Indocyanine green-based fluorescent angiography in breast reconstruction

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Background: Fluorescent angiography (FA) has been useful for assessing blood flow and assessing tissue perfusion in ophthalmology and other surgical disciplines for decades. In plastic surgery, indocyanine green (ICG) dye-based FA is a relatively novel imaging technology with high potential in various applications. We review the various FA detector systems currently available and critically appraise its utility in breast reconstruction.

Methods: A review of the published English literature dating from 1950 to 2015 using databases, such as PubMed, Medline, Web of Science, and EMBASE was undertaken.

Results: In comparison to the old fluorescein dye, ICG has a superior side effect profile and can be accurately detected by various commercial devices, such as SPY Elite (Novadaq, Canada), FLARE (Curadel LLC, USA), PDE-Neo (Hamamatsu Photonics, Japan), Fluobeam 800 (Fluoptics, France), and IC-View (Pulsion Medical Systems AG, Germany). In breast reconstruction, ICG has established as a safer, more accurate tracer agent, in lieu of the traditional blue dyes, for detection of sentinel lymph nodes with radioactive isotopes (^{99m}-Technetium). In prosthesis-based breast reconstruction, intraoperative assessment of the mastectomy skin flap to guide excision of hypoperfused areas translates to improved clinical outcomes. Similarly, in autologous breast reconstructions, FA can be utilized to detect poorly perfused areas of the free flap, evaluate microvascular anastomosis for patency, and assess SIEA vascular territory for use as an alternative free flap with minimal donor site morbidity.

Conclusions: ICG-based FA is a novel, useful tool for various applications in breast reconstruction. More studies with higher level of evidence are currently lacking to validate this technology.

Keywords: Fluorescent angiography (FA); indocyanine green (ICG); fluorescein; sentinel lymph node biopsy; mastectomy skin flap; perfusion; anastomotic patency; superficial inferior epigastric artery flap (SIEA flap)

Background

Breast cancer is the most common type of cancer worldwide and accounts for the most common cause of cancer-related deaths worldwide (1,2). More patients are electing to undergo mastectomy (3,4). As a result, postmastectomy breast reconstruction has become an essential component of the holistic management of patients with breast cancer. Encouraged by the advancement of imaging technologies in

Table 1 Comparison of fluorescein and ICG dye (11,15)

Characteristic	Fluoroescein	ICG
Molecular weight	375 kD	775 kD
Absorption wavelength	494 nm	800 nm
Emission wavelength	521 nm	830 nm
Half-life	23 min	2.5 min
Protein-binding	+	+++
Excretion	Urinary	Biliary
Waiting time after injection	15 min	2 min
Data	Qualitative	Quantitative
Side effect profile	++	+

ICG, indocyanine green; kD, kilodalton; nm, nanometer.

recent times, complex breast reconstructive procedures have become increasingly safer and more reliable (5-10).

Fluorescent angiography (FA) is a real-time imaging modality where an intravenous dye—namely, fluorescein and indocyanine green (ICG)—fluoresces and emits infrared energy upon excitation by a light source (11,12). It enables the assessment of blood flow and tissue perfusion in preoperative, intraoperative, and postoperative setting. For decades, FA has demonstrated useful in ophthalmic angiography (13-15), cardiothoracic surgery (16,17), hepatobilliary surgery (18,19), and neurosurgery (20).

Despite being readily accessible and affordable, fluorescein dye has a slow onset of action (15), prone to inter-observer variability (21,22), and has a significant side effect profile (23). As a result, it has been largely replaced by ICG. It has a superior side effect profile (22,24-28), shorter half-life (2.5 *vs*. 23.0 minutes), which enables multiple image captures (29), and is currently FDA-approved for evaluation of cardiac output, hepatic function, hepatic blood flow and ophthalmic vasculature (30). Currently, numerous commercial near-infrared (NIR) light detection devices are available (31). In breast reconstruction, SPY Elite System (Novadaq, Mississauga, Ontario, Canada), FLARE System (Curadel LLC, Worcester, MA, USA), PDE-Neo System (Hamamatsu Photonics, Hamamatsu, Japan), Fluobeam 800 System (Fluoptics, Grenoble, France), and IC-View System (Pulsion Medical Systems AG, Munich, Germany) have been studied, but SPY Elite System has been most frequently reported sensor (32-35).

In plastic surgery, FA has been used for various indications (35-43). However, its application has been most extensively reported in breast reconstructive surgery and, in this review, we investigate the role of FA in sentinel lymph node biopsy, prosthesis-based reconstructions, and autologous free flap reconstructions.

Methods

We reviewed the published English literature from 1950 to 2015 from well-established databases, such as PubMed, Medline, Web of Science, and EMBASE, using the following search terms in various combinations: "fluorescent angiography", "indocyanine green", "fluorescein", "sentinel lymph node biopsy", "mastectomy skin flap", "prosthesis breast reconstruction", "autologous breast reconstruction", "DIEP", "TRAM", "flap perfusion", "anastomotic patency", and "SIEA".

Results

Fluorescent angiography (FA)

FA is a real-time imaging modality where an intravenous dye fluoresces and emits infrared energy upon excitation by a light source (11,12). As a result, it enables the assessment of blood flow and tissue perfusion in preoperative, intraoperative, and postoperative setting. To date, investigators have demonstrated its utility in various surgical disciplines, such as ophthalmology to evaluate the chorioretinal vasculature (13-15), cardiothoracic surgery to assess the patency of the coronary artery bypass graft (16,17), hepatobilliary surgery to identify the haptic segment and subsegment for anatomical hepatic resection (18,19), and neurosurgery to assess the patency of the superficial temporal artery-middle cerebral artery bypass graft in cerebral revascularization procedure (20). Historically, two fluorescent dyes have been studied for FA: fluorescein and ICG (*Table 1*), along with numerous commercial detector devices (*Table 2*).

Dyes
Fluorescein
Early studies have used fluorescein dye, which is readily accessible and affordable. Upon exposure to UV light using the Woods lamp, it emits yellow-green fluorescent light and is really excreted. It was first synthesized and used topically by von Baeyer to diagnose corneal abrasions (44). Since then, it has been utilized widely to assess skin flap perfusion and viability (23,28,45-48). One of the major disadvantages of fluorescein lies in its slow action, requiring 15 minutes to reach maximum fluorescence, and potentially

Table 2 Comparison of fluorescent angiography devices used in breast reconstruction

Feature	SPY Elite	FLARE	PDE-Neo	Fluobeam 800	IC-View
Cost per case (USD)	650	109	60	13	N/A
Cost of machine (USD)	250,000	120,000	75,000	40,000	N/A
Structure	Trolley with articulating arm	Trolley with articulating arm	Handheld	Suspension equipment	Handheld
Working distance (cm)	34	45	25	20	100
Field view (cm^2)	10.1×7.4	15×11	13×9	10×7.5	40×20
Pixel	300,000	307,200	300,000	316,000	N/A
Resolution	30 fps	30 fps	2.83 cycles/mm	4 cycles/mm	N/A
Zoom	No	Yes	No	No	N/A
Operating room light compatibility	No	Yes	No	Yes	N/A
Data	Quantitative	Quantitative	Qualitative	Qualitative	Quantitative
Software	SPY-Q	XIP	None	None	IC-CALC

FLARE, Fluorescence-Assisted Resection and Exploration; PDE, photodynamic element; N/A, not available; fps, frames per second; XIP, eXtensible Imaging Platform.

increasing operating time, exposure to general anaesthesia, and operating cost (15). Furthermore, fluorescein yields qualitative data, which is subject to inter-observer variability (21,22). In addition, it has a significant side effect profile, a high rate of allergic reaction (0.6%) (23), and the use of the Woods lamp has a steep learning curve. As a result, fluorescein has been largely replaced by ICG dyes.

Indocyanine green (ICG)

ICG is a water-soluble, biliary-excreted dye that is excited by laser light and emits infrared energy within 2 minutes of intravenous injection (11). Kogure et al. first used it to image choroidal veins (49) and, currently, it is approved by the US Food and Drug Administration (FDA) to evaluate cardiac output, hepatic function, hepatic blood flow and ophthalmic vasculature (30). In comparison to fluorescein, ICG is a larger molecule (775 vs. 375 kD) and binds to plasma proteins more strongly (50). As a result, it stays in the intravascular compartment and undergoes rapid washout from the circulation leading to a superior side effect profile (22,24-28). Furthermore, ICG has a shorter half-life than fluorescein (2.5 vs. 23 minutes), which enables multiple image captures intraoperatively (29). However, one of the major limiting factors of ICG is that with the current technology the emitted light can only be detected up to 1 cm deep (31).

Devices

Numerous commercial NIR light detection devices can be used to derive quantitative data from the ICG-derived fluorescence (31). In breast reconstruction, SPY Elite System (Novadaq), FLARE System (Curadel LLC), PDE-Neo System (Hamamatsu Photonics), Fluobeam 800 System (Fluoptics), and IC-View System (Pulsion Medical Systems AG) have been studied (Table 2).

SPY Elite system

SPY Elite system is the most extensively reported NIR light detection device in breast reconstructive surgery (32-35). The machine is mounted on to a trolley and the illumination probe is attached to an articulating arm. Compared to the other commercial devices, SPY System has a smaller field of view (10.1×7.4 cm^2) and lacks operating room light compatibility, which makes it cumbersome for a regular use. The data is analyzed quantitatively using the proprietary SPY-Q software (Novadaq, Mississauga, Ontario, Canada). It allows the storage of both static pictures and videos, and moreover, clinicians can perform various quantitative analyses on it. However, it incurs a significant learning curve. To date, SPY Elite System is FDA-approved for applications in plastic and reconstructive surgery, cardiothoracic surgery, visceral surgery, and transplant surgery (51).

FLARE system

In contrast to most of the FA devices, Fluorescence-Assisted Resection and Exploration (FLARE™) system consists of two NIR cameras that are capable of detecting multiple wavelengths, both ICG and methylene blue, and are synchronized to a color video camera (52). The NIR and color images are overlaid using eXtensible Imaging

Platform (XIP) (Electronic Radiology Lab, St Louis, MO, USA), an open-source software developed by the National Cancer Institute (NCI) (53). The merged images display real-time tissue fluorescence in the context of the surgical anatomy (54). Furthermore, FLARE has the longest working distance (45 cm) and the largest field view (15×11 cm^2), compared to all the other systems (*Table 2*). To date, FLARE has been reported useful in detecting sentinel lymph nodes (54) and assessing free flap perfusion and perforator selection in animal models (39).

PDE-Neo system

Photodynamic Eye (PDE) system is the oldest FA device available in the market and has been recently upgraded to the PDE-Neo system. It is manufactured in a handheld probe that contains a series of light-emitting diodes (LED) and a charge-coupled device (CCD) sensor that filters out wavelengths of less than 820 nm. PDE-Neo is relatively affordable and has an adequate working distance (25 cm) and a field of view (13×9 cm^2). However, it is restricted to only producing qualitative data and is not compatible with operating theater lights. Numerous investigators have reported the utility of PDE-Neo in sentinel lymph node dissection, evaluation of microvascular anastomosis, and skin flap perfusion (38,55-59).

Fluobeam 800 system

Fluobeam 800 system is a novel and affordable NIR detector developed in France. The device is small and can be fitted into a suspension equipment found in an operating room. Moreover, it is compatible with the operating room light. However, in comparison to the other systems, it has the shortest working distance (20 cm) and a small field of view (10×7.5 cm^2). Furthermore, it only produces subjective qualitative information. Currently, only preclinical studies in animal models of skin flaps have been reported using this device (60-63).

IC-View system

Similar to the PDE-Neo system, IC View is manufactured in a handheld probe. Amongst all commercial FA devices, it has the farthest working distance (100 cm) and the largest field of view (40×20 cm^2). Furthermore, its accompanying proprietary IC-CALC software (Pulsion Medical Systems AG, Munich, Germany) enables quantitative analysis. Investigators have utilized this system to demonstrate mesenteric vasculature (64), bowel wall vasculature (65), perfusion of kidney allograft (66) and free flaps (42,67-69), sentinel lymph node diagnosis (31,70-72), and deep inferior epigastric artery perforator (DIEP) flap monitoring (73). However, it is no longer available in the market.

FA in breast reconstruction

In plastic and reconstructive surgery, FA has so far demonstrated utility in the assessment of breast reduction skin flaps (36,37), selection of dominant perforator in free flap transfers (35,38), assessment of flap perfusion (39,40) and patency of microvascular anastomosis (41), postoperative flap monitoring (42), and in the assessment of burns injury (43). To date, its application has been most extensively explored and reported in breast reconstructive surgery, mainly to aid sentinel lymph node biopsy, evaluate mastectomy skin flaps in prosthesis-based reconstructions, and autologous free flap reconstructions.

Sentinel lymph node biopsy

Sentinel lymph node biopsy is a crucial component of axillary staging in patients with breast cancer (74,75). Accurate diagnosis is paramount since axillary clearance in sentinel node-negative patients has demonstrated no clinical benefits but creates morbidity from the subsequent lymphedema (74). Currently, the gold standard investigation involves using methylene or patent blue dye for node detection and radioisotope for lymphoscintigraphy (74,76,77). However, the blue dye is associated with cutaneous staining and a significant rate of allergic reaction and anaphylaxis (75). In contrast, ICG is a safe, accurate, and reliable tracer agent (57,70,71,78,79) (*Table 3*).

ICG facilitates a superior means of sentinel lymph node dissection from three-dimensional (3D) visualization of the lymphatic vasculature, as shown in animal models (54). Furthermore, investigators have reported that ICG may be more accurate than methylene blue (83) and its nodal detection rate may be decreased if its use is combined with the blue dye (56,59). Compared to the radioisotope, ICG has a similar nodal detection rate (55,80,83). In combination with radioisotopes, ICG have shown to improve the sensitivity of detecting positive sentinel nodes (80,82). Recently, Samorani *et al*. have demonstrated, in a prospective study involving 301 patients and 589 lymph nodes excised, that ICG has a superior node detection rate than technetium, a standard radioisotope (99% *vs*. 76.7%) (81). Interestingly, Onishi *et al*. report that the nodal detection rate of ICG can be enhanced by incubating it with human serum albumin (HSA) to form a 1:1 complex, which increases its quantum yield (i.e., fluorescence signal) and its hydrodynamic diameter (i.e., nodal retention) (54,84). However, this novel development currently requires more investigation. In summary, ICG has become more

Table 3 Summary of all clinical studies comparing the node detection rate (i.e., over the total number of patients) and node uptake rate (i.e., over the total number of sentinel lymph nodes detected)

Author	Year	P/R	Patient	Nodes	Node detection rate (%)					Node uptake rate (%)					
					Blue	ICG	99mTc	Blue + ICG	ICG + 99mTc	Blue	ICG	99mTc	Blue + ICG	Blue + 99mTc	ICG + 99mTc
Sugie (80)	2015	P	821	N/A	N/A	97.2	97	N/A	99.8	N/A	93.3	90	N/A	N/A	N/A
Samorani (81)	2015	P	301	589	N/A	98.7	95.4	N/A	98.7	N/A	99	77.7	N/A	N/A	76.7
Pitsinis (56)	2015	P	50	87	96	96	N/A	96	N/A	96.6	100	N/A	96.6	N/A	N/A
Verbeek (82)	2014	P	95	177	N/A	99	N/A	N/A	99	78	100	88	N/A	N/A	N/A
Ballardini (55)	2013	P	134	246	N/A	N/A	N/A	N/A	N/A	N/A	99.6	93.9	N/A	N/A	N/A
Wishant (59)	2012	P	99	242	99	100	91.3	N/A	N/A	78.9	83.1	64.5	95	73.1	N/A
Tagaya (57)	2011	P	50	N/A	N/A	100	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Sugie (71)	2010	P	411	950	93	99	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Murawa (70)	2009	P	30	N/A	N/A	96.7	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Kitai (78)	2005	P	18	50	N/A	94	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

P, prospective; R, retrospective; ICG, indocyanine green; 99mTc, technetium radioisotope; N/A, not available.

established as an alternative tracer agent to the traditional blue dye for investigation with radioactive isotope in sentinel lymph node biopsy.

Prosthesis-based breast reconstruction

In the recent decades, the rate of prosthesis-based breast reconstruction has increased rapidly (203% rise from 1998 to 2008) and has exceeded autologous reconstruction as the most common approach, accounting for 65% of all breast reconstructions (85). To date, two-stage tissue expander approach has been the most common mode of implant reconstructions (86). However, with the advancement of surgical techniques and adjuvant technologies, single-stage implant reconstruction is becoming more popular where indicated (87-89). One-stage procedure simplifies the reconstructive process, limits exposure to general anesthesia and is potentially more cost-effective (90,91). Yet, majority of clinicians still perform the two-stage reconstruction due to a relatively high risk of implant-related complications and prosthesis failure associated with the single-stage procedure (92-94).

Overall, postmastectomy implant reconstructions are associated with 40–50% of complications and the most common complication is mastectomy skin flap necrosis (32,95-98). The risk is higher in smokers, obese patients, large breasts, and adjuvant radiotherapy (93). Subsequently, this can lead to an implant failure or loss (99). Similarly, timely re-exploration and necrosis excision can salvage the reconstruction (32). Some clinicians have utilized acellular dermal matrix to reduce the skin tension and prevent implant exposure, but with minimal improvement in the overall rate of mastectomy skin flap necrosis and (6.9%) and implant loss (1.1%) (98). To this effect, using FA to facilitate intraoperative assessment of the mastectomy skin perfusion and guide appropriate excision has been studied to be beneficial (100) (*Table 4*).

Fluorescein

In a case series, Singer *et al.* first reported the use of fluorescein-based FA as an adjunct to assess the viability of the mastectomy skin flap in implant reconstructions (103). However, the authors noted that the extent of necrosis could not be accurately predicted using fluorescein and the hypofluorescent areas underestimated the tissue survival. Using fiberoptic dermofluorometer on various animal models of skin flaps, investigators were able to quantitate fluorescence and produce numerous formulae to predict tissue necrosis and survival, such as perfusion ratio (22), dye fluorescence index (DFI) (48,104), and fluorescein flowmetry (105). The manual nature of the operation of the sensors meant that the result is prone to subjective interpretation and selection bias (22). Interestingly, Losken *et al.* attempted to classify the fluorescence pattern categorically into homogenous yellow, mottled appearance, and complete failure of fluorescence (21). The authors demonstrated that their algorithm was highly predictive of flap survival, but would overestimate flap necrosis (21). With the introduction of ICG, Phillips *et al.* compared the two dyes in a prospective study involving 51 implant reconstructions in 32 patients (93). They showed that

Table 4 Summary of all clinical studies reporting the utility of ICG in detecting mastectomy skin flap necrosis in prosthesis-based breast reconstructions

Author	Year	Implants	Patient	Control	P/R	Device	Rate of implant-related necrosis (%)	Findings
Kanuri (99)	2014	710	508	N/A	R	SPY	11.1	Indiscriminate used of ICG is more expensive than the complication-related costs by 65% Cost savings per flap necrosis prevented: USD 2,098.80 for smokers, USD 5,162.30 for BMI >30, USD 1,892.70 for mastectomy weight >800 g
Duggal (94)	2014	N/A	184	184	R	SPY	13	ICG decreased necrosis (13% *vs.* 23.4%, P=0.01) Cost savings per patient: USD 614
Munabi (101)	2014	50	42	N/A	P	SPY	12	SPY-Q perfusion unit ≤7.0: 88% sensitivity, 83% specificity SPY-Q perfusion unit ≤10.0: 100% sensitivity, 72% specificity 18% false positive rate
Phillips (93)	2012	51	32	N/A	P	SPY	41.2	ICG: 90% sensitivity, 50% specificity for necrosis ICG overpredicts hypoperfusion by 66.57 cm^2 SPY-Q perfusion unit <3.7: 90% sensitivity, 100% specificity for necrosis SPY-Q perfusion unit <8.0: 100% sensitivity, 70% specificity for necrosis
Moyer (100)	2012	15	14	N/A	R	SPY	14	SPY-Q perfusion score ≤25%: 90% sensitivity for necrosis SPY-Q perfusion score ≥45%: 98% sensitivity for survival SPY-Q perfusion score 33%: 88% PPV for necrosis, 16% NPV for survival
Newman (102)	2010	19	11	N/A	R	SPY	45	95% correlation between ICG and postoperative necrosis 100% sensitivity, 91% specificity
Komorowska-Timek (33)	2010	16	12	148	P	SPY	4	ICG decreased necrosis (4% *vs.* 15.1%, P<0.01)

ICG, indocyanine green; P, prospective; R, retrospective; N/A, not available; BMI, body mass index; PPV, positive predictive value; NPV, negative predictive value.

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both fluorescein and ICG have similar sensitivity (90%) in detecting skin flap necrosis, but ICG has a superior specificity (P=0.002) (93).

ICG

An earlier study by De Lorenzi *et al*. demonstrated that ICG-based FA is a safe, accurate and quick method of determining soft tissue perfusion intraoperatively in implant breast reconstructions (106). In a retrospective study of 19 prosthesis-based reconstructions using acellular dermal matrix, Newman *et al*. reported the potential benefits of ICG in identifying subclinical mastectomy skin flap necrosis (102). From their retrospective analysis of intraoperative FA images, the authors noted a 95% correlation between ICG findings and subsequent skin necrosis with sensitivity and specificity of 100% and 91%, respectively (102).

Subsequently, investigators have attempted to define threshold values, using the SPY-Q software, which enables reliable prediction of mastectomy skin flap perfusion and necrosis (93,100,101). Moyer *et al*. utilized the SPY-Q perfusion score where the fluorescence is recorded relative to the surrounding well-perfused tissues designated as "100% fluorescent" (100). They showed that a score of less than 33% has a positive predictive value of 88% for necrosis and a negative predictive value of 16% for survival (100). However, this scoring system was prone to inter-observer variability. In contrast, Phillips *et al*. and Munabi *et al*. employed absolute measurement of tissue fluorescence to derive sensitivity and specificity of ICG (93,101). However, the authors also documented that this measurement can be confounded in smokers and in the presence of epinephrine containing tumescent solution (101). As yet, a standardized, reliable and reproducible threshold value has not been established.

Current evidences indicate that using ICG-based FA to guide excision of hypoperfused mastectomy skin flap in the operating room results in a significant reduction in necrosis (33,94). Furthermore, in comparison to the historical control, Duggal *et al*. report a reduction in the severity of the skin flap necrosis (25% *vs*. 44.1%) and also the rate of re-operation (6% *vs*. 14%) (94). These findings translate to a cost saving of USD 614 per patient (94). However, given the high cost of leasing or purchasing an ICG detector device currently, Kanuri *et al*. show that an indiscriminate use of ICG in all breast reconstructions is more expensive than cost related to flap complications by 65% (99). They recommend that reserving the use of FA in high-risk patients—smokers, body mass index (BMI) of greater than 30 kg/m^2, and mastectomy weight of greater than 800 g—leads to significant cost-savings (99).

Autologous breast reconstruction

In contrast to the prosthesis-based reconstructions, autologous breast reconstructions using perforator-based free flaps are in general more natural-appearing, aesthetically pleasing, and long-lasting (107,108). Historically, various donor sites have been studied for breast volume replacement, such as omentum (109), gluteal artery perforator flap (110), latissimus dorsi (111), deep circumflex iliac artery (groin) flaps (112), tensor fascia latae (lateral thigh) flap (113), triceps flap (114), superficial inferior epigastric artery (SIEA) perforator flap (115), transverse upper gracilis (TUG) flap (116), and profunda femoris artery perforator (PAP) flap (117). However, the abdominal wall remains the most popular donor site due to its consistent large volume and the added aesthetic benefit to the donor site, akin to an abdominoplasty. Originally, transverse rectus abdominis muscle (TRAM) flaps have been successful at providing sufficient volume in breast reconstructions (118-120). However, they are associated with a significant number of partial flap necrosis (7%–31%), especially in the periphery of the flap, and donor site morbidity from subsequent rectus muscle weakness and ventral hernia (0.3%–11.0%) (121,122). As a result, muscle-sparing techniques have evolved and DIEP flaps have become popular.

The advent of preoperative planning with advanced modern imaging modalities has assisted surgeons in the appropriate selection of donor site, perforator, and flap, and led to improved flap outcomes (9,123). To this effect, ICG-based FA has been studied to evaluate perforator caliber and location for breast reconstructions (38,124). However, since FA can only assess tissues up to 1 cm deep and thick pannus is preferred in DIEP flaps, it is less frequently utilized in the preoperative setting, compared to computed tomographic angiography (CTA) and magnetic resonance angiography (MRA) (8-10,125-129). Similarly, FA has been explored as a postoperative free flap monitoring tool in the postoperative setting (48). Despite promising early results (12,130), Mothes *et al*. demonstrate that ICG-based FA is not superior to the conventional clinical monitoring techniques (42). Hitherto, in autologous breast reconstruction, FA has been most beneficial in the intraoperative setting for the assessment of free flap perfusion and blood flow across microvascular anastomosis in a range of free flaps.

Flap perfusion

Numerous studies have reported that ICG-indicated hypoperfused areas correlate accurately with areas of postoperative flap necrosis in TRAM and DIEP flaps

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(33-35,131-133). Francisco *et al*. describe, in a case series of five DIEP flaps, their technique of using ICG during flap insetting to determine poorly perfused areas and guide excision (124). Newman *et al*. note that flap adjustments performed in three out of four cases, where FA demonstrated hypoperfusion, led to successful reconstruction and no postoperative complications (34). Recently, Duggal *et al*. have retrospectively compared the clinical outcomes from ICG-guided excision in 71 consecutive TRAM flaps to 59 flaps performed prior to the introduction of FA in a single institution (94). The authors report a trend in the reduction of the rate of flap necrosis (14% *vs*. 22%, P=0.237) and flap loss (1.4% *vs*. 3.4%, P=1.00). Although promising, more studies with higher power and a stronger level of evidence are required to validate the use of ICG for intraoperative assessment of free flap perfusion in breast reconstruction (*Table 5*) (*Figure 1*).

Microvascular anastomotic patency

FA enables direct visualization of blood flow through microvascular anastomosis and facilitates assessment of its patency. Flow defect may indicate arterial occlusion, venous thrombosis, or pedicle torsion (134). In a retrospective analysis of 50 consecutive free flap reconstructions, including DIEP flaps, 22% of anastomosis at re-exploration appeared occluded using ICG-based FA but clinically patent (135). Where clinical reasoning suggested temporary causes, such as vasospasm and reversible venous thrombosis, accounted for the subclinical vascular compromise, the anastomosis was left unrevised. All three cases resulted in flap loss or re-exploration. Later study by Holm *et al*. demonstrated that FA can detect thrombotic occlusions with sensitivity of 100% and specificity of 86% (136). Subsequently, the same group calculated the anastomotic intrinsic transit time (ITT), the time taken for the dye to travel from the arterial anastomosis to the venous anastomosis, and applied it to 100 consecutive free flaps including autologous breast reconstructions to predict vascular compromise (137). ITT of 50 seconds or greater would indicate postoperative re-exploration or flap loss with sensitivity of 92% and specificity of 98%.

SIEA flaps

Despite having no donor site morbidity, SIEA flap has been less commonly utilized due to its inconsistent vascular anatomy and variable size of its vascular territory (138,139). However, more recent cadaveric and clinical studies suggest that SIEA may be present more consistently and approximately in 27–35% of all patients (115,140-144). Numerous reports devised guidelines that SIEA flaps are

only indicated for breast reconstruction when its diameter is greater than 1 or 1.5 mm at the origin (115,141,144,145). However, these guidelines are oversimplified and fail to acknowledge individual variances. Ulusal *et al*. and Holm *et al*. used laser Doppler flowmetry and ICG-based FA, respectively, to determine the vascular territory of SIEA and design its flap (142,143). In the following study, Holm *et al*. proposed a management algorithm where SIEA flap is indicated when sufficient vessel caliber and vascular territory are present using intraoperative FA (146). Where SIEA is not indicated, the algorithm recommended translation to a DIEP flap or a stacked flap involving both the deep and the superficial system. However, more evidences are still required to validate this algorithm.

Discussion

Breast cancer is the most common type of cancer worldwide and accounts for the most common cause of cancer-related deaths worldwide (1,2). Approximately 25% of the patients will undergo mastectomy (3) and an increasing number of patients are opting for more aggressive types of mastectomy (4). As a result, postmastectomy breast reconstruction has become an essential component of the holistic care in patients with breast cancer. Encouraged by the advancement of imaging technologies, complex breast reconstructive procedures have become increasingly safe and reliable (5-10). FA is such imaging modality that has been studied to show usefulness in breast reconstructions.

FA is a real-time imaging modality where an intravenous dye—mainly, fluorescein and ICG—fluoresces and emits infrared energy upon excitation by a light source (11,12). It enables the assessment of blood flow and tissue perfusion in preoperative, intraoperative, and postoperative setting. To date, investigators have demonstrated its utility in ophthalmic angiography (13-15), cardiothoracic surgery (16,17), hepatobilliary surgery (18,19), and neurosurgery (20). Despite being readily accessible and affordable, fluorescein has a slow onset of action, requiring 15 minutes to reach maximum fluorescence (15). This potentially increases the operating time, exposure to general anaesthesia, and consequently the operating cost (*Table 1*). Furthermore, fluorescein produces only qualitative data, subject to inter-observer variability (21,22), and has a significant side effect profile (23). As a result, it has been largely replaced by ICG dyes. ICG is a water-soluble, biliary-excreted dye that is already FDA-approved to evaluate cardiac output, hepatic function, hepatic blood flow and ophthalmic vasculature (30).

Table 5 Summary of all clinical studies reporting the utility of ICG in detecting flap and fat necrosis in autologous breast reconstructions

Author	Year	Type	Auto	Patient	Control	P/R	Device	Rate of necrosis (%)	Findings
Duggal (94)	2014	TRAM	71	N/A	59	R	SPY	10	ICG-guided excision showed a trend in the reduction of TRAM flap necrosis (14% vs. 22%, P=0.237) and flap loss (1.4% vs. 3.4%, P=1.00)
Wu (131)	2013	TRAM, DIEP	N/A	17	N/A	R	SPY	7	Overestimation of perfusion 7%; Underestimation of perfusion 7%; ICG may be more unreliable in patients with dark skin (overestimation of 22% and underestimation of 22%)
Komorowska-Timek (33)	2010	TRAM, DIEP, SIEA, LD	8	8	148	P	SPY	4	1 case of partial necrosis occurred reconstruction with LD flap and tissue expander where ICG detected subclinical hypoperfusion
Francisco (124)	2010	DIEP	5	N/A	N/A	R	SPY	0	ICG is useful for perforator selection, SIEA assessment, microvascular anastomosis patency assessment, and flap perfusion assessment
Jones (132)	2009	TRAM, DIEP, LD	64	43	N/A	R	SPY	6.3	ICG correlated 100% with areas of necrosis
Newman (34)	2009	TRAM,DIEP	10	8	N/A	P	SPY	N/A	3 out of 4 flaps showing poor perfusion by ICG were improved by intraoperative adjustments; 1 out of 4 flaps showing poor perfusion by ICG was not adjusted intraoperatively and required re-exploration
Pestana (35)	2009	TRAM, DIEP, SGAP, SIEA, TUG	12	10	N/A	R	SPY	8	ICG is safe and requires minimal additional operative time and general anesthesia
Yamaguchi (133)	2004	TRAM	10	10	N/A	R	IC-View	40	ICG accurately predicted 3 out 4 cases of partial necrosis

ICG, indocyanine green; auto, number of autologous breast reconstructions; P, prospective; R, retrospective; TRAM, transverse rectus abdominis muscle; LD, latissimus dorsi; DIEP, deep inferior epigastric artery perforator; SIEA, superficial inferior epigastric artery; SGAP, superior gluteal artery perforator; TUG, transverse upper gracilis.
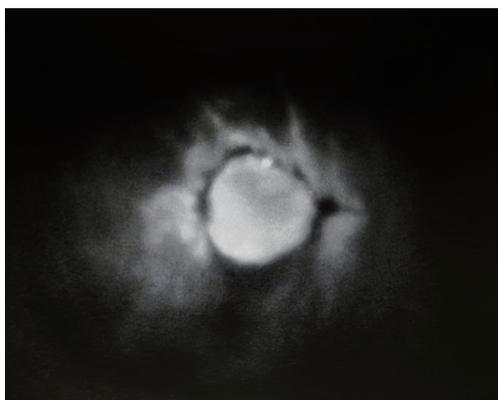
Figure 1 Indocyanine green (ICG) immunofluorescence intraoperative screen of a deep inferior epigastric artery perforator (DIEP) flap and surrounding mastectomy flaps. The flap is seen well-perfused, while an infra-flap area of mastectomy skin is poorly perfused.

In comparison to fluorescein, ICG has a superior side effect profile (22,24-28) and a shorter half-life than fluorescein (2.5 *vs*. 23.0 minutes), which enables multiple image captures (29). One of the major drawbacks of ICG is that the emitted light can only be detected up to 1 cm deep (31).

Numerous commercial NIR light detection devices are currently available (31). In breast reconstruction, SPY Elite system (Novadaq), FLARE system (Curadel LLC), PDE-Neo system (Hamamatsu Photonics), Fluobeam 800 system (Fluoptics), and IC-View system (Pulsion Medical systems AG) have been studied (*Table 2*). SPY Elite system has been most frequently reported (32-35). Despite having a relatively small field of view (10.1×7.4 cm^2) and lacking operating room light compatibility, in conjunction with the accompanying SPY-Q software (Novadaq), it allows storage of both static pictures and videos and performs complex quantitative analyses. To date, SPY Elite System has been FDA-approved for applications in plastic and reconstructive surgery, cardiothoracic surgery, visceral surgery, and transplant surgery (51). In contrast to the other devices, FLARE system consists of two separate NIR cameras synchronized to a color video camera, which enables display of real-time tissue fluorescence in the context of the surgical anatomy (54). Furthermore, FLARE has the longest working distance (45 cm) and the largest field view (15×11 cm^2). To date, the evaluation of FLARE system has been limited to preclinical animal models (39,54). PDE system has been available in the market longest. It is relatively affordable and has respectable

specifications. However, it only yields qualitative data and is not compatible with operating theater lights (38,55-59). Fluobeam 800 system is a small novel device that can be fitted into a suspension equipment in an operating theater. However, it produces qualitative data and has the shortest working distance (20 cm) and the smallest field of view (10×7.5 cm^2). Furthermore, similar to the FLARE system, it has only been investigated in animal models (60-63). IC-View has been well studied (31,42,64-73), but unfortunately, it is no longer available.

In plastic surgery, FA has been useful in the assessment of breast reduction skin flaps (36,37), selection of dominant perforator in free flap transfers (35,38), assessment of flap perfusion (39,40) and patency of microvascular anastomosis (41), postoperative flap monitoring (42), and in the assessment of burns injury (43). However, its application has been most extensively reported in breast reconstructive surgery, to aid sentinel lymph node biopsy, evaluate mastectomy skin flaps in prosthesis-based reconstructions, and autologous free flap reconstructions.

Sentinel lymph node biopsy is a crucial component of axillary staging in patients with breast cancer (74,75). Accurate diagnosis is paramount since axillary clearance in sentinel node-negative patients has demonstrated no clinical benefits but creates morbidity from the subsequent lymphedema (74). Currently, the gold standard investigation involves the use of methylene or patent blue dye for node detection and radioisotope for lymphoscintigraphy (74,76,77). However, the blue dye has a high side effect profile (75). In contrast, ICG is a safe, accurate, and reliable tracer agent (56,57,59,70,71,79-83) (*Table 3*). Furthermore, ICG enables 3D visualization of the lymphatic vasculature (54). Compared to the radioisotope, ICG has a similar or superior nodal detection rate (55,80,81,83) and when they are combined, the rate of positive sentinel node detection is improved (80,82). Moreover, the nodal detection rate of ICG can be enhanced by incubating it with HSA (54,84). In summary, ICG is a superior tracer agent to the traditional blue dye for investigation with radioactive isotope in sentinel lymph node biopsy.

The rate of prosthesis-based breast reconstruction is rising rapidly (85). In comparison to the traditional two-stage tissue expander approach, a single-stage implant reconstruction is potentially more attractive since it simplifies the reconstructive process, limits exposure to general anesthesia and hence, more cost-effective (87-91). However, majority of clinicians still perform the two-stage reconstruction due to relatively high risk of implant-related complications and

prosthesis failure associated with the single-stage procedure (92-94). Using acellular dermal matrix has only demonstrated small benefit in the overall rate of mastectomy skin flap necrosis and (6.9%) and implant loss (1.1%) (98). To this effect, FA can useful by enabling clinicians to detect subclinical hypoperfused tissue and guide appropriate excision (100,102,106) (*Table 4*). Numerous studies have attempted to define a threshold value using both relative and absolute measurements to reliably predict perfusion and potential necrosis (93,100,101). However, a standardized, reproducible threshold value has not been established. Nonetheless, evidences indicate that using ICG-based FA to guide excision of hypoperfused mastectomy skin flap results in a significant reduction in skin necrosis (33,94). Furthermore, Duggal *et al*. report a reduction in the severity of skin flap necrosis (25% *vs*. 44.1%) and the rate of re-operation (6% *vs*. 14%), compared to the historical control (94). Additionally, these findings translate to a cost saving of USD 614 per patient (94). However, Kanuri *et al*. mention that an indiscriminate use of ICG can be expensive and recommend reserving the use of FA in high-risk patients—smokers, BMI of greater than 30 kg/m^2, and mastectomy weight of greater than 800 g (99).

In contrast to the prosthesis-based reconstructions, autologous breast reconstructions are more natural-appearing, aesthetically pleasing, and long-lasting (107,108). Historically, various donor sites have been studied for breast volume replacement, such as omentum (109), gluteal artery perforator flap (110), latissimus dorsi (111), deep circumflex iliac artery (groin) flaps (112), tensor fascia latae (lateral thigh) flap (113), triceps flap (114), SIEA flap (115), TUG flap (116), and PAP flap (117). However, the abdominal wall remains the most popular donor site due to its consistent large volume and the added aesthetic benefit to the donor site, akin to an abdominoplasty. TRAM flaps have been successful at supplying adequate volume (118-120). However, they are associated with a significant number of partial flap necrosis (7%–31%) and donor site morbidity from subsequent rectus muscle weakness and ventral hernia (0.3%–11.0%) (121,122). As a result, muscle-sparing techniques have evolved and DIEP flaps have become popular. Despite being associated with longer microsurgical dissection and a substantial rate of fat necrosis, the introduction advanced modern imaging modalities, such as CTA, MRA, and FA, have improved flap outcomes in DIEP flaps (9,123). Since FA can only assess tissues up to 1 cm deep and a thick pannus is preferred in DIEP, it is less frequently utilized in the preoperative setting for perforator selection (8-10,125-129). Similarly, FA has a minimal role as a postoperative monitoring tool (12,42,48,130). Currently, FA has demonstrated most utility as an intraoperative tool to assess flap perfusion, microvascular anastomosis, and SIEA vascular territory.

Early studies have reported that ICG-indicated hypoperfused areas correlate accurately with areas of postoperative flap necrosis in TRAM and DIEP flaps (33-35,124,131-133). As a result, Newman *et al*. note that flap adjustments performed where FA demonstrated hypoperfusion led to successful reconstruction (34). In a larger retrospective analysis, Duggal *et al*. demonstrate a trend in the reduction of rate of flap necrosis (14% *vs*. 22%, P=0.237) and flap loss (1.4% *vs*. 3.4%, P=1.00) using ICG-guided excisions. Likewise, FA enables direct visualization of flow defect that may indicate anastomotic or vascular compromise in the early stages (134,135). Holm *et al*. report that FA can detect thrombotic occlusions with sensitivity of 100% and specificity of 86% (136). The same group calculated the time taken for the dye to travel from the arterial anastomosis to the venous anastomosis, and ITT of 50 seconds or greater would indicate postoperative re-exploration or flap loss with sensitivity of 92% and specificity of 98% (137). Despite being an attractive abdominal wall free flap option due to having no donor site morbidity, SIEA flap has been less commonly utilized due to its inconsistent vascular anatomy and variable size of its vascular territory (138,139). Encouraged by recent cadaveric and clinical studies suggesting that SIEA may be present more consistently (115,140-144), investigators have devised various management algorithms using laser Doppler flowmetry or ICG-based FA to reliably determine the vascular territory of SIEA for planning breast reconstruction (142,143,146). Currently, more evidences are still required to validate these algorithms.

Conclusions

For decades, FA has used for ophthalmic angiography, cardiothoracic surgery, hepatobilliary surgery, and neurosurgery for assessment of flow and perfusion and currently numerous commercial ICG detector systems are available. In plastic surgery and breast reconstruction, ICG-based FA is a relatively novel imaging technology shown promise in various applications. During sentinel lymph node biopsy, ICG has demonstrated a safer and a more accurate tracer agent, in lieu of the traditional blue dyes, for use with radioactive isotope. Using FA to guide excision of hypoperfused areas in implant-based breast reconstruction

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for high-risk patients—smoking, high BMI, and large breasts—has shown to improve clinical outcomes and be cost-effective. In autologous reconstructions, FA displays most promise in the intraoperative assessment of the flap perfusion, microvascular anastomosis, and SIEA flap.

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Footnote

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