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WJGS mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal surgery and covering a wide range of topics including biliary tract surgical procedures, biliopancreatic diversion, colectomy, esophagectomy, esophagostomy, pancreas transplantation, and pancreatectomy, etc.

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Application of indocyanine green in surgery: A review of current evidence and implementation in trauma patients

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Abstract

Background: Modern surgical medicine strives to manage trauma while improving outcomes using functional imaging. Identification of viable tissues is crucial for the surgical management of polytrauma and burn patients presenting with soft tissue and hollow viscus injuries. Bowel anastomosis after trauma-related resection is associated with a high rate of leakage. The ability of the surgeon's bare eye to determine bowel viability remains limited, and the need for a more standardized objective assessment has not yet been fulfilled. Hence, there is a need for more precise diagnostic tools to enhance surgical evaluation and visualization to aid early diagnosis and timely management to minimize trauma-associated complications. Indocyanine green (ICG) coupled with fluorescence angiography is a potential solution for this problem. ICG is a fluorescent dye that responds to near-infrared irradiation. **Methods:** We conducted a narrative review to address the utility of ICG in the surgical management of patients with trauma as well as elective surgery. **Discussion:** ICG has many applications in different medical fields and has recently become an important clinical indicator for surgical guidance. However, there is a paucity of information regarding the use of this technology to treat traumas. Recently, angiography with ICG has been introduced in clinical practice to visualize and quantify organ perfusion under several conditions, leading to fewer cases of anastomotic insufficiency. This has great potential to bridge this gap and enhance the clinical outcomes of surgery and patient safety. However, there is no consensus on the ideal dose, time, and manner of administration nor the indications that ICG provides a genuine advantage through greater safety in trauma surgical settings. **Conclusions:** There is a scarcity of publications describing the use of ICG in trauma patients as a potentially useful strategy to facilitate intraoperative decisions and to limit the extent of surgical resection. This review will improve our understanding of the utility of intraoperative ICG fluorescence in guiding and assisting trauma

surgeons to deal with the intraoperative challenges and thus improve the patients' operative care and safety in the field of trauma surgery.

Key Words: Trauma; Indocyanine green; Fluorescence angiography; Perfusion imaging; Fluorescence guided surgery; Acute care surgery

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Core Tip: There is no consensus on the ideal dose, time, and manner of administration of Indocyanine green Fluorescence (ICG) as well as its indications in the acute surgical settings. There is a scarcity of publications describing the use of ICG in trauma patients as a useful adjunct to facilitate intraoperative decisions and to safely limit the extent of surgical resection. ICG has been increasingly used for surgical guidance as an intraoperative localizing technique, tissue perfusion evaluation, and imaging for anatomy identification and leaks as well as to provide targeted therapies. This review explored the potential utility of ICG in trauma surgery.

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INTRODUCTION

Hollow viscus injury is relatively uncommon[1,2]. Early diagnosis and timely management are essential to minimize the associated complications[3,4]. Identifying structures that need to be resected and spared during traumatic surgery is of paramount importance. Surgical resection of the damaged or devascularized bowel segments is often required. In daily practice, resection is guided primarily by the surgeon's ability to recognize and assess injured segments using conventional room light (white-light imaging), which relies on visual inspection. Resection is often followed by immediate bowel anastomosis.

Bowel anastomosis after trauma-related bowel resection may be associated with high leak rates[5]. Although the etiology of these leaks may be multifactorial, tissue perfusion at the ends of the resected bowel remains one of the most important determining factors for anastomotic leaks and strictures[5,6].

Technological developments have transformed human lives and medical practice in several fields. The ability of the bare eye of surgeons to determine bowel viability remains limited, and the need to obtain a more standardized objective assessment has not been fulfilled[7]. There is a need for tools to enhance surgical evaluation and visualization while eliminating the risk of damage to vital structures. Fluorescence angiography (FA) with indocyanine green (ICG-FA) is a potential solution to this perplexing problem[7] and is used worldwide to assess visceral perfusion[8]. The fluorescent signal obtained following intravenous ICG injection is thought to be proportional to blood flow. This allows surgeons to address poor regional perfusion that is otherwise challenging to detect intraoperatively[9, 10]. Evidence in elective surgeries is available; however, reports on this technology in trauma are sparse [11].

ICG is a fluorophore dye with fluorescent properties that respond to near-infrared (NIR) irradiation. ICG has many applications in different medical fields and has been used for several decades to determine the cardiac output, hepatic function, and fluorescence-guided surgery (FGS). Examples include intraoperative localization techniques (*e.g.*, sentinel lymph node mapping or metastasis), tissue perfusion evaluation (for resection and anastomosis), imaging for vital structure identification (*e.g.*, cholangiogram, ophthalmic structures, and neurovascular structures), leaks, and targeted therapies[8, 12-15].

ICG for real-time tissue perfusion assessment is feasible in open and minimally invasive surgeries (MIS). This has been proposed as a potential solution to the limitations of bowel viability assessments, particularly for MIS[16]. Fluorescence angiography helps surgeons assess bowel perfusion and viability for better resection margins, preserve normally perfused bowel, and minimize the potential for ischemia-related anastomotic leaks[17]. It has great potential to bridge this gap and enhance the clinical outcomes of surgery and patient safety[18].

Advances in imaging and intraoperative tools have impacted medical and surgical practices and may help resolve this precision surgery dilemma[19,20]. Adopting technology for surgical procedures and trauma care is a natural process. Despite these advances, surgical complications remain high, with implications for mortality, cost, and long-term complications; thus, the game is not over[8,11,21-24]. We

conducted a narrative review to address the utility of ICG in the surgical management of patients with trauma as well as elective surgery. This will guide and help trauma surgeons to deal with the intraoperative challenges, improve the patients' operative care, and improve the safety in trauma surgery.

INTRAOPERATIVE INDOCYANINE GREEN FLUORESCENCE GUIDANCE

Indocyanine green fluorescence (IO-ICGF) guidance is an evolving and exciting concept. The limitations of the human senses are well-documented: Sight and touch, which open the door for technological augmentation and support (guide) of the surgeon's visual and tactile localization. The need is amplified in MIS[16,17]. Evidence shows that surgeons' assessment of tissue perfusion concerning future anastomotic leaks has low sensitivity and specificity[25]. The potential benefits of such guidance include increased safety, reduced operating time, decreased need for second look operations, and decreased risk of complications such as leaks, infections, dehiscence, strictures, and reoperations. Proper resection margins are achieved by removing damaged tissue while protecting the normal tissue and enhancing adequate healing.

Residual ischemia on extrapolation resembles residual tumors after surgical resection; residual ischemia strongly predicts anastomotic failure, and residual tumors predict tumor recurrence. In the event of cancer, histopathological evaluation of the margins of frozen sections (FS) is a viable intraoperative solution for some tumors. Nonetheless, the literature discloses various FS-related problems, and the FS results differ by up to 15% from the permanent pathological data. However, solutions for residual ischemia are yet to be adequately addressed[26]. This problem can be exploited for the use of IO imaging, such as computed tomography/magnetic resonance imaging, as described in Neuro Surgical practice with apparent complexities of the cost, the needed space, logistics, and the potential interruption of operative time, which makes them non-practical solutions in many setups[27].

ICG, as an example of FGS, has been a strong competitor since 1948 in the search for a practical solution to the dilemma of perfusion assessment. ICG was first used in biological applications in 1956 and was authorized by the Food and Drug Administration (FDA) for diagnostic use in cardio-circulatory and hepatic functions[28].

Fluorescence angiography is a potential solution to the perfusion problem with reported high sensitivity, specificity, contrast, safety, low cost, ease of use, and seamless real-time imaging utility when it comes to interrupting operative processes[27,29]. ICG is the primary agent with a long history of use and high safety profile.

Owing to several merits, FGS has excellent potential for improving surgical practices and associated outcomes. It can direct IO image-guidance margin assessments and detect microscopic tumors, residual lesions, and tissue perfusion. Furthermore, it may aid in avoiding surgical complications, and the benefits of ICG may open new applications in various trauma-related subspecialties. Nonetheless, most surgeons continue to rely heavily on conventional visual and tactile cues and preoperative imaging to make resection decisions[19,20].

There is explosive interest in FGS research, fluorescence imaging devices, and system development and adoption. Nevertheless, a common problem is that evolving technology requires long standardization[18,30]. These arrangements include a wide range of technological issues, such as determining the appropriate agents (fluorophores or dyes), specific indications and clinical utility, acquiring supporting data and evidence, selecting the correct dose, and determining the optimal time for administration (whether before the operation, intraoperatively, or both). Nevertheless, the adoption of FGS is on the rise. The industry is actively introducing new probes and devices, including improved portable cameras with real-time imaging and easy non-distracting integration, enriching this attention and growing interest[18,31].

Furthermore, other technical aspects of this technology need to be addressed in the future: whether we need a subjective dose (individualized) is also a possible way to optimize the tissue dosage and effects; can we measure real-time quantity at the tissue level? Tissue-to-background ratio optimization is an ongoing discussion in the literature[32]. A recent consensus paper surveyed 19 international experts in FGS and reported strong agreement on its safety and effectiveness. Although it is no longer considered experimental, there is a considerable need to study ICG administration details (dose, concentration, route, and timing for optimal use)[18].

In many oncological practices, using NIR fluorescence imaging with ICG has become commonplace, both in open surgery and MIS, such as during staging laparoscopy for cancer[33]. This fact makes ICG the primary available dye with considerable literature support and wide use. The equipment available is designed to handle this agent and is one of the few FDA-approved agents.

Regarding MIS, Laparoscopic systems [high-definition (HD) cameras attached to a laparoscope with an NIR filter to detect fluorescence] were reported by Boni *et al*[34]. NIFICG allows real-time direct image assessment of tissue perfusion and vascularization related to anastomotic and stapler line leaks [35]. A full HD image 1 S camera, switching to NIR mode within a few seconds after the injection of ICG, provides real-time angiography of bowel perfusion before the anastomosis and another additional dose after establishing the anastomosis to confirm anastomotic perfusion with adequate vascularization.

TECHNOLOGY AND APPROVED FLUOROPHORES

The imaging step requires an NIR fluorescent agent (or fluorophore) and imaging system to excite and detect fluorophore signals within milliseconds. Two approved generic agents are used clinically by the FDA and the European Medicines Agency: ICG and methylene blue. Methylene blue is a weak fluorescent dye with low yield, which is why it is not commonly used. On the other hand, ICG is the most widely used fluorophore for this purpose for all the reasons mentioned above; historical, safe, and practical. There is increasing interest in the development of new tracers for expanding clinical applications[29].

CHARACTERIZATION, METABOLIZATION, ADMINISTRATION, AND OPTICAL PROPERTIES OF ICG

ICG is a water-soluble, anionic, amphiphilic tri-carbo-cyanine iodide dye probe with a molecular weight of 776 Da[36,37]. It binds to plasma proteins, has a short half-life (150-180 s), and is rapidly eliminated by hepatic clearance[37,38]. It was used in human health at the Mayo Clinic after it was launched as a dye in photography by the Kodak research facilities in 1955. The FDA approved it in 1959 as an indicator material (*e.g.*, photometric hepatic function diagnostics and fluorescence angiography) in circulatory, hepatic, cardiac output, and ophthalmic research. It is injected intravenously and depending on liver function, has a half-life of approximately 3-4 min in the body[8,38]. ICG sodium salt is often available in powder form and is soluble in a variety of solvents; 5% (depending on the batch) sodium iodide is typically added to improve its solubility[15]. ICG is limited to the vascular system after forming a strong bond with plasma proteins. ICG is only eliminated from the circulation by the liver and converted to bile[15]. The recommended dose is 2.5 mg before indulging in the anastomosis performance or 0.2-0.5 mg/kg[34,39,40]. The vasculature was visible within 60 s, and the anastomotic site was visible on NIR fluorescence imaging[41-43]. A second bolus of 2.5 mg, usually 15 min after the first injection, can be repeated if the signal begins to fade. Good perfusion supports completing the anastomosis as planned; furthermore, the check for perfusion (ischemia) should be performed before or after the anastomosis or both[44]. A similar dosage is also used for liver resection margins, where liver segment perfusion happens within one-two minutes (similar time frame). There are two routes: The peripheral veins and portal vein[45-47].

The lag in advancing the technique was related to the technical limitations associated with film-based photography. Since 1980, several technological challenges have been resolved, owing to the invention of new camera types, improved films, and higher-resolution photometric measurement tools. ICG is now routinely used in medicine, which has happened in the meantime. Since its early inception in the medical field, more than 5000 scientific papers on ICG in Surgery have been published worldwide[15].

ICG exhibited NIR absorption and fluorescence spectra. Both parameters varied significantly, depending on the concentration and solvent used[48]. ICG emits fluorescence between 750 nm and 950 nm and absorbs mostly between 600 nm and 900 nm[48]. The significant overlap between the absorption and fluorescence spectra caused ICG to absorb light significantly. The fluorescence spectra were highly diverse. It reaches its highest levels in water at 820 nm and in blood at approximately 830 nm[48]. ICG becomes a fluorescent (or light-emitting) form of luminescence upon excitation with a specific wavelength of light (about 820 nm) in the NIR spectrum.

Furthermore, NIR light (700-900 nm) is more valuable than visible light, as it allows for up to 10 mm of tissue penetration, provides maximum tissue contrast because auto-fluorescence is not observed, and maximizes signal-to-background ratios[49]. The emitted signal can be detected even within deep structures because it is transmitted through the tissue. This feature allows for less invasive real-time imaging of vessels and lymphatic ducts inside organs during surgery[50,51]. NIR ray illumination of ICG generates NIR fluorescence, permitting real-time transcutaneous intraoperative visualization of structures, such as superficial lymphatics and vessels. Merging these signals with normal RGB (red, green, and blue) color videos facilitates anatomical orientation, recording, and analysis.

Several NIR fluorescence imaging devices have been developed for intraoperative clinical use. Despite differences in the technical parameters, all these devices offer the surgeon an image of the NIR fluorescence signal[52]. Color imaging using imaging systems such as the HyperEye Medical System can simultaneously detect NIR rays under ambient light with outstanding diagnostic precision[53].

Literature on ICG use in trauma is limited, and our search identified only a few reports. The first is a recent case series demonstrating the utility of this technique in guiding anastomosis after post-traumatic damage-controlled resection. In one case, it led to further resection; in the other two, it assured good perfusion and permitted anastomosis without subsequent leaks[54].

Secondly, a retrospective study by Yamaguchi *et al*[11] explored the use of ICG NIR fluorescence to reduce postoperative complications in operative cases of mesenteric and bowel injuries. They concluded that ICG NIR tended to be associated with fewer complications after traumatic damage, regardless of the need for resection. This procedure is easy and quick. However, the study had several limitations. The authors called for randomized controlled trials to explore this technology for its routine use in

stable patients[11]. Unfortunately, in the setup of trauma, recruitment would be very challenging.

Furthermore, Aggarwal *et al*[55] reported a case of ICG FA guiding the resection of post-traumatic bowel ischemic ileal strictures. It provides real-time objective perfusion assessment to show the length of the ischemic segment to be resected.

Despite the availability of few reports (even small case series), Smyth *et al*[56] commented on the use of ICG in trauma settings to predict anastomotic leaks considering it a very new and promising concept [54,56].

SAFETY AND ADVERSE EVENTS ASSOCIATED WITH ICG

ICG has been used successfully in clinical research for over 50 years, has been shown to have a favorable safety profile, and is rarely associated with adverse reactions. ICG is very safe, with rare cases of anaphylaxis and caution regarding potential cross-reactions in patients with iodine sensitivity[57]. It has a long history of use, and a high safety index with rarely reported allergies (1:10000) supports this growing interest[28,37]. The intestinal mucosal membrane does not absorb ICG, and therefore, its toxicity is minimal. It is microsomal digested in the liver and eliminated by the liver and bile ducts. There are risks associated with administration during pregnancy[58].

It has been understood that ICG breaks down into harmful waste products when exposed to UV radiation, producing a multitude of as-yet-unidentified compounds[59,60]. In one of every 42000 instances, people experienced minor side effects, including sore throats and heat flashes[58,59]. Anaphylactic shock, hypotension, tachycardia, dyspnea, and urticaria were only seen in a few instances; the risk of severe side effects increases in patients with chronic renal impairment[58,60].

THE NEED FOR ICG IN TRAUMA SURGERY

Anastomotic leakage is a perplexing and frequently clinically challenging issue in elective and emergency surgeries with significant morbidity and mortality. Hypoperfusion near resection margins is thought to be a powerful indicator of anastomotic failure and subsequent leakage[5]. Gross surgical assessment is the gold standard for perfusion (vascularity) assessment[11]. This assessment involved visual inspection, palpation of the mesentery, and intraoperative ultrasound assessment. Naked eye assessment is limited, whereas palpation and ultrasound assessments may not be an option for MIS[25]. There is an urgent need to augment perfusion assessment using a simple and affordable tool without interrupting the flow of the surgery[8], and it can also be applied for MIS.

The merits of Intraoperative NIR fluorescence or simple fluorescence imaging include high contrast, low cost, safety (no ionizing radiation, low incidence of allergic reactions), ease of use, high sensitivity, and specificity[27,31,61], and the MIS option make it the best available solution.

Along with other oncological surgical benefits, such as lymph node mapping and tumor tissue identification, intraoperative vascularity assessment may increase the extent of resection, shorten the surgical time, protect viable tissues, lessen the need for second-look surgeries, and identify vital structures. As a result, there has been growing acceptance in recent years. Our literature review found that tissue perfusion adequacy is the primary determinant of visceral tissue viability[62] and is the main reason for its use during trauma. Theoretically, all the other reported uses are potential areas for use in trauma surgery, with only a few supporting reports.

The recent clinical trials on the use of ICG in trauma and surgery

Table 1 summarizes most of the concurrent clinical trials addressing the utility of ICG in trauma ($n = 18$) and general surgery ($n = 13$), and most of the latter was for cancer surgery. Moreover, Figure 1 illustrates the different utilities of ICG that also can be used as an algorithm for bowel injury management.

THE USES OF ICG IN TRAUMA

The use of ICG in trauma surgery is primarily associated with anatomical identification (visualization of vital structures). Examples include the cystic duct, ureters, nerves, vessels (angiography), and thoracic ducts (lymphography)[11]. Every operation has the unique risk of causing inadvertent harm to a neighboring vital structure. Effective intraoperative procedures are required to locate and safeguard structures. Based on their clearance characteristics, fluorescence imaging with ICG can identify and map the biliary tree, cystic artery, and ureter *via* different routes of administration[8].

Biliary mapping/leak detection after DCS in severe liver injuries (fluorescence cholangiography)

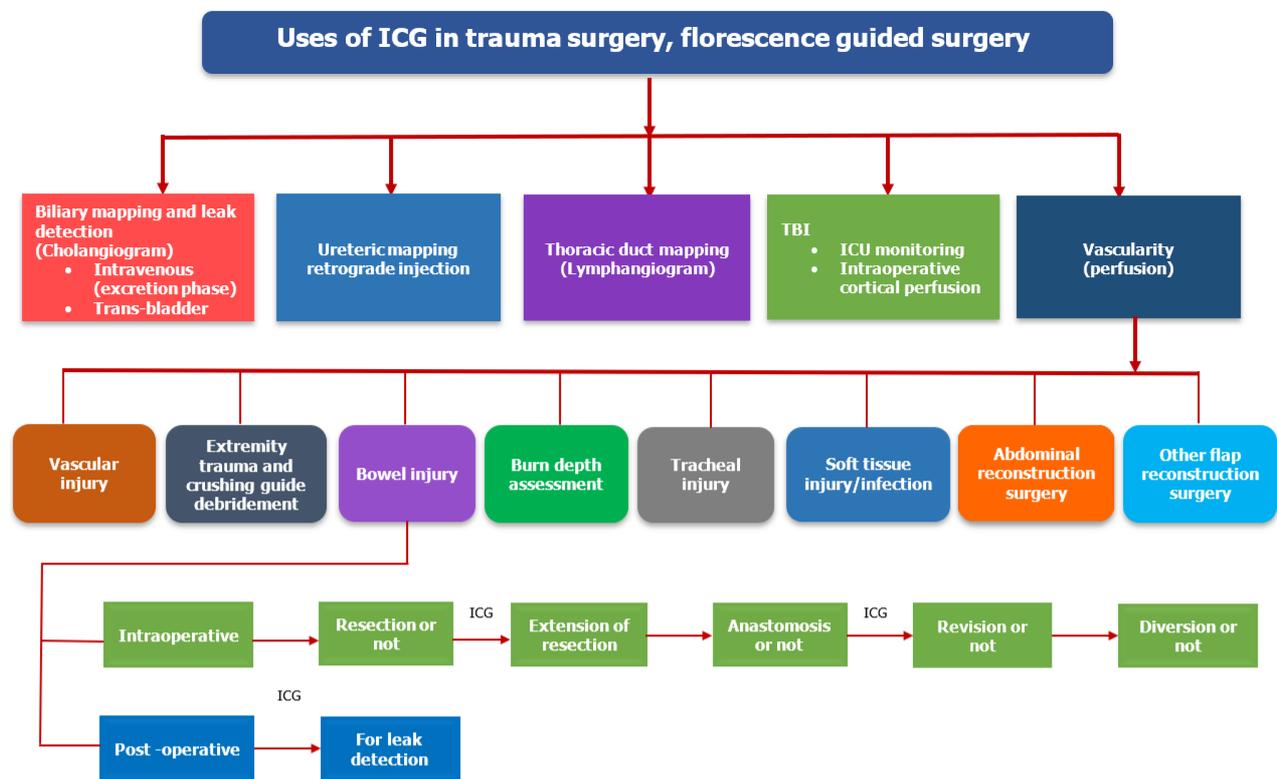
This technique has not been reported to be used in trauma patients; however, it has been extensively

Table 1 Recent clinical trials for indocyanine green fluorescence use in trauma and surgery

Trial title	Subject/field	Status
ICG fluorescence imaging in trauma patients	Bone/soft tissue perfusion in fracture patients and surgical site infection	Completed
ICG fluorescence imaging in open fracture trauma patients	Open extremity fracture	Recruiting
ICG 24 h Prior to operative treatment of orthopedic infection	Bone trauma and soft tissue infection	Active, not recruiting
The role of indocyanine green angiography fluorescence on intestinal resections in pediatric surgery	Intestinal resection margins during elective and emergency pediatric surgeries	Completed
ICG fluorescence imaging in lower extremity amputation patients	Lower extremity amputation in and trauma	Recruiting
ICG fluorescence imaging in post-traumatic infection	Trauma injury	Recruiting
Feasibility and usability of intraoperative fluorescent angiography with indocyanine green in penetrating abdominal trauma	Abdominal trauma	Completed
Non-invasive measuring of cerebral perfusion after severe brain injury with near-infrared-spectroscopy and ICG	Subarachnoid hemorrhage, intracerebral hemorrhage, TBI	Recruiting
Dynamic contrast-enhanced fluorescence arthroscopy of meniscus pilot	Knee injury	Recruiting
ICG 24 h prior to operative treatment of orthopedic infection	Trauma injury, infection	Active not recruiting
A study assessing circulation around surgical incisions at the time of laparotomy closure	Laparotomy	Completed
Application	Fractures, comminuted, surgical wound dehiscence, necrosis	Terminated has results
NIRST and ICG-based perfusion imaging in acute compartment syndrome	Compartment syndrome lower limb, forearm	Recruiting
ICG and SPY imaging for assessment of burn healing	Burns	Completed
NIR arthroscopic fluorescence angiography of menisci	Meniscus rupture	Not yet recruiting
Detection of cerebral ischemia with a non-invasive neurometabolic optical monitor	TBI, ischemic stroke, intracerebral hemorrhage	Completed
A new multi-parameter neuromonitoring system to save patients' lives in stroke and brain injury	Subarachnoid hemorrhage	Completed
Pilot study to assess the use of spy elite for assessment of amputation healing	Wound healing lower extremity amputation	Completed
Near-infrared fluorescence with indocyanine green for identification of sentinels and parathyroid during thyroidectomy	Thyroid cancer	Unknown
Near infrared fluorescence imaging with ICG	Lung cancer	Completed
A study of perfusion of colorectal anastomosis using FLAG-trial	Colorectal cancer	Completed
Near-infrared fluorescence imaging as a supportive tool for localization of deep infiltrating endometriosis during laparoscopy	Endometriosis	Completed
Prospective evaluation of near-infrared fluorescence imaging use as a supportive tool in deep infiltrating endometriosis surgery	Endometriosis	Completed
NIF-guided ramie using ICG <i>vs</i> OTE feasibility randomized controlled trial	Esophageal cancer	Recruiting
Falcon: A multicenter randomized controlled trial	Cholecystitis	Unknown status
Quantitative ICG fluorescence angiography in colorectal surgery	Colorectal cancer	Recruiting

Effect and long-term outcomes of indocyanine green fluorescence imaging method <i>vs</i> modified inflation-deflation method in identification of intersegmental plane	Lung cancer	Recruiting
Intraoperative ICG fluorescence angiography in colorectal surgery to prevent anastomotic leakage	Colorectal cancer	Not yet recruiting
Synapse 3D with intravascular ICG	Lung cancer	Not yet recruiting
The role of ICG fluorescence imaging on anastomotic leak in robotic colorectal surgery	Colorectal diseases	Unknown status
ICG molecular fluorescence imaging technique using in diagnosis and treatment of primary liver cancer	Liver cancer	Recruiting

Adopted from: <https://clinicaltrials.gov/ct2/results?cond=indocyanine+green+fluorescence+clinical+trials&term=&cntry=&state=&city=&dist=> & <https://clinicaltrials.gov/ct2/results?cond=Indocyanine+Green+%28ICG%29+Fluorescence+in+trauma&term=&cntry=&state=&city=&dist=> & <https://clinicaltrials.gov/ct2/show/NCT04245111>; <https://clinicaltrials.gov/ct2/results?cond=Trauma&term=ICG&cntry=&state=&city=&dist=>. Accessed on 11 January 2023. ICG: Indocyanine green; NIR: Near-infrared; FLAG: Fluorescence angiography; TBI: Traumatic brain injury; NIRST: Near-infrared spectroscopic tomography; OTE: Open transthoracic esophagectomy.



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Figure 1 Utility of indocyanine green in trauma and surgery. ICG: Indocyanine green; TBI: Traumatic brain injury.

studied and utilized in biliary surgery. The literature has shown no agreement on dosage and time; the biliary in elective should be done roughly 5 h beforehand for the best contrast, and mapping may start as soon as 30 min after the IV injection and can be repeated[52]. This is a potential limitation in emergency setup and trauma; though intra-gall bladder injection is a feasible alternative route; no substantial evidence is available[63]; although it may be used as an alternative to other cholangiogram techniques such as traditional trans-cystic or methylene blue in cases when it is necessary to rule out bile duct damage or bile leaks after penetrating trauma or during second-look laparotomy for serious liver injuries. If identified, the leaking duct should have been overlooked. No consensus on the optimal dose was reached in published literature; however, a dose of 5 mg was injected 3-7 h before incision in elective cases, but even shorter intervals were described, with no significant practical differences[52,64].

Ureteric mapping using ICG

The use of ureteric mapping is less widespread than other available agents, such as methylene blue or the newer ZW800-1, a novel dye exclusively secreted by the kidneys[62]. Santi *et al*[65], in a recent report

on the use of ICG for laparoscopic colorectal resections, commented on the avoidance of iatrogenic ureteric injuries through injection of the dye through the urinary catheter to identify the ureter in difficult dissection due to adhesions when the tumor is tightly attached to the ureter; the ICG solution was retrogradely injected through a ureteric catheter. Siddighi *et al*[66] reported 10 cases of retrograde ICG injection using a 6F ureteral catheter, allowing ureteral identification in colorectal, urological, and gynecological surgeries. The literature reflects the search for renally excreted fluorophores that permit non-invasive ureteric visualization. Mahalingam *et al*[67] reported UreterGow-11 as the most promising, with near-exclusive renal excretion and observed fluorescence for more than 12 h with optical and biodistribution characteristics. Once again, we might infer a possible use in situations of challenging trauma exploration with retroperitoneal and pelvic hematoma to identify these structures and to attempt to safeguard them.

ICG for thoracic duct in chylothorax

Trans thoracic esophagectomy may result in a dangerous complication called chylothorax. It hinders oral intake, lengthens hospital stay, and is detrimental to overall survival[68]. Additionally, a thoracic duct (TD) lesion decreases body fluids and albumin, which causes hypovolemia and depletes T-cells[69]. Even with a high-definition thoracoscopy, intraoperative TD identification is often tricky. The best preventative approach to stop lesions is precise intraoperative diagnosis of TD. However, it is often tricky to identify the TD route or leaking location intraoperatively[70]. The same report commented on the intraoperative use of ICG with NIR fluorescence during minimally invasive esophageal surgery as an emerging approach for assessing gastric conduit perfusion. Vecchiato *et al*[70] percutaneously injected ICG (0.5 mg/kg solution) in the inguinal nodes of 19 patients undergoing MIS esophagectomy. The rationale for this was to identify the duct. The prone position was used before the thoracoscopy. The TD was determined after a mean of 52.7 min from injection time. No postoperative chylothorax or adverse effects of ICG green were observed. This study concluded that it is simple, effective, and not time-consuming and may become a new standard to prevent postoperative chylothorax[70].

Other case reports have described the inguinal injections of indocyanine green. Controlling postoperative leaks allows easy visualization of lymphatic leakage points during minimally invasive video-assisted thoracotomy (VATS). A potential trauma application is in cases of traumatic chylothorax, a rare entity that is difficult to control[71].

Jardinet *et al*[72] described a technique to facilitate thoracic duct identification and ligation control when required during robot-assisted esophagectomy. Lymphangiography-guided injection of indocyanine green into the right groin of a patient in the left-lateral position. Coratti *et al*[73] further simplified the complex intranodal injection of ICG subcutaneously 12-18 h before surgery compared with the operator-dependent United States-guided procedure. There have been no reports of trauma; however, extrapolation represents a potential use of traumatic chylothorax to identify and control leakage from the duct during operative management, whether open or minimally invasive approaches like VATS.

ICG in traumatic brain injury

Traumatic brain injury (TBI) pathophysiology of TBI is primarily related to the structural integrity of the brain. Multimodal monitoring is gaining popularity in the critical care of patients with TBI. ICG-NIR fluorescence has been used for TBI treatment. Although ICG has been described in ophthalmic studies for a long time[28], ICG and other fluorescent dyes have not been used in emergency neurosurgical interventions and traumatic brain injuries in contrast to elective tumor resections[74].

Although ICG is currently a research technique under study with limited clinical applications to meet numerous necessary characteristics, head injuries represent a possible application area. Potential clinical applications of NIR spectroscopy with ICG for non-invasive bedside continuous neuromonitoring include benefits in terms of logistics, radiation exposure, and cost. It can help measure brain perfusion and blood-brain barrier integrity in a critical care setup; however, several limitations exist. One of them is that the available devices do not correlate with invasive techniques for ischemic episodes, which is a significant drawback[75].

Kamp *et al*[76] used intraoperative ICG cortical perfusion assessment to predict long-term severe head injuries and short-term outcomes. This small retrospective study was based on using ICG FA to monitor regional cerebral blood flow during decompressive craniectomies. Microscopic add-on tool to assess ICG-induced Fluorescence. Ten patients underwent a standard surgical procedure and fluorescence assessment immediately after decompression. The parameters were correlated with 3-mo outcomes (favorable or unfavorable based on the Glasgow Outcome Scale and modified Rankin Scale). The authors concluded that the ICG-derived fluorescence curve was different in unfavorable patients. Fluorescence reflects underlying increased ICP, capillary leaks, and venous congestion, which are common pathophysiological changes in the body in response to severe TBIs.

This technology can potentially delineate outcomes if more extensive studies are conducted, and the heterogeneity of patients can be mitigated[76]. It is not currently a type of surgical guidance, experimental neuromonitoring, or exploratory prognostic tool to predict functional outcomes. The use of ICG-NIR technology in all stages of TBI treatment appears promising. It can be used to identify clinically important biomarkers from patients and provide more information about their comprehensive

physiological state.

Assessment of vascularity post-trauma (tissue perfusion)

The Intraoperative evaluation of tissue perfusion in patients with peripheral artery disease or vascular injury is crucial for predicting wound healing or symptom improvement. Currently, there are no commonly accepted standards for monitoring intraoperative tissue perfusion[77].

Tissue perfusion is critical for determining the return of normal function and post-injury healing. Decreased perfusion results in ischemia and contributes to secondary damage and healing failures. Identifying hypoperfusion at one or both bowel segments to be anastomosed dictates the broadening of resection margins and the need for new anastomosis or revision[78]. This information can also inform decisions to create a protective stoma for challenging and risky anastomoses. Simply put, it is probably the most important application in general and trauma to assist in intraoperative decision-making. The ICG-based imaging system was developed to examine the most recent degree of necrosis, capillary perfusion inside the tissue in question, and real-time arterial blood flow[77]. With the passage of the fluorophore in tissues after peripheral injection, illumination of the tissues under assessment generates fluorescence signals that correlate with the microvascular flow, that is, perfusion.

Bowel injury: As previously mentioned, anastomotic failures and leaks are among the most frequently challenging clinical problems after the restoration of resected bowel continuity[5,6,79,80].

The current standard of care supports intraoperative clinical evaluation of anastomotic perfusion by operating surgeons. Observing the color of the bowel, bleeding at the borders, and peristalsis of the segment are examples of visual and tactile feedback used in the subjective processes. Which is still a blind process with interobserver variability among surgeons; Furthermore, in traumatic cases, the naked eye is limited in appreciating the extent of blunt damage to the bowel, and it is mesentery and blood vessels; palpation is limited and is not an option in minimally invasive surgical options[25,31].

Historical techniques have been described; however, owing to their limitations, many have failed in terms of popularity and practice. Traditional intraoperative imaging (non-optical): These systems are costly, complex, space-demanding, and interrupt the operative flow, which makes them non-practical and available only in a few centers[81].

IO fluorescence imaging has many advantages that support its practical value in helping with visualization and providing surgeon guidance (*e.g.*, surgical GPS). As mentioned, it has many benefits, such as high contrast, sensitivity, specificity, low cost, user-friendliness, and absence of ionization, and thus, a high safety profile. Therefore, these applications have been widely investigated[27,29-31,82].

Literature reflects an increase in the use of this technology to guide resection and anastomosis to solve this issue by reducing the incidence of leaks and their sequelae related to fistula formation, reoperation, permanent stomas, bowel dysfunction, wound-related complications, stricture formation, quality of life, and mortality. It appears to be a reliable predictive tool to address the need to reduce anastomotic leaks in cancer-related resection of the colon, rectum, and other GI locations[5,82,83].

Arezzo *et al*[84], in a recent systematic review and individual participant database meta-analysis, assessed the effectiveness of ICG NIR intraoperative imaging in determining anastomosis perfusion in rectal cancer surgery and concluded that it has the potential to reduce the risk of anastomotic leaks compared to standard practice, independent of other factors such as sex, age, BMI, and anal border distance. In addition, more extensive, prospective, and randomized studies on this topic will help determine whether the occurrence of AL may be decreased by the routine use of ICG fluorescence imaging during surgery for rectal cancer[84].

ICG fluorescence blood flow speed in the gastric conduit wall can predict anastomotic leakage after esophagectomy, and microvascular perfusion of the capillary vessels of the gastric conduit may be impaired by systemic atherosclerosis. Why is ICG a perfect candidate for perfusion imaging[85]? This could be because it binds to plasma proteins and thus remains intravascular after the IV injection. Many reports on the use of ICG in esophagogastric and colorectal anastomoses, often after selecting the anastomotic site, help determine the right site with an influence site change between 3.7%-40.0%. Also reported on decreasing the anastomotic leak rate; in a systematic review, Degett *et al*[86] reported a decrease from 8.5% to 3.3% in the ICG group. In an earlier article, Campbell *et al*[87] reported a drop in the leak in the esophagus from 20% to 0%. Nevertheless, others reported no significant difference; even after a site change of 5%, the leak did not change significantly in a retrospective colorectal analysis[88]. This feasible technique can be conveniently obtained with minimal added time to the operations[89].

Extremity trauma, guide debridement, and decision on wound closure: Another potential application is to guide vital tissue and perfusion assessments in crushed limbs and combined vascular and orthopedic injuries to the extremities and infected wounds.

The surgical goal was timely and meticulous debridement was performed. ICG can help surgeons interpret the local circulation (perfusion) and demarcate debridement zones (identify necrotic devitalized tissues, both soft and bony). The wound (tissue) status is dynamic and may change over time. Factors such as aggressive debridement, infection, and local complications, may have contributed to this finding. Nevertheless, it remains an excellent area for bedside technique utilization. There are few reports of orthopedic and vascular trauma and other surgical wounds[90].

In addition, it can potentially guide decisions regarding wound closure and predict smooth healing, which might be an issue in some traumatic injuries, especially after angioembolization. These cases are challenging because of the double hits of the original trauma and ischemic tissue injury. Controlling bleeding by interventional radiology embolization or surgical ligation often results in collateral damage; the second hit is ischemia and extensive tissue necrosis[77,91]. Michi *et al*[92], in a recent systematic review regarding the use of ICG to assess bony perfusion, concluded that studies and evidence were limited and more clinical studies are needed.

Endoscopic anastomotic assessments such as tracheal anastomosis have potential clinical applications. In a prospective study, Schweiger *et al*[93] reported the feasibility of ICG perfusion assessment during bronchoscopy for elective cases and was theoretically feasible in selected post-traumatic cases.

War-related traumatic soft tissue and orthopedic injuries: One known challenge in high-energy war-related injury mechanisms, such as blast and ballistic injuries, is determining the viability of soft and bony structures in heavily contaminated fields. This is further confounded by the evolving and secondary infection-related necrosis. Green *et al*[94] reviewed and illustrated the use of IO fluorescence angiography for case series of war-related trauma. He reported the ability of this adjunctive tool to critically and rapidly assess traumatized tissue perfusion to avoid near misses, morbidities, and perfusion-related problems, by objectively permitting effective surgical modifications and enhancing clinical outcomes. Nineteen percent (35 patients) required operative modifications for better-perfused tissues; nine patients used NIR ICG for bowel perfusion[94].

Reconstructive surgery: In cases where tissue perfusion is a concern and clinical and physical assessments are unclear, ICG angiography can be a beneficial tool (adjunct) for serving hands and reconstructive surgeons. ICG real-time angiography visualizes contemporary tissue physiology and enhances decision-making during crushing and traumatic avulsions. The flow to digit tips is a particulate example where small-vessel spasms (common and proper digital vessels) confound the clinical assessment. Ghareeb *et al*[95] described three cases in which this utility proved to be of great help (two were traumatic, while the third was a case of Reynaud's ischemia): Injection of 5 mL dye solution with a 10cc NS flush. At the same time, the tissues of concern were centered on the device's screen. The device was activated, the initial fluorescence test of the arterial inflow was followed, and the scan was repeated for 10 min to check for venous outflow and congestion. A repeat is feasible within 10-15 min, and data can be stored, allowing comparison with normally perfused tissues.

Moreover, the percentage of fluorescence helps quantify the perfusion adequacy. These findings can help salvage decisions and attempt revascularization, replantation, or conservative amputation[95]. Mothes *et al*[96] modified ICG angiography treatments and predicted failure in a superior manner to traditional clinical indicators (capillary refill, turgor, bleeding, and temperature)[93]. Along with the guidance of free flaps in identifying perforators in the abdomen, thigh, and forearm to facilitate flap creation and predict flap necrosis and loss[96-98].

Similarly, lower-limb trauma and vascular injury applications are also of great interest because the convenience of quickly repeating ICG angiography compromises circulation both during surgical exploration and postoperatively compared to traditional angiography[99]. This versatility provides clinicians with an advantage in terms of tissue perfusion and viability. It permits a precise surgical plan in complex situations and injuries, and consent and counseling can be performed in collaboration with an awake patient[100,101].

These advantages have also been reported for bony flap reconstruction[101]. The cut-off tissue viability determination was 30%, which is the current device manufacturer's recommendation[102,103].

ICG helps in intraoperative and postoperative flap design, especially with newer systems such as the VSIONsense real-time fusion image of both NIR and white light with highlighted perfusion NS flow scale color-coded to enhance the interpretation of anatomy and perfusion. Bigdeli *et al*[104] addressed this technique in 8 patients and proved its practicability.

In a recent systematic review, Li *et al*[105] concluded that ICG for detecting flap perforators and microcirculation(perfusion) evaluation informs surgical decision-making regarding the selection of dominant cutaneous nerves, anastomosis quality, and thrombosis identification[105].

Patel *et al*[106] used ICG to identify poorly perfused tissues in complex abdominal reconstruction. Concerning the potential to decrease delayed healing, the authors reported accuracy in identifying perfusion, abnormalities, and skin viability in complex hernia repairs. Thus, wound healing-related complications. Adams *et al*[107], in a recent scoping review of ICG in complex abdominal wall reconstruction, suggested a role, while others did not. Therefore, guidelines on ICGFA in this aspect will require more studies and future meta-analyses[107].

The tool expands the armamentarium for reconstructive surgeries. It is highly useful for decision-making during accurate debridement and soft tissue coverage of extensive plantar degloving before obvious demarcation, reducing the number of interventions and risk of infection[108].

Application of ICG in the detection of intestinal fistula (leaks)

Peng *et al*[109] reported a new preliminary application of ICG imaging in a postoperative case in which the initial fistula was identified using oral methylene blue dye, imaging contrast leakage, and ICG

fluorescence in the drain. Subsequently, on follow-up, the output decreased and cleared. The first two tests failed to demonstrate the leak, and ICG showed a persistent leak on fluorescence imaging of the drained fluid. The patient received 25 mg of oral ICG in 50 mL sterilized water. After approximately one hour, at the bedside, the NIR system detected ICG fluorescence in the drainage fluid at the bedside. The output decline with a fluorescence check was used to determine fistula closure. Therefore, the treatment was terminated. This reflects the low sensitivity and high false-negative rates of the contrast and methylene blue studies. This case report presents ICG as a highly sensitive, convenient, and low-cost bedside imaging modality without the risk of radiation or side effects[109,110].

Application in burns depth assessment

The assessment of burn depth remains challenging, and its determination of burn depth is critical in deciding the treatment approach for thermal injuries[111]. The current trend is the early excision of deep dermal and full-thickness burns, followed by wound grafting to reduce costs, infection concerns, and severe scarring. Assessment of sites with unknown burn depths remains difficult. The traditional approach is subjective clinical judgment. Many objective clinical assessment techniques have been tested but did not gain acceptance. ICG video angiography helps assess vascular patency, precise marking of burns, and depth estimation and has the advantages of being a practical, accurate, and effective adjunct.

Additionally, it enables the dynamic follow-up (objective, qualitative, and quantitative) of changes in burn wound depth throughout the acute post-burn period to improve prompt therapies[107]. Moreover, animal studies have also performed histopathological comparisons[112-114]. A recent prospective multicenter, double-blind study demonstrated the guidance of ICGA with excellent healing (closure) rates and concluded that it is a competent method for their purpose. In a previous prospective triple-blinded experimental study, the same author came to the same conclusion regarding the superiority of ICGA over clinical assessment (100% diagnostic accuracy *vs.* 50% for clinical evaluation) in identifying excising burns of unknown depth and stronger associations with long-term wound outcomes[115]. In a recent animal study, Second Window Indocyanine Green imaging was shown to be a potential imaging modality to objectively predict burn wound healing potential and guide intraoperative burn excision [116]. Simply put, it helps reduce unnecessary excision and prevent inadequate excision with better secondary results regarding the number of surgeries, healing, length of stay, and indirect costs[112-114, 116,117].

Technological limitations of ICG

The comprehensive evaluation of NIR FI in the past decades was mainly in non-traumatic situations. This technology is used for the anatomical identification of tumors (both primary and secondary), vital structure identification, mapping of structures, and assessment of perfusion. There is still wide variation in agent dosage and administration timing among different tissues and applications[86]. Intraoperative perfusion assessment techniques such as transabdominal Doppler ultrasound, transabdominal laser Doppler flowmetry, and oxygen spectroscopy have not been widely accepted because such techniques cannot be easily applied in routine clinical practice or have not proven reliable. A disadvantage of ICG-enhanced Fluorescence is that the assessment of the fluorescence intensity is subjective, making it a real-time intraoperative navigation modality.

However, the use of ICG in routine practice, particularly in trauma surgery, is currently lagging. This technique is simple, straightforward, and easy to implement. The logistics and costs are feasible[11,54-56,86]. Therefore, there is a need to develop a consensus regarding the choice, dosage, and timing of treatment. There is a need for prospective trials on whether it effectively predicts or decreases the risk of anastomotic leaks. It identifies other vital structures such as nerves, ureters, bile ducts, and thoracic ducts.

Unfortunately, published studies lack a quantitative comparison of fluorescence signals. There is a risk of overestimating the fluorescence signals in vascularized tissues due to the NIR fluorophore's over-time diffusion. Diana *et al*[118] attempted to address this drawback and developed a quantitative software-based analysis. The software calculated the peak slope of the fluorescence signal stiffness. Virtual bowel perfusion cartography is fashioned and overlaid on white-light images, allowing real-time quantitative perfusion assessment[118-121]. Several custom and commercial Quantification of ICG fluorescence (Q-ICG) software solutions uses inflow parameters rather than intensity parameters as well as mass-adjusted ICG dosing and fixed camera position[122].

A recent survey of colorectal surgeons in Italy concluded that FI is widely used; however, its indications and methods vary. The perception and acceptance among surgeons are not sufficient to determine whether this additional technological tool is essential. This reflects the need for future research to develop a solid foundation for implications in the practice of colorectal surgery and to extrapolate this to other fields of surgery, including trauma.

FUTURE PERSPECTIVES

Despite expanded clinical trials, fluorescent agents, and imaging systems for intraoperative FI, there

currently needs to be a standardized strategy for evaluating the imaging system performance and post-acquisition image processing[19,123]. There is a paucity of high-level evidence and the need for rigorous ways to address this continuous shortfall despite recent increases in publications, notably the number of meta-analyses and systematic reviews and the poor quality of the included data. Therefore, surgeons need to embrace and explore technological adjuncts to guided surgery[124].

Currently, two fluorescent compounds are FDA-approved and are used clinically (ICG and methylene blue). There is increasing interest in expanding fluorescence-guided surgery, and there is a need to develop other tissue-specific agents that would enhance surgical anatomical identification and protect important structures, such as nerve-specific agents, which are currently at the animal study level, to avoid accidental nerve damage with their sequelae[125].

The future is anticipated to accelerate the development of specific molecular tracers that are expected to introduce a paradigm shift in surgical decisions regarding resection based on additional molecular information. Fluorescein- and 5-aminolevulinic acid-induced protoporphyrin IX (PpIX-an endogenous metabolic fluorophore) imaging for neurosurgery and certain superficial cancers such as the urinary bladder. Technology (*i.e.*, FGS systems and imaging) is evolving in terms of specifications and performance differences. Desirable criteria or optimum systems have been published to define standards of care for evaluating new systems. A set of desirable criteria were presented to guide the evaluation of the instruments in this regard including: (1) Real-time overlay of white-light and fluorescence images; (2) operation within ambient room lighting; (3) nanomolar-level sensitivity; (4) quantitative capabilities; (5) simultaneous multiple fluorophore imaging; and (6) ergonomic utility for open surgery[30,126]. There is no perfect system; nevertheless, knowing the differences and limitations of available systems helps define clinical utility more precisely.

Furthermore, hybrid tracers (radioactive and fluorescent) are being researched to aid in expanding image navigation and precision procedures in elective settings, as well as oncologic excision[127]. Quantitative assessment of suitable or unsuitable pre-anastomotic perfusion is not well determined, mostly because most real-time imaging systems cannot assess tissue perfusion. However, some experimental studies have evaluated fluorescence quantification in animal models[124]. A technological upgrade would undoubtedly benefit the outcome of ICG application; nonetheless, system development has recently undergone a significant trial to establish a benchmark.

There is an interest in the objective assessment of tissue perfusion as a predictor of healing failure, which is performed in a poorly perfused segment of the bowel and is subjective based on the surgeon's experience with the previously mentioned limitations of human senses and ill-defined experience. This review discusses ICG-based fluorescence angiography as a practical solution. However, there are other options, such as hyperspectral imaging (HIS). Briefly, the tissue was illuminated with a broadband light source, and reflectance was measured with an image sensor in various bands of the electromagnetic spectrum in the visual and NIR range (400-1000 nm). Tissue composition permits absorption, scattering, or reflection; measuring this information works like a tissue fingerprint and can be used to measure perfusion status without the need for an exogenous fluorophore, and it can easily be repeated. The clinical use of this technique has been less studied in the literature, and the comparison of this technique with older ICG FA is limited. Pfahl *et al*[127] combined the data of the two techniques for the first time after an initial surgeon transaction-line decision; however, before resection, the complementary information of the two techniques may provide better tissue vascularization data. They concluded that more studies are needed to define the roles and recommend the routine integration of these techniques. Therefore, the future may determine the most promising, reliable, and safe method for assessing tissue perfusion during surgical resection and anastomosis in different disease processes, including trauma, tumors, and inflammatory bowel disease.

The combined application of ICG-FA and HIS within one imaging system may provide supportive and complementary information regarding tissue vascularization, minimize perioperative mortality, and shorten the surgical time. Different degrees of infusion[127]. To compensate for the scarcity of approved fluorophores, some groups have used NIR coating of equipment with materials that have a similar spectral ICG range to allow the use of already available ICG cameras such as ureteric stents, magnetic anastomotic devices, tumor endoscopic clips for laparoscopic identification, and Foley[128]. The future may integrate the artificial intelligence system with functional imaging into the challenging trauma surgery arena.

REVIEW LIMITATIONS

This narrative review is based on an interpretation of the literature on the topic rather than a systematic literature review. This study overlooks a few of these issues. Additionally, the arguments and views presented in this review are based on the authors' interpretation of NIR FA, which remains a novel tool. The heterogeneity between published studies may limit the possibility of conducting a meta-analysis.

CONCLUSION

FGS is a surgical navigation tool with evolving uses. Although ICG is extensively used for various reasons in monitoring organ perfusion, developments in existing systems are continually being made to define standards, quantify fluorescent signals, and discover new prospective tracers. This represents a paradigm change and the possibility of using molecular data in surgical decision-making for trauma, elective, and emergency surgeries. ICG, a relatively safe, sensitive, and nonspecific fluorophore widely used in NIR fluorescence imaging, can help surgeons to operate on injured patients. Minimizing the risk of anastomotic leakage remains a core goal of clinical practice. The large-scale use of ICG and further standardization and training of this technique are necessary to obtain specific and robust evidence to confirm its clinical value and define specific indications in trauma surgery. Additionally, a successful program for the development and application of FGS would require solid collaboration with optical engineers (for the development of hardware), computer scientists (for the development of the software), chemists (for the engineering of fluorophores), and medical professionals to enable clinical translation. Defining the therapeutic value of this method in trauma, including the timing, doses, and damage pattern indications, further research, including prospective trials, could offer great information and value for both surgeons and patients.

FOOTNOTES

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