senior doctors in the

Department of Plastic and Reconstructive Surgery in Shanghai Ninth People's Hospital who are likely to suffer from flap necrosis were included from November of 2019 to January of 2022. All patients gave their written informed consent prior to inclusion in the study.

The inclusion criteria for this clinical study are patients between 6 and 50 years of age, regardless of gender, who intend to undergo expanded flap surgery and are at high risk of flap necrosis based on clinical judgment during the operation. The criteria of clinical judgment include color, temperature, texture, degree of swelling, capillary response of the flap and the bleeding of the raw wound edge. Purple blood oozing out slowly at the flap edge, along with another abnormal circumstance led to inclusion of the patient in the cohort. Patients with cardiovascular and cerebrovascular diseases, peripheral vascular lesions, postoperative flap infection, long-term smoking and alcohol use, severe liver and kidney insufficiency, iodine allergy, mental illness and inability to cooperate were excluded from this study.

During surgery, the expanded flap was transferred freely or pedicled to the recipient site along with the corresponding vascular anastomosis (Table S1, see online supplementary material). Surgeons then evaluated the perfusion of the flap and marked the potential area of necrosis based on clinical experience. Subsequently, this region was subdivided into multiple perfusion units (1 × 1 cm each), with the center of each unit marked as an observation point. Then, ICGA was carried out via intravenous injection of a 2 ml bolus of ICG (2.5 mg/ml) (Dandong Yichuang Pharmaceutical Co.,

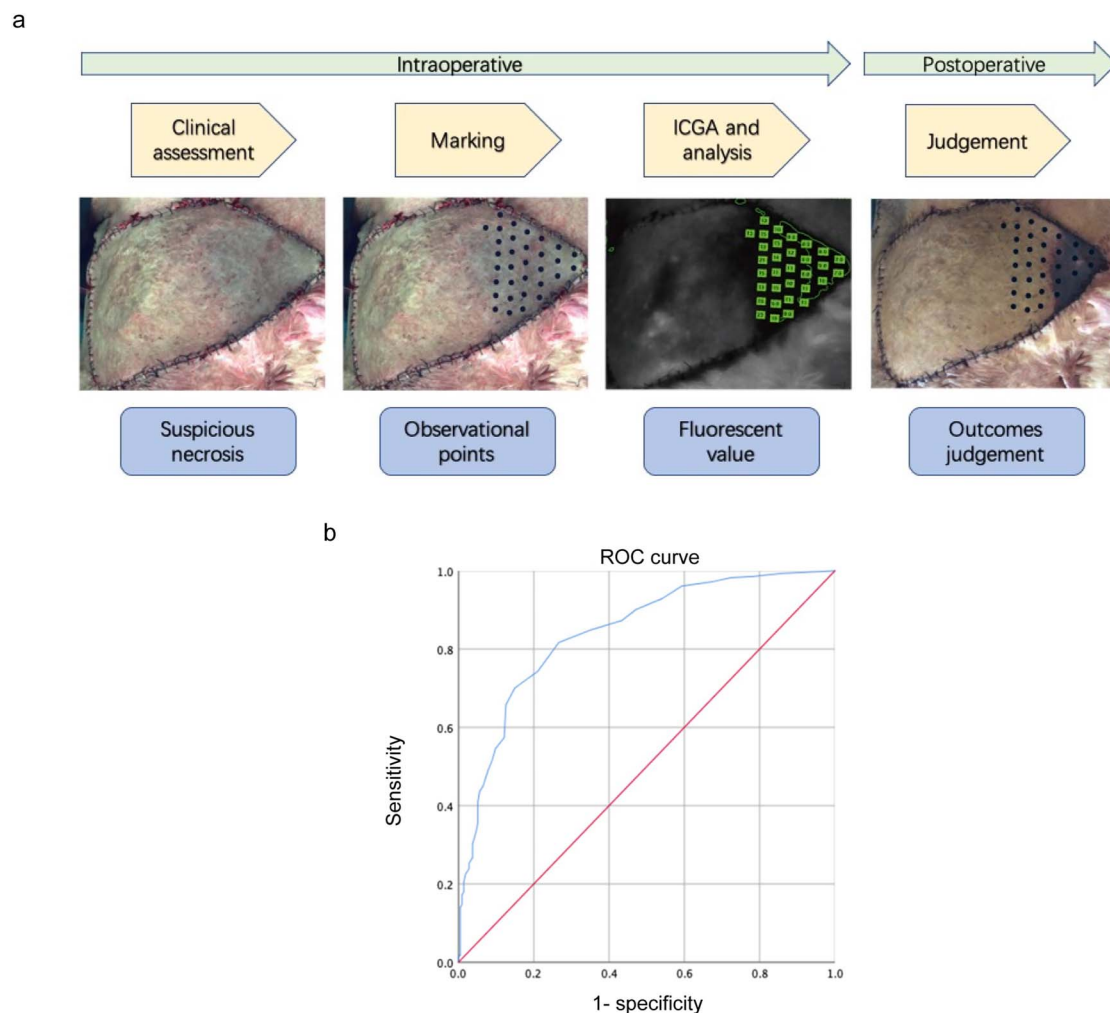


Figure 1. Study protocol. (a) The possible area of necrosis was marked through clinical assessment, and this area was further divided into perfusion units ($1 \times 1 \text{ cm}^2$ for each). The center of each perfusion unit was marked. Indocyanine green angiography (ICGA) was conducted immediately after flap transplantation, with the fluorescence value of each perfusion unit at the maximum perfusion timepoint analyzed by the SPY-Q imaging system. Partial flap necrosis occurred at day 7 postoperatively and the outcomes of the observational points were recorded. (b) Receiver operating characteristic (ROC) curve based on fluorescence values and clinical outcomes with an area under the curve of 0.842 (95% confidence interval = 0.808–0.877, $p < 0.001$)

Dandong, Liaoning, People's Republic of China). For fluorescence image acquisition, the detector of the SPY-Q imaging system (Novadaq Technologies Inc., Mississauga, Ontario, Canada) was positioned $\sim 30 \text{ cm}$ above the flap, and the fluorescence values at the maximum perfusion timepoint were recorded. At postoperative day 7, the clinical outcome of each observation point was classified as necrosis or viable (Figure 1a). The portion of the flap that has turned black, developed a hard texture and does not bleed when pricked with a needle is deemed necrotic.

By analyzing the intraoperative fluorescence values and their corresponding clinical outcomes on postoperative day 7, namely survival or necrosis, at each observational point, a 4-fold table was used for the classification of the diagnostic test results. With logistic regression analysis, the receiver operating characteristic (ROC) curve and the area under the curve (AUC) were analyzed by IBM SPSS Statistics (version 26, Chicago, IL, USA). The optimal cutoff value was further identified using the maximal value of the Youden index (YI)

as the criterion, which is necessary for improving the utility and accuracy of ICGA in predicting the postoperative skin viability of expanded flaps. Additionally, positive predictive value (PPV) and negative predictive value (NPV), positive likelihood ratio (PLR) and negative likelihood ratio (NLR) were calculated according to the data in the 4-fold table to evaluate the cutoff value.

From November 2019 to January 2022, 20 patients with expanded flap surgery and suspected flap necrosis were initially enrolled in this study; however, only 15 of them developed necrosis and were ultimately included in the study and completed the follow-up, bringing the total number of cases in this study to 15. The average age of these patients was 22.7 years (range: 6 to 43), and the sizes of their expanded flaps ranged from 12×8 to $35 \times 22 \text{ cm}^2$, with 10 pedicled and 6 free flaps. Table S1 and Table S2 summarize the specific demographic characteristics and surgical procedures of these 15 patients. In the majority of cases, the back was used as the donor site. The flap necrosis of all patients

Table 1. The 4-fold table of the diagnostic test with indocyanine green angiography (ICGA) prediction using 11.5 as the cutoff value

ICGA prediction	Postoperative outcomes	
	Necrotic observation units	Surviving observation units
ICGA predicted necrosis	181	85
ICGA predicted survival	33	199

was considered to be partial necrosis; all were subsequently recovered through routine dressing change, and none required additional surgical repair.

In this study, the subdivision of flap necrosis suspect areas yielded a total of 498 perfusion units, which ultimately developed into 284 viable units and 214 necrotic units on postoperative day 7. Based on the corresponding fluorescence values collected at the maximum perfusion timepoint, a ROC curve with an AUC of 0.842 [95% confidence interval (CI) = 0.808–0.877, $p < 0.001$] was generated (Figure 1b). When the fluorescence value was 11.5, the YI reached a maximum of 0.551 (Table S3, see online supplementary materials). A fluorescence value < 11.5 was highly predictive of postoperative flap necrosis, with sensitivity and specificity of 85.0 and 70.1%, respectively. The diagnostic test results utilizing a cutoff value of 11.5 are displayed in Table 1. Based on the data provided in this table, the PPV, NPV, PLR and NLR were calculated as 68.0%, 85.8%, 1.53 and 0.12 respectively (Table S4).

The use of ICGA technology in plastic surgery has skyrocketed in recent years. In contrast to previous studies conducted on physiologic non-expanded flaps, we determined the optimal cutoff value for predicting necrosis in an expanded flap using ICGA in this study. We chose ICGA over other imaging modalities because of its unique ability to perform synchronized and accurate real-time perforator mapping and quantitative flap perfusion evaluation. Although CDU and DIRT are also capable of performing these tasks, CDU lacks the precision to delineate perforators with a diameter of less than 0.5 mm and cannot display the perfusion of the entire flap, which would be problematic if a larger flap is involved, whereas DIRT is easily affected by the ambient temperature [3]. In contrast, ICGA, in addition to being able to delineate delicate perforator branches up to the intradermal level of < 0.2 mm diameter and in thin flaps of ≤ 8 mm thickness, could provide an accurate real-time hemodynamic overview of a specific zone instead of a single vessel, which would be more appropriate for perioperative flap monitoring [4]. A meta-analysis also discovered that when used in intraoperative flap perfusion evaluation, ICGA has a high accuracy of 98.6% and sensitivity of 90.9% [5].

There are several reasons why we chose to concentrate on the application of ICGA to expanded flaps specifically. Although expanded flaps are commonly used in plastic surgery, the existing research only covers their use in

conjunction with non-expanded flaps when it comes to ICGA. Due to the vastly different natures of non-expanded and expanded flaps, the conclusion drawn from the studies of non-expanded flaps cannot be directly applied to expanded flaps. Despite the significant advantages of expanded flaps, their hemodynamics are relatively unpredictable. Indeed, the expansion procedure can resemble a flap delay procedure, and the presence of mechanical stretch tends to elicit permanent opening of choke anastomosis and neovascularization in the early stages of expansion [6]. However, the tendency of the expanded flap to retract upon expander removal could result in unanticipated obstruction of blood supply in the later stages due to arterial insufficiency and venous congestion. Besides, their distal perfusion may be constrained by the perfusion territory of the perforasome due to their large sizes [7].

According to our experience, the actual area of expanded flap necrosis postoperatively was typically smaller than the hypo-perfused area depicted on the intraoperative ICGA mapping, indicating that certain defined areas of the non-excised dark areas were actually able to survive postoperatively. Similar phenomenon has also been observed and reported for non-expanded flaps [8, 9]. In order to achieve a balance between minimizing postoperative necrosis and avoiding unnecessary flap wastage due to excessive resection, one of the key issues that must be resolved is how to prevent this potential for underestimation.

ICGA, as an effective and real-time method for evaluating flap perfusion, has been gradually used to guide intraoperative clinical decision-making. This study identified an absolute fluorescence value of 11.5 as a cutoff value for prediction of postoperative expanded flap necrosis, and is expected to provide scientific and quantitative evidence for future intraoperative decision-making.

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Supplementary data

Supplementary data is available at Burns & Trauma Journal online.

Abbreviations

AUC: Area under the curve; CDU: Color Doppler ultrasound; DIRT: Dynamic infrared thermography; ICGA: Indocyanine green angiography; NLR: Negative likelihood ratio; NPV: Negative predictive value; PLR: Positive likelihood ratio; PPV: Positive predictive value; ROC: Receiver operating characteristic; RCT: Randomize controlled trial; YI: Youden index.

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Authors' contributions

SG, YK and XH designed the clinical trial, collected the data, and drafted and revised the manuscript. YG and HL enrolled the patients, and conducted the surgery and ICGA. BG, FX and TZ were responsible for the entire treatment process including tissue expansion, flap design and surgery. SG, YK, XH and TZ discussed and participated in the data interpretation. XH and TZ revised and approved the manuscript. All the authors reviewed and approved the final version of the manuscript.

Conflict of interest

None declared.

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