The role of near-infrared fluorescence imaging with indocyanine green dye in pedicle division with the paramedian forehead flap

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Abstract
The paramedian forehead flap is considered the gold standard for nasal reconstruction following oncologic surgery. During the 21-day delay in two-stage surgery protocols, many patients report considerably reduced quality of life because of the pedicle. This prospective case series study examined the usefulness of near-infrared (NIR) fluorescence with indocyanine green (ICG) for flap perfusion assessment and identified variables associated with time to flap perfusion. Ten patients (mean age 75.3 ± 11.6 years) with diagnosis of basal cell carcinoma (n = 9) or squamous cell carcinoma (n = 1) underwent intravenous indocyanine injection and NIR fluorescence imaging for assessment of flap vascularisation 2 to 3 weeks after stage 1 surgery. NIR fluorescence imaging showed 90% to 100% perfusion areas in all patients after 14 to 21 days. Early pedicle division occurred in two patients on postoperative days 14 and 16. One minor complication (wound healing disorder) was seen following flap take-down after 14 days. There were no associations between time to flap perfusion and defect size or flap area. NIR fluorescence imaging with ICG dye is a useful method for non-invasive perfusion assessment when used in conjunction with clinical assessment criteria. However, a decision for early pedicle division may raise risk of complications in specific patient groups and must therefore be made with great care.

KEYWORDS
indocyanine green angiography, nasal reconstruction, near-infrared fluorescence imaging, paramedian forehead flap

1 | INTRODUCTION
Oncologic surgery of the external nose often leaves the patient with large defects, oftentimes affecting not only the skin, but also the underlying nasal cartilage and mucosa. The paramedian forehead flap is one of the most widely used flaps for full thickness reconstruction of nasal defects and is considered the gold standard for...
nose reconstruction. Although this technique is known for its viability in patients of all ages, having few contraindications, producing reliable and aesthetically pleasing results, as well as achieving high rates of patient satisfaction and having low complication rates, the paramedian forehead flap procedure has one major drawback, namely that it is a two-stage surgery design. Traditionally, the paramedian forehead flap is transferred in two stages: stage 1 involves raising the flap and reconstructing the nasal tissues according to the nasal subunit principles, while leaving a pedicle to the donor site. During the second stage of the surgery 3 weeks later, pedicle division and flap inset are performed. During this timeframe, patients are under considerable stress due to difficult wound care and flap inconvenience, which is heightened in persons wearing glasses. Furthermore, younger patients under 70 years of age report greatly reduced quality of life due to the pedicle, which prevented them from participating in activities of daily life and also work. Thus, minimising the delay between the two stages of nasal reconstruction is increasingly gaining importance.

The precise timing of pedicle division is extremely important as early flap division increases the risk of flap necrosis, which is why most pedicles are divided on the 21st postoperative day. Currently, not a single patient-based clinical assessment technique for determining ideal flap division timing has gained widespread acceptance. Thus, the timing of pedicle division is mainly dependent on the surgeon’s subjective opinion and is influenced by personal experience, patient age, and comorbidities, among other variables.

Recently, near-infrared (NIR) fluorescence imaging using indocyanine green (ICG) dye has been increasingly applied in plastic surgery settings where assessment of flap revascularisation is needed for clinical decision-making. This angiography technique is non-invasive to the flap, in that ICG dye is injected intravenously after temporary pedicle clamping. The fluorophore ICG has excellent properties for NIR imaging, with its high safety profile and short plasma half-life (3-5 minutes). The dye binds to blood proteins and therefore does not leave the vasculature when injected intravenously. Although no standard protocols on dosage and timing of the ICG dye administration exist, several commercial ICG imaging systems allowing quantitative assessment of flap revascularisation are in use in plastic and reconstructive surgery today. Furthermore, recent studies indicate that ICG angiography can be used to objectively determine the degree of flap neovascularisation and shorten delay times in patients with paramedian forehead flaps. However, little is known about possible variables influencing flap perfusion.

The aim of this prospective case series study was 2-fold. First, the authors sought to examine the utility of NIR fluorescence imaging with ICG dye for evaluation of neovascularisation of paramedian forehead flaps in an attempt to establish pedicle division timing on an individual, patient-specific basis. Second, the authors sought to identify the relationship between time to flap perfusion and defect- and flap-related variables.

2 METHODS

2.1 Patients

The authors prospectively evaluated a case series of 10 patients scheduled to have two-stage nasal reconstruction surgery with traditional paramedian forehead flap. Nine patients had been diagnosed with basal cell carcinoma (BCC) of the outer nose and one patient had received the diagnosis of squamous cell carcinoma (BCC) of the outer nose and one patient had received the diagnosis of squamous cell carcinoma of the nose. Two of the nine patients with BCC diagnosis had local cancer recurrence.

All surgeries were performed between June 2017 and October 2019 at the Department for Plastic and Aesthetic, Reconstructive and Hand Surgery at the AGAPLESION Markus Hospital in Frankfurt am Main, Germany. All patients underwent peripheral ICG application and NIR fluorescence imaging for assessment of flap vascularisation 2 to 3 weeks following stage 1 surgery. Subsequent pedicle division was performed according to the gold standard of 21 days for the first eight patients irrespective of ICG perfusion assessment. For the final two patients in this case series, pedicle division took place after 14 and 16 days, as the flaps examined showed...
full (100%) perfusion after temporary clamping of the pedicle.

For the study, the investigators documented information on the following parameters: age, diagnosis, relevant medication, smoking habits, surgical technique, defect depth, defect size, size of pedicled flap, pedicle width, time of pedicle division (postoperative day), surgical complications, area of ICG perfusion in percent, time to ICG perfusion in seconds and time of ICG application (days postsurgery).

2.2 | Surgical technique and postoperative protocols

During the first stage of the surgical procedure, a paramedian forehead flap was designed in accordance with the defect size and depth as well as nasal subunit principles. Wherever necessary, auricular cartilage was used for reconstruction of the cartilaginous nasal framework. Postoperative outpatient care consisted in daily wound cleaning and application of antibiotic ointments, and sutures were removed after 5 to 7 days following the initial nasal reconstruction surgery.

For the second stage of surgery, the pedicle was temporarily clamped. The preparation of the ICG solution was performed as follows: 5 mg of ICG dye was diluted in 5 mL of distilled water, then 1 mL of the solution was further diluted by adding 9 mL of distilled water, and 5 mL of ICG solution was applied intravenously, and then care was taken to ensure that each patient received the exact same amount. Time to flap perfusion was measured and the area of perfusion was visualised and photographed using the ICG fluorescence camera system Photo Dynamic Eye (pde- neoII) NIR fluorescence imager C10935-300 manufactured by Hamamatsu Photonics K.K. (Hamamatsu City, Japan). The area of perfusion was qualitatively assessed using percentages. If neovascularisation of the forehead flap was sufficient, pedicle division and flap inset could be performed and the patient was once again released to care on an outpatient basis.

2.3 | Ethical considerations

Prior to surgery, all patients were informed in detail of all the benefits and possible risks surrounding the procedures planned as well as treatment options. Furthermore, study participation was only made possible if the patient had given written consent to both the surgery and application of ICG for assessment of neovascularisation. The authors obtained ethics approval for this study from the institutional ethics committee before commencing. The study protocol follows the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines for observational studies and adheres to the ethical standards laid down in the most current version of the Declaration of Helsinki. Informed consent was obtained from all individual participants included in the study. Additional informed consent was obtained from all individual participants for whom identifying information is included in this article.

2.4 | Data analysis

Data analysis was mainly performed using descriptive statistics, with metric variables being presented as means ± SD as well as minimum, maximum, and median. As the nature of the relationship between the variables seemed to be monotonic rather than linear, the Spearman’s rank correlation was used to test for possible associations.

3 | RESULTS

The mean patient age among the 10 patients recruited for this study was 75.3 ± 11.6 years. The youngest patient was 59 years of age and the oldest patient was 98 years old at the time of surgery. Six patients were on low-dose aspirin at the time of surgery and two patients were on antidiabetics (insulin and metformin). The vast majority (nine patients) were non-smokers. Nine patients underwent nasal reconstruction via paramedian forehead flap for BCC of the nose and one patient had a diagnosis of squamous cell carcinoma of the nose. Paramedian forehead flaps were raised contralaterally in most patients. Delayed flap transfer was performed in one case and another patient needed a full-thickness skin graft from the supraclavicular area in addition to the ipsilateral paramedian forehead flap. Detailed information on the defect depths and size as well as surgical technique and individual patient characteristics is given in Table 1.

Pedicle width was kept between 2 and 3 cm in nine patients, whereas one patient had a wider pedicle measuring 4 cm. NIR fluorescence angiography with ICG dye solution was performed after 21 days in most (six) patients. With neovascularisation at 100% in five patients and 90% in one patient, the second stage for pedicle division and flap inset was performed. The remaining four patients also showed a 100% flap perfusion at neovascularisation perfusion assessment. Two of the remaining four patients underwent ICG angiography 14 days after stage 1 surgery and another patient after 16 days. Pedicle division was performed on the 14th and
16th postoperative day for two patients, while the third patient underwent pedicle division after 21 days per the current literature. The final patient had ICG angiography and pedicle division on day 25 following stage 1 surgery. Postoperative complications were recorded on only the one patient who had stage 2 surgery after 14 days. The complication was a minor wound healing disorder, which was treated conservatively. An overview of the individual surgical data is presented in Table 2.

The average nasal defect depth was 8.3 ± 3.5 mm and ranged from as little as 3 mm to 15 mm for the deepest defect. The mean total defect area measured 650.0 ± 421.6 mm². The smallest total defect area measured 150 mm² and the largest total defect area was 1600 mm². The average area of the flap measured 44.2 ± 13.3 cm² and ranged from 27 cm² to 72 cm². Mean time to ICG perfusion of the flap following intravenous application was 32.3 ± 12.8 seconds (minimum: 18 seconds; maximum: 62 seconds; median 28 seconds). Data on metric variables are listed in Table 3. Spearman’s rank correlation was calculated to test for possible relationships between ICG perfusion time and defect depth \( r_s = -0.047, P = .897 \), defect size \( r_s = -0.181, P = .617 \), and flap area \( r_s = 0.542, P = .106 \). ICG perfusion time showed no correlation to any of the three variables examined (Figures 1-3).

### Table 1: Patient characteristics and preoperative data

| Patient | Age (y) | Diagnosis | Site | Medication | Smoking | Defect depth (mm) | Defect size (mm) | Surgical technique |
|---------|---------|-----------|------|------------|---------|------------------|-----------------|-------------------|
| 1       | 75      | BCC       | L nasal ala | ASS       | No      | 10               | 25 × 20         | R PFF             |
| 2       | 59      | BCC       | L nasal ala | —         | No      | 15               | 40 × 15         | R PFF + full-thickness graft from supraclavicular area |
| 3       | 74      | BCC       | Nasal tip | ASS       | No      | 3                | 15 × 10         | L PFF             |
| 4       | 80      | Recurrent BCC | L nasal ala | Insulin | No      | 5                | 25 × 14         | R PFF (delayed)   |
| 5       | 64      | Recurrent BCC | L nasal ala/ sidewall | Metformin | No      | 7                | 35 × 20         | L PFF             |
| 6       | 75      | SCC       | n.a.      | ASS       | No      | 8                | 30 × 30         | L PFF             |
| 7       | 68      | BCC       | L nasal ala | —         | No      | 5                | 20 × 10         | R PFF             |
| 8       | 98      | BCC       | L nasal ala | ASS       | No      | 10               | 40 × 40         | R PFF             |
| 9       | 85      | BCC       | L nasal ala | —         | No      | 10               | 30 × 20         | R PFF             |
| 10      | n.a.    | BCC       | L nasal ala | ASS       | No      | 10               | 30 × 30         | R PFF             |

Abbreviations: ASS, acetylsalicylic acid; BCC, basal cell carcinoma; L, left, n.a., not available; PFF, paramedian forehead flap; py, pack-years; SCC, squamous cell carcinoma.

### Table 2: Patient-specific surgical data

| Patient | Size of flap (cm) | Pedicle width (cm) | NIR angiography (postoperative days) | Perfusion area (%) | Pedicle division (postoperative days) | Complications |
|---------|-------------------|--------------------|--------------------------------------|-------------------|---------------------------------------|---------------|
| 1       | 9 × 4             | 2                  | 21                                   | 100               | 21                                    | —             |
| 2       | 10 × 6            | 3                  | 21                                   | 100               | 21                                    | —             |
| 3       | 9 × 4             | 2                  | 21                                   | 100               | 21                                    | —             |
| 4       | 9 × 5             | 2                  | 21                                   | 100               | 21                                    | —             |
| 5       | 12 × 6            | 2                  | 14                                   | 100               | 21                                    | —             |
| 6       | 10 × 5            | 2                  | 21                                   | 100               | 21                                    | —             |
| 7       | 9 × 3             | 3                  | 14                                   | 100               | 14                                    | Wound healing disorder, conservative treatment |
| 8       | 10 × 4            | 4                  | 21                                   | 100               | 21                                    | —             |
| 9       | 10 × 4            | 2                  | 25                                   | 100               | 25                                    | —             |
| 10      | 9 × 4             | 2,5                | 16                                   | 100               | 16                                    | —             |
DISCUSSION

Shortening the delay time between the two stages of nasal reconstruction using traditional paramedian forehead flap in order to minimise negative impacts on patient quality of life is becoming increasingly important. In this study, we were able to show that NIR fluorescence imaging with ICG dye is an objective tool for assessing degree of perfusion in flaps and determining the ideal time for pedicle division, when used in conjunction with clinical assessment. The results also indicate that pedicle division may be performed sooner than the 20- or 21-day mark currently used as the gold standard if NIR imaging shows adequate neovascularisation (Figure 4).

Reports on earlier pedicle division in the literature are far and few between and mainly consist of case studies, case series, and retrospective studies with smaller patient cohorts. The first report of laser-assisted ICG angiography was published in 2012 by Woodard et al, who demonstrated the utility of the technique as a means of objectively quantifying forehead flap perfusion after transfer to the recipient bed.21 Although neovascularisation was significant after only week postsurgery, concerns on adequate flap survival independent of the pedicle led to pedicle division being performed after 21 days. Surowitz et al prospectively assessed flap revascularisation and relative flap perfusion on the 14th postoperative day in 10 healthy, non-smoking patients.17 Although one patient in our study with early pedicle division and flap inset after

| Variable                  | Mean ± SD   | Minimum | Maximum |
|---------------------------|-------------|---------|---------|
| Age (y)                   | 75.3 ± 11.6 | 59      | 98      |
| Nasal defect depth (mm)   | 8.3 ± 3.5   | 3       | 15      |
| Total defect area (mm²)   | 650.0 ± 421.6 | 150     | 1600    |
| Flap area (cm²)           | 44.2 ± 13.3 | 27      | 72      |
| Time to ICG perfusion (s) | 32.3 ± 12.8 | 18      | 62      |

Abbreviation: ICG, indocyanine green.

FIGURE 1 Relationships between indocyanine green perfusion time and defect depth (Spearman’s rank correlation)

FIGURE 2 Relationships between indocyanine green perfusion time and defect size (Spearman’s rank correlation)

FIGURE 3 Relationships between indocyanine green perfusion time and flap area (Spearman’s rank correlation)

4 | DISCUSSION
14 days developed a wound healing disorder, our study results still seem to be in line with the literature as the patient affected was a heavy smoker (50 pack-years).

An accelerated flap takedown after only 1 week has also been performed—based on clinical assessment alone as well as in combination with laser-assisted ICG angiography. Somoano et al reported routinely performing flap takedown on the seventh postoperative day after observing a case of accidental premature pedicle division after only 3 days heal without complications. Early pedicle division did not lead to flap failure or other complications in any of the 26 patients treated, even though many of the patients had comorbidities such as diabetes or coronary artery disease. However, conventional contouring was performed after 3 weeks. In nine additional patients, pedicle division was postponed until 2 or 3 weeks based on clinical signs such as perioperative bleeding and/or suspicion of infection. Accelerated forehead flap takedown after 7 days using laser-assisted ICG angiography was successful in all 10 patients.

In this study, the authors found no correlations between flap perfusion and defect depth, defect size, or flap area. To date, there is a lack of research on factors influencing flap perfusion variables. A larger retrospective study was able to identify time lapse between stage 1 and stage 2 surgeries as having a positive influence on
flap-to-cheek ingress ratio. In the same study, use of cartilage graft and diabetes had negative associations with flap perfusion.

Predicting the exact time for pedicle division is challenging even for experienced surgeons. Although NIR fluorescence imaging with ICG dye can help provide an objective basis for planning stage 2 surgery, more research is needed to establish general guidelines and cut-off criteria. Although time between placement of the paramedian forehead flap and pedicle division was positively associated with flap perfusion, a flap-to-cheek vascularity of 44% was sufficient for flap success in another study. A systematic review of ICG angiography vascularity of 44% was sufficient for flap success in another study. 

This study is mainly limited by the small sample size and data stemming from a single institution, which precluded more in-depth statistical analyses.

5 CONCLUSION

NIR fluorescence imaging with ICG dye is a useful method for non-invasive perfusion assessment when used in conjunction with clinical assessment criteria. However, a decision for early pedicle division may raise the risk of complications in specific patient groups and must, therefore, be made with great care.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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How to cite this article: Schlosshauer T, Rothenberger J, Heiss C, Rieger UM. The role of near-infrared fluorescence imaging with indocyanine green dye in pedicle division with the paramedian forehead flap. Int Wound J. 2021;1–8. https://doi.org/10.1111/iwj.13590