Indocyanine green fluorescence in gastrointestinal surgery: Appraisal of current evidence

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Abstract

Applying indocyanine green (ICG) fluorescence in surgery has created a new dimension of navigation surgery to advance in various disciplines. The research in this field is nascent and fragmented, necessitating academic efforts to gain a comprehensive understanding. The present review aims to integrate diverse perspectives and recent advances in its application in gastrointestinal surgery. The relevant articles were selected by using the appropriate keyword search in PubMed. The angiography and cholangiography property of ICG fluorescence is helpful in various hepatobiliary disorders. In gastroesophageal and colorectal surgery, the lymphangiography and angiography property of ICG is applied to evaluate bowel vascularity and guide lymphadenectomy. The lack of objective parameters to assess ICG fluorescence has been the primary limitation when ICG is used to evaluate bowel perfusion. The optimum dose and timing of ICG administration need to be standardized in some new application areas in gastrointestinal surgery. Binding tumor-specific ligands with fluorophores can potentially widen the fluorescence application to detect primary and metastatic gastrointestinal tumors. The narrative review outlines prior contributions, limitations, and research opportunities for future studies across gastrointestinal sub-specialty. The findings of the present review would be helpful for scholars and practitioners to explore and progress in this exciting domain of gastrointestinal surgery.

Key Words: Indocyanine green; Fluorescence; Navigation surgery; Angiography; Cholangiography; Lymphangiography

Core Tip: Indocyanine green (ICG)'s unique absorption and emission spectrum allows its wide application in gastrointestinal surgery. The fluorescence cholangiography property of ICG is widely used in hepatobiliary surgery to identify bile ducts. Its angiography property is used in liver surgery for tumor identification and to facilitate anatomic liver resection. Also, the angiography function is helpful in luminal surgeries to assess bowel perfusion. The limitations of ICG fluorescence highlighted in the present review could guide future research on ICG in gastrointestinal surgery.

INTRODUCTION

Fluorescence is the property of a substance to absorb light at one wavelength and emits at a higher wavelength, primarily within the visible spectrum, with a loss of photons. Since the late 19th century, the fluorescence property of many agents has been used in microscopic labelling for antigen or antibody detection[1]. Most commonly used fluorescence agents absorb and emit light within the visible spectrum. However, its use is limited *in-vivo* due to the absorption of wavelengths of visible light less than 650 nm and greater than 900 nm by blood hemoglobin and water, respectively. Hence, for *in-vivo* application, the fluorescence agent should be within the optical window of 650-900 nm[2]. Indocyanine green (ICG) absorbs light at 760 nm and emits at 820-830 nm, which is outside the visible human spectrum but can be identified with infrared camera devices[3]. The unique absorption and emission spectrum allow its wide application in gastrointestinal surgery.

ICG, approved for human use in 1956, is a non-toxic, anionic, hydrophilic tricarbocyanine with a wide safety margin. It is excreted unmetabolized by the liver with no enterohepatic circulation. ICG has a short half-life of 3-5 min. When administered parenterally, ICG binds to plasma proteins and remains within the intravascular compartment with insignificant interstitial space translocation. The initial application of ICG for cardiac output, renal blood flow, and hepatic function monitoring was based on its metabolic characteristics[4]. However, the fluorescence property of ICG expanded its application manifold, as documented by the phenomenal growth in publications and scholarly interest (Figure 1).

Kogure *et al*[5] incidentally detected the fluorescence property of the ICG in an animal study. The development of near infra-red video camera facilitated its use in real-time surgery as an angiography, cholangiography or lymphangiography agent. With extravascular administration, ICG is taken by draining lymph nodes through lymphatic channels. Utilizing this property, Kitai *et al*[6] used ICG for breast cancer sentinel lymph node mapping. Subsequently, Miyashiro *et al*[7] demonstrated its usefulness in identifying lymphatic vessels and sentinel lymph nodes draining primary gastric tumors using intraoperative endoscopic peritumoral ICG injection. Aoki *et al*[8] reported the role of ICG fluorescence in liver segmentation and cholangiography. In 2011, Kawaguchi *et al*[9] demonstrated fusion imaging of ICG fluorescence and white light for real-time liver resection. ICG-related publications peaked at 293 for 2022, making it the most productive year in this domain. Further, most ICG-related publications are from Japan (*n* = 527), followed by the United States (*n* = 451) and China (*n* = 201) (Figure 2).

SEARCH STRATEGY

All the authors did a PubMed search of relevant articles. The keywords and combinations included in the search were: "fluorescence"; "Indocyanine green"; "surgery"; "liver segmentation"; "hepatectomy"; "liver resection"; "cholangiography"; "transplantation"; "esophagectomy"; "gastrectomy"; "gastric conduit"; "colonic conduit"; "lymphadenectomy". Appropriate search syntaxes, such as parentheses and Boolean operators, were used as required for each topic. The search was limited to human studies and articles in English.

ICG FLUORESCENCE IN LIVER SURGERY

ICG fluorescence imaging facilitates intraoperative decision-making and improves patient safety through applications like liver segmentation, tumor detection, cholangiography and perfusion assessment.

Anatomical segmentation for liver resection

The surgical anatomy of the liver is complex, with the intersection of the portal pedicle and the hepatic vein in the liver parenchyma. It employs the imaginary plane of the portal pedicle and hepatic vein for liver segmentation. Surgical resection is the primary treatment for both primary and secondary liver tumors. Also, anatomical liver resection is preferred for less intraoperative bleeding and superior oncological outcomes in selected patients[10]. The surgeon utilizes preoperative computed tomography and intraoperative ultrasound images to create an imaginary visual plane of
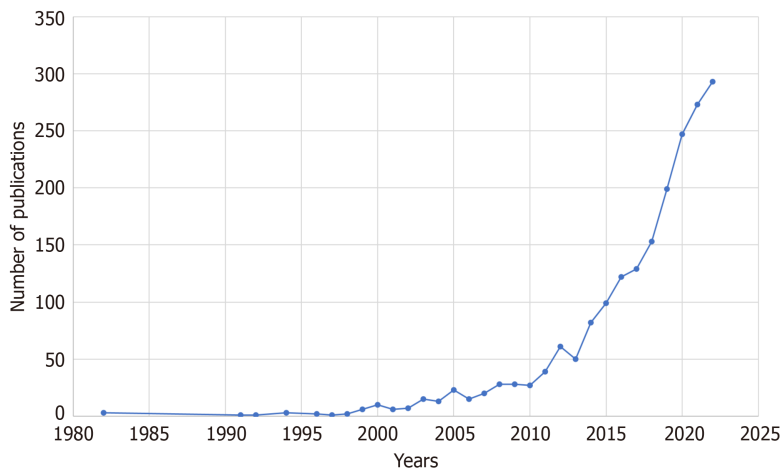
Figure 1 Annual publication trend of articles related to indocyanine green fluorescence.
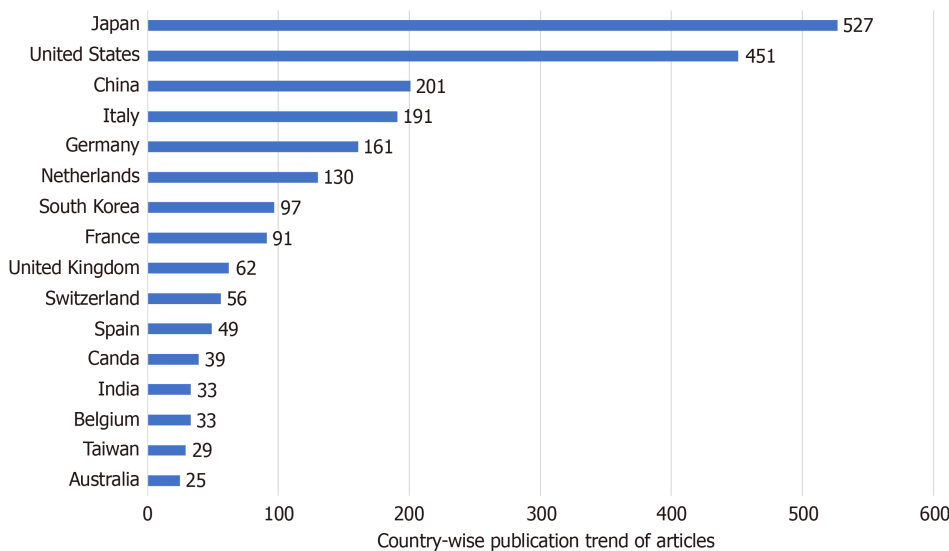
Country-wise publication trend of articles

Figure 2 Country-wise publication trend of articles related to indocyanine green fluorescence.

anatomical transection. ICG fluorescence with fusion image enables precise real-time visualization of this imaginary plane[11].

Kobayashi *et al*[12] demonstrated five techniques of staining portal vein territory for intraoperative liver segmentation. It includes single staining, multiple staining, counterstaining, paradoxical negative and negative staining. In single and multiple staining, ICG is directly injected into the portal pedicle of interest under ultrasound guidance, and the area of interest shows fluorescence. In counterstaining and paradoxical negative staining, the portal or hepatic vein to the region of interest is blocked by tumor thrombus, invasion, or embolism. Hence, direct injection of ICG to the portal vein results in positive staining of the liver parenchyma adjacent to the area of interest. In negative staining, the portal pedicle supplying the area of interest is clamped, and ICG is given intravenously to stain the normal area (Figure 3). The initial four techniques require direct puncture of portal vein branches. The ICG dose for positive and negative staining is 0.25 mg/kg of body weight and 2.5 mg/kg of body weight, respectively[12].

The negative staining technique is primarily used for major hepatectomy where the Glissonean pedicle of the hemi-liver or sector to be resected is ligated. For mono-segmentectomy and sub-segmentectomy, positive staining techniques are preferred[13]. However, the success of positive staining depends on the operator's ability to accurately puncture the segmental or sub-segmental portal vein under ultrasound guidance and inject the dye slowly without reflux to adjacent segments. Also, with the increasing use of the minimal access approach in liver surgery, positive staining by direct portal vein puncture using laparoscopic intraoperative ultrasound is challenging. To overcome that, Ueno *et al*[14] reported the use of interventional radiology-guided placement of microcatheter in the target segmental hepatic artery branch. 2 mL of diluted ICG saline solution (0.125 mg/mL) is injected with the embolic agent (gelatin particles) to retain ICG in the area of interest (Tables 1 and 2)[14-16]. Qian *et al*[16] reported a high success rate of 80% in trans-arterial staining compared to 60% in portal venous staining method. Li *et al*[17] reported a similar technique of super-selective arterial injection of ICG

Table 1 Studies on liver segmentation and mapping using direct staining technique

Ref.	Country	Study type	Patient	Camera device	ICG dose and time	Guide/approach	Target liver	Success rate	Procedure time
Qian *et al* [16], 2022	China	Prospective cohort	Grp A: 10. Grp C: 20	-	0.0125 mg/mL, up to 10 mL	DSA: Hepatic artery. USG: Portal vein	Grp A: Seg, sub-seg. Grp C: Seg	Grp A: 80 %. Grp C: 60 %	Grp A: 305.3 ± 23.2 min. Grp C: 268.4 ± 34.7 min
Li *et al* [17], 2021	Taiwan	Prospective cohort	8	Karl storz, Pinpoint Stryker	Conc -0.125 mg/mL, rate of 1 mL/min	DSA: Hepatic artery	Segment bisegment	100%	DSA: 32.7 +/5.3 min, operative time: 242 +/118 min
Lan *et al* [18], 2022	China	Retrospective cohort	24	Pinpoint Stryker	5 mL of 0.025 mg/mL	Glissonian pedicle approach	Hemiliver: 10. Left lateral: 7. Segment: 7	79.40%	Staining time: 25.92 ± 14.64, operative time: 334.17 ± 98.65
Xu *et al* [15], 2020	China	Retrospective cohort	9	Pinpoint Stryker	0.025 mg/mL, 5-10 mL	Intraoperative ultrasound. Glissonian pedicle approach	Segment, section	56%	Median operative time: 260 min (range 150-360 min)
Ueno *et al* [13], 2019	Japan	Prospective cohort	10	Pinpoint Stryker	0.125 mg/mL, 2 mL ICG, 2 mL Indigo carmine, 1 mL Sonazoid embolic agent-Gelatin particles	DSA	Segment	100%	IVR procedures- 41 (30-102) min. Median operating time with IVR time: 432 min
Ueno *et al* [14], 2018	Japan	Prospective cohort	5	Pinpoint Stryker	0.125 mg/mL, 2 mL ICG, 2 mL Indigo carmine, 1 mL Sonazoid embolic agent-Gelatin particles	DSA	Segment	100%	Operative time: 432 (293-572) min
Aoki *et al* [11], 2010	Japan	Prospective cohort	81	PDE: 2	5 mg/mL	IOUS	Segment. Sub-segment	73/81 (90.1%)	NA

ICG: Indocyanine green; IOUS: Intraoperative ultrasound; DSA: Digital subtraction angiography; USG: Trans abdominal ultrasound; NA: Not available; PDE: Photodynamic eye.
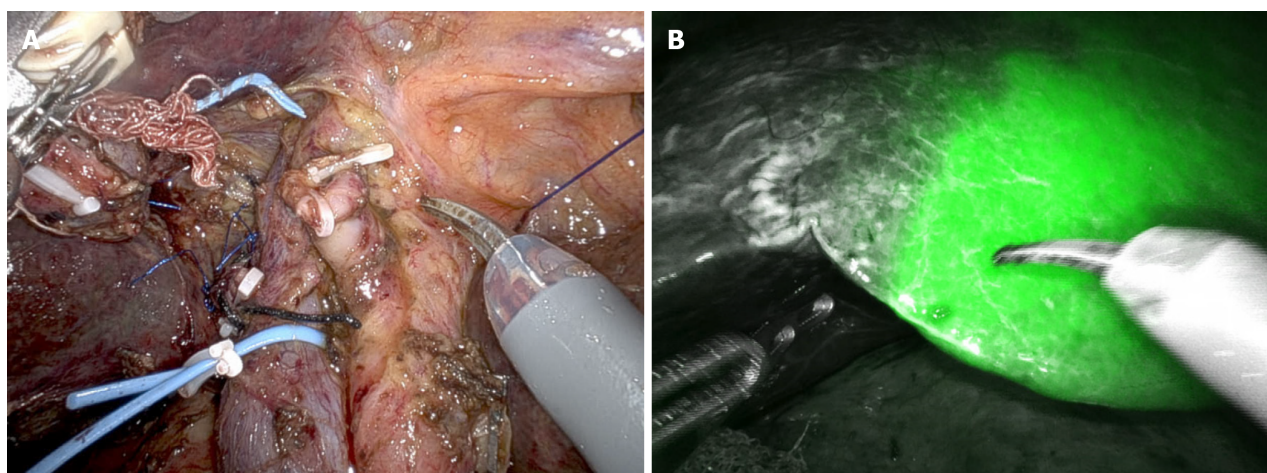
DOI: 10.4240/wjgs.v15.i12.2693 **Copyright** ©The Author(s) 2023.

Figure 3 Negative indocyanine green staining technique used in a patient with hilar cholangiocarcinoma planned for right hepatectomy with caudate lobectomy. A: Portal and hepatic artery branches of the right hemiliver to be resected are ligated; B: Line of transection for right hepatectomy identified with the help of indocyanine green fluorescence.

Table 2 Studies on liver segmentation and mapping using counterstaining technique

Ref.	Country	Study type	Patients	Camera device	ICG dose and time	Approach	Target liver	Success rate	Median (range) operative time, in minutes
Funamizu *et al*[21], 2021	Japan	Retrospective cohort	74	Viscera Elite II, Olympus, Pinpoint, Stryker, Hopkins II, Karl storz	0.5 mg	Glissonian pedicle approach	Monosegmectomy	100%	351
Xu *et al*[15], 2020	China	Retrospective cohort	27	Pinpoint, Stryker	2.5 mg/mL	Glissonian pedicle approach	Hemiliver. Section. Segment	52%	260 (150-360)
Uchiyama *et al*[19], 2011	Japan	Prospective cohort	22	PDE; Hamamatsu Photonic	0.5 mg/kg	CE-IOUS: Glissonian pedicle approach	Hemiliver: 8. Section: 8. Segment: 6	100%	280 (140-380)
Berardi *et al*[20], 2021	Japan	Retrospective cohort	86 patients: HCC: 55; CRLM: 31	Viscera Elite II, Olympus, Pinpoint, Stryker, Hopkins II, Karl storz	0.5 mg	Glissonian approach	Section: 14. Segment: 56. Sub-segment: 16	98.80%	328 (270-437)

ICG: Indocyanine green; HCC: Hepatocellular carcinoma; CRLM: Colorectal liver metastasis; CE-IOUS: Contrast enhanced intraoperative ultrasound.

and noted a 100% success rate in identifying an appropriate intersegmental plane for hepatic resection. However, this technique is contraindicated in patients with significant arteriovenous shunting in the region of interest. In addition to failure to cannulate the target portal vein branch, reflux to the non-target segment, collateral to adjacent segment and uneven uptake due to tumor obstructing the pedicle are other causes of failure with a positive staining technique[18,19]. The main advantage of ICG fluorescence over other staining techniques is the ability to identify the intersegmental plane during deep parenchymal transection and the application of the pringle maneuver[20,21].

Hepatic tumor detection

ICG bound to lipoprotein is taken up by hepatocytes *via* organic anions-transporting polypeptides and sodium taurocholate co-transporting polypeptides channels. Subsequently, ICG is secreted unmetabolized into the bile *via* multidrug resistance-associated proteins 2. In well and moderately differentiated hepatocellular carcinoma (HCC) tumor cells, the ICG uptake mechanism is intact, but the excretion is impaired. Hence, HCC shows complete or partial fluorescence, depending upon the differentiation grade. In poorly differentiated HCC and metastatic liver tumors ICG uptake is also impaired, resulting in negative staining. However, some of these lesions may show rim fluorescence. It is due to immature hepatocytes in the peritumoral region that take up ICG but unable to secrete it into bile canaliculus[22]. Fluorescence imaging is primarily helpful for detecting subcapsular tumors within 10 mm of the liver surface. However, it is not useful for deep parenchymal tumors except those on the cut surface of the liver parenchyma. Thus, ICG fluorescence and intraoperative ultrasound supplement each other (Table 3). Despite the high sensitivity of fluorescence imaging to detect liver tumors, a false positive rate close to 40% due to regenerative nodules in cirrhosis patients and Von-Meyenburg complex underscores the need for further clinical assessment of fluorescent liver lesions[23]. Cai *et al*[24] reported the application of ICG for tumor margin identification in patients undergoing laparoscopic liver resection for HCC and colorectal liver metastases in 86 patients (Table 3). The authors reported a 96% positive rate of ICG staining for the hepatic malignant lesions.

Similarly, Piccolo *et al*[25] and Terasawa *et al*[26] reported a 100% and 85% high success rate in identifying malignant liver lesions. The dose and timing of ICG injection for tumor imaging depend on the indication[27,28]. If ICG is primarily used for preoperative estimation of liver function with an added indication of tumor detection recommended dose is 0.5 mg/kg of body weight 7-14 d before surgery. If the primary indication is tumor detection 0.2 mg/kg of body weight is administered 1-2 d before surgery[29,30].

Liver transplantation

In living donor transplantation optimal site of bile duct division is critical to prevent biliary complications in both donor and recipient. Mizuno *et al*[31] documented its usefulness in delineating the right posterior sectoral bile duct following intrabiliary injection into the left hepatic duct in a donor undergoing left hepatectomy. Hong *et al*[32] reported that intravenous ICG injection allowed real-time identification of the biliary tree around the hilar plate and facilitated optimal bile duct division in patients undergoing laparoscopic living donor hepatectomy. The optimal route and timing of ICG administration in living donor transplantation are not standardized. However, intravenous ICG injection following inflow control of the ipsilateral hemi-liver facilitates the identification of the transection plane and bile duct division, as

Table 3 Studies on hepatic tumor detection with indocyanine green fluorescence

Ref.	Country	Study type	Patients	Device	ICG dose and time	Tumor detection rate	New lesions	Correlation with histology	Micro metastases detection
Cai *et al* [24], 2023	China	Retrospective cohort	Total: 86. HCC: 52, CRLM: 34	Pinpoint, Stryker	Dose: 0.5 mg/kg, ICG < 7: 5 d prior; ICG > 7: 7 d prior	96%	8	Positive (*P* = 0.001)	False positive: 3/8 (37.5 %)
Franz *et al* [23], 2021	Germany	Prospective cohort	Total: 18. HCC: 9, CRLM: 4, IHCC: 2	Firefly, DaVinci NIR-ICG, Karl storz	Dose: 0.5 mg/kg, 2-14 d prior	100%	27.8	-	False positive: 39%
Piccolo *et al*[25], 2021	Italy	Prospective cohort	Total lesions: 29. HCC: 14, CRLM: 13, IHCC: 1, non-CRLM: 1	NIR-ICG, Karl storz	0.5 mg/kg, HCC/IHCC: 7 d prior; CRLM: 5 d prior	ICG: 100%, LUS: 72.4%	-	R0: 100%	-
Marino *et al*[27], 2020	Spain	Retrospective cohort	Total lesions: 59. HCC: 23, CRLM: 27, IHCC: 6, hemangioma: 2, steatosis: 1	Davinci-Firefly	0.5 mg/kg 5 d prior	52/59 (88.1%)	6 (11.5%)	R0: 100%	False positive: 3/52
Zhou *et al* [29], 2019	China	Retrospective cohort	ICG: 21, IOUS: 21	Pinpoint, Stryker	0.25 mg/kg 3-5 d prior	100%	-	-	NA
Terasawa *et al*[26], 2017	Japan	Prospective cohort	Total lesions: 59. CRLM: 46, HCC: 7, others: 6	Pinpoint, Stryker	0.5 mg/kg body within 3 d	45/53 (85%)	22/45	R0: 100%	True negative: 100%
Kudo *et al* [30], 2014	Japan	Prospective cohort	Total lesions: 32. HCC: 16, CRLM: 16	Olympus	0.5 mg/kg within 14 d	23/32 (71.8%)	-	-	-

ICG: Indocyanine green; HCC: Hepatocellular carcinoma; CRLM: Colorectal liver metastasis; IHCC: Intrahepatic cholangiocarcinoma; CE-IOUS: Contrast enhanced intraoperative ultrasound; ICG: Indocyanine green; LUS: Laparoscopic ultrasound; NA: Not available.

by the time the liver transection is completed, ICG would have been excreted into the bile duct.

ICG fluorescence imaging also allows the evaluation of graft perfusion and veno-occlusive regions. Hepatic venous outflow obstruction is a significant cause of graft dysfunction due to a reduction in functional liver volume. Kawaguchi *et al*[33] documented the usefulness of ICG fluorescence intensity in evaluating veno-occlusive regions. They calculated the ICG concentration of the veno-occlusive and non-veno-occlusive regions from the plateau fluorescence intensity. The study showed that portal uptake is diminished to 40% in the veno-occlusive area compared to the non-veno-occlusive region. It allows real-time evaluation of functional liver volume and guides the need for venous reconstruction in veno-occlusive regions. Also, they documented that the reduction in portal uptake function in the veno-occlusive areas of S5 tends to be smaller compared to the similar regions in S8. The difference is due to a more prominent communication vein to the right hepatic vein in segment 5 compared to segment 8. Hence, reconstruction is often needed for the segment 8 vein. Traditionally intraoperative ultrasound with Doppler is used for the evaluation of vascular anastomosis. However, intravenous ICG administration facilitates real-time evaluation of graft perfusion and complements Doppler evaluation for vascular thrombosis[33].

ICG FLUORESCENCE IN BILIARY SURGERY

The feasibility of fluorescence cholangiography-guided laparoscopic cholecystectomy was documented by Ishizawa *et al* [34]. Subsequently, multiple studies, including an randomized controlled trial (RCT), have shown that fluorescence cholangiography is superior to conventional white-light imaging for identifying extrahepatic biliary anatomy before and after the dissection of the Calot triangle. While the first RCT comparing fluorescence cholangiography with conventional white light imaging was not adequately powered to identify differences in the rates of bile duct injuries between the two techniques, fluorescence cholangiography could reduce the risk of bile duct injuries related to anatomical variation or visual misperception of biliary anatomy[35]. Also, fluorescence cholangiography is helpful in delineating the biliary anatomy clearly in challenging cases such as acute cholecystitis and Mirizzi syndrome, thereby reducing conversion rate and bile duct injuries[36].

Compared to conventional intraoperative radiographic cholangiography, fluorescence cholangiography does not require ionizing radiation and provides images in real-time, even before the dissection of the Calot triangle. However, fluorescence cholangiography does not help visualize common bile duct stones and intrahepatic biliary anatomy. Also, fluorescence cholangiography is not helpful in obese patients with thick fat in the Calot triangle due to limited penetration of near infra-red light. While fluorescence cholangiography could reduce the need for radiographic cholan-

giography in the future, it cannot wholly replace the radiographic technique, and both will have a complementary role [37].

For fluorescence cholangiography, ICG can be injected intravenously or intrabiliary. Intravenous ICG can be injected from 30 min up to 24 h before surgery at a dose of 0.05 mg/kg body weight or a total dose of 2.5 mg. Until 24 h, as the interval between intravenous injection and surgery increases, the bile duct to background liver contrast ratio improves, thereby facilitating the identification of the biliary tree[38]. As most laparoscopic cholecystectomy is done as a day-care surgical procedure, intravenous ICG is often administered at the time of induction of anaesthesia or 3-6 h before surgery. For intrabiliary administration, like direct portal vein injection, dilute ICG (0.025 mg/mL) is administered through a trans cystic tube. While intrabiliary injection permits immediate visualization without background liver fluorescence, intravenous ICG injection is more convenient and avoids bile duct injuries associated with inserting a trans cystic tube. Also, spillage of ICG during an injection can obscure adequate visualization of the biliary tree due to background fluorescence. However, intrabiliary injection is preferred in patients with a preoperative percutaneous biliary drainage tube.

ICG FLUORESCENCE IN PANCREATIC SURGERY

In pancreatic surgery, ICG is helpful for tumor localization, assessing pancreatic stump vascularity, and obtaining retroperitoneal margin in patients undergoing pancreaticoduodenectomy. Also, in patients undergoing duodenum preserving pancreas head resection, ICG helps localize the bile duct and assess duodenal vascularity. Pancreas is a highly vascular organ, and most pancreatic tumors, except neuroendocrine tumors, are poorly vascular[39]. In contrast to the fluorescence mechanism of liver tumors, pancreatic lesions were visualized based on the difference in vascularity between the lesions and the surrounding parenchyma. ICG fluorescence is more sensitive to detecting pancreatic neuroendocrine tumors and cystic neoplasms than pancreatic ductal adenocarcinoma. Pancreatic neuroendocrine tumors appear highly fluorescent, whereas cystic neoplasms appear as fluorescence defect lesions. Real-time visualization of pancreatic tumors permits parenchyma-preserving surgeries for low-grade tumors and improves the R0 resection rate with malignant tumors. Tumor visualization is potentially helpful in patients undergoing minimally invasive resection without tactile feedback. As fluorescence imaging fails to visualize minor differences in fluorescence intensity between tumor and pancreatic parenchyma, pancreatic duct adenocarcinomas are not detected well with ICG. Also, fluorescence imaging cannot detect deeper parenchymal lesions. Hence, the current role of ICG fluorescence imaging is to complement conventional intraoperative tumor detection techniques like visual inspection, palpation, and intra-operative ultrasound.

Strasberg *et al*[40] reported that the pancreatic neck region commonly used for pancreaticoenteric anastomosis following pancreaticoduodenectomy is the vascular watershed region of the pancreas. Ischemia of the pancreatic stump following pancreas mobilization was proposed as a contributing factor for pancreaticojejunostomy leak. Rho *et al*[41] reported the usefulness of ICG in assessing the perfusion of the pancreatic stump. Pancreatic perfusion was observed within 30 s after an intravenous injection of 5 mg ICG. However, this technique's current limitations are the lack of objective quantification of perfusion, optimum ICG dosage, and time to assess perfusion. As pancreatic hypo perfusion is not the only contributor to pancreatic leak, documenting the potential usefulness of ICG-fluorescence imaging in reducing pancreatic fistula is challenging.

A negative retroperitoneal margin is a significant predictor of long-term oncological outcomes in patients undergoing pancreaticoduodenectomy. In open pancreaticoduodenectomy, frequent palpation of the superior mesenteric artery guides the correct dissection plane. However, in a minimally invasive approach, due to the lack of tactile feedback differentiating pancreatic tissue of the uncinate process from the nerve plexus around the superior mesenteric artery could be a challenge. Rho *et al*[42] reported the usefulness of ICG-fluorescence-guided uncinate dissection in 10 patients undergoing laparoscopic pancreaticoduodenectomy. Following the intravenous injection of ICG, the initially detected fluorescence signal disappeared from the superior mesenteric artery. Whereas fluorescence signal gradually accumulated in the pancreas providing good contrast between the ICG-stained uncinate process of the pancreas and the superior mesenteric artery. However, their study could not demonstrate the oncological advantage of ICG-guided uncinate dissection due to the small sample size.

Duodenum preserving pancreatic head resection is indicated in patients with non-invasive tumors of the pancreas head and chronic pancreatitis patients with head mass. However, the reported incidence of bile leak due to injury to the intrapancreatic bile duct ranges from 11.8% to 16.7%. Lu *et al*[43] reported that intravenous administration of ICG 12-24 h before surgery identified intrapancreatic bile duct in 93.3% of patients. Also, ICG injected 24 h before surgery at a dose of 0.5 mg/kg had the highest signal-to-noise ratio (Figure 4). Also, in this group of patients, intraoperative administration of ICG permits the assessment of duodenal vascularity through the pancreaticoduodenal arcade along the medial wall of the duodenum.

ICG FLUORESCENCE IN ESOPHAGEAL SURGERY

In esophageal surgery, lymphangiography function of the ICG fluorescence is used for lymphatic mapping and visualization of the thoracic duct. The angiography function of the ICG is used to assess the vascularity of the conduit for esophageal reconstruction.
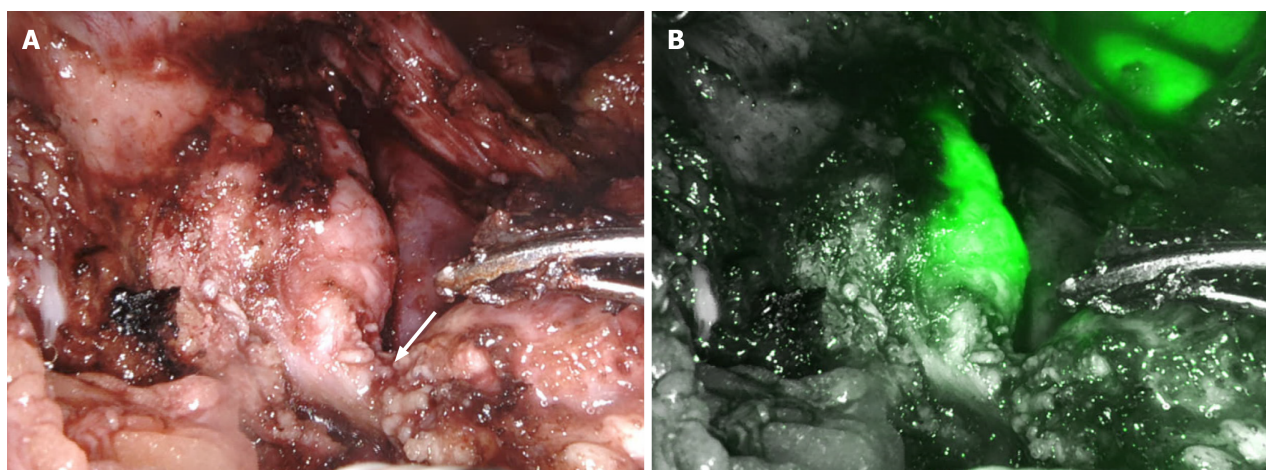
Figure 4 Identification of bile duct during robotic duodenum preserving pancreas head resection. A: Pancreatic duct (arrow) divided at its junction with the bile duct; B: Indocyanine green fluorescence demonstrates bile duct.

Vascular assessment of oesophageal replacement conduit

Evaluation of conduit vascularity is the most studied application of ICG fluorescence in esophageal surgery. Anastomotic leak is a significant complication after esophageal replacement, and poor conduit perfusion is a considerable risk factor. After esophagectomy, ICG is used to assess the vascularity of the gastric or colon conduit before anastomosis. A meta-analysis of 17 studies reported a pooled anastomotic leak rate of 10.8%, comparable to the control group (without ICG), with a cervical leak rate of 12.3% and a thoracic anastomotic leak rate of 9.3%. However, when the analysis is restricted to six studies where specific intraoperative intervention was used to correct regions that showed poor perfusion, there was a 69% (5.7% *vs* 22.9%) absolute risk reduction of the anastomotic leak. Interventions commonly used in patients with low conduit perfusion are changing the site of anastomosis and supercharging the conduit with microvascular anastomosis [44]. In contrast to cervical anastomosis, in patients undergoing intrathoracic anastomosis, a recent meta-analysis reported that the use of ICG fluorescence for perfusion assessment did not reduce the anastomotic leak rate[45]. The discordant results regarding the usefulness of ICG fluorescence in reducing anastomotic leak rate could be explained by including many observational studies with small sample size and using subjective assessment tools like good and poor perfusion. Recent studies support using more objective parameters like time of appearance and disappearance of ICG fluorescence to assess arterial perfusion and venous congestion, the correlation of time of perfusion to the size of the area perfused, and software to quantitatively evaluate the ICG fluorescence[46]. Future studies should incorporate these objective parameters as primary endpoints.

Fluorescence guided lymphadenectomy

The lymphangiography property of ICG helps evaluate sentinel lymph nodes and visualization of nodal stations draining the primary tumor to improve the quality of lymphadenectomy. Yuasa *et al*[47] studied the role of ICG-fluorescence in detecting sentinel nodes in esophageal cancer. Although ICG fluorescence had a sentinel node detection rate of 95%, a high false-negative rate of 25% is concerning. Hence, ICG fluorescence may not be helpful in avoiding lymphadenectomy in patients with negative sentinel node. Hachey *et al*[48] first reported the feasibility of fluorescent lymphatic mapping in esophageal adenocarcinoma patients undergoing Ivor-Lewis esophagectomy. Four quadrant submucosal injection of diluted ICG mixture with human serum albumin or normal saline is given endoscopically before positioning the patient. Six out of 9 patients had an uptake of fluorescence in regional nodes aiding dissection. Further, the mixture of ICG to 25% human serum albumin resulted in better fluorescence retention in the lymphatics than normal saline. As the dissection of recurrent laryngeal nodes is an important cause of lymphadenectomy-related morbidity, a prospective study evaluated the feasibility of mapping bilateral recurrent laryngeal nerve nodes. Authors reported that ICG-guided lymphatic mapping had 100% negative predictive value for recurrent laryngeal nodes, thereby guiding the optimum extent of lymphadenectomy (Table 4). However, the study had only 29 patients with squamous cell carcinoma and more studies with larger sample sizes are required to confirm the findings[49]. While ICG fluorescence could facilitate lymphaden-ectomy, the basic principles of lymphadenectomy in esophageal cancer should be followed to ensure good oncological outcomes.

Identification of thoracic duct

Chyle leak is a potentially morbid complication of esophagectomy, and recent studies have shown the usefulness of ICG fluorescence in thoracic duct identification (Figure 5). Compared to subcutaneous injection of ICG in the dorsum of the foot between toes, injection into groin nodes under sonographic guidance has produced more consistent results. Vecchiato *et al*[50] demonstrated thoracic duct after a mean time of 52.7 min in 19 patients undergoing thoracoscopic esophagectomy by injecting 0.5 mg/kg ICG in the bilateral superficial inguinal nodes with ultrasound guidance. However, the ICG dose is not standardized; while some studies have used 0.2 mg/kg, others have used 0.5 mg/kg. In addition

Table 4 Studies on lymphatic mapping in esophageal and gastric surgery

Ref.	Country	Study type	Patient	Device	ICG dose and time	Surgery	Results	Long term outcome
Esophageal								
Hachey *et al*[48], 2016	United States	Prospective PFS	EAC: 9	NOVADAQ, Stryker	2.5 mg/mL, 1 cc, 4 sites, endoscopic injection diluted with sterile water/HSA 25%	Ivor Lewis esophagectomy	6/9 patients showed 2-6 regional NIR +	NA
Park *et al* [49], 2018	Korea	Prospective PFS	ESCC, cT1: 29	Firefly, Da Vinci	0.5 mg/m, 0.5 m: Each quadrant 1 d prior	Robotic Mckeown esophagectomy	High NPV	NA
Stomach								
Chen *et al* [58], 2020	China	RCT	ICG 129; non-ICG: 129	NOVADAQ, Stryker	Submucosal endoscopic 1 d prior 2 mL, 0.5 mL/quadrant 0.625 mg/m	Laparoscopic distal and total gastrectomy	Lymph node yield, mean ± SD: ICG: 50.5 ± 15.9; non-ICG: 42.0 ± 10.3	3-yr: DFS: 81.4% *vs* 68.2%; OS: 86.0% *vs* 73.6%
Park *et al* [51], 2020	Korea	Prospective feasibility study, PSM	ICG: 20; non-ICG: 60	NOVADAQ, Stryker	Endoscopic sub-mucosal 0.1 mg/mL, 1 mL 5 sites	Laparoscopic distal gastrectomy, station 6 dissection	ICG *vs* non-CIG lymph node yield 30.15 *vs* 32.55, bleeding events 4 (20.0) *vs* 41 (68.3)	NA
Cianchi *et al*[53], 2020	Italy	Retrospective, PSM	ICG: 37; non-ICG: 37	Firefly, Da Vinci	Endoscopic sub-mucosal 0.1 mg/mL, 0.5 mL, 4 quatrants	Robotic distal or total gastrectomy	Operative time mean ± SD: 293.1 ± 6 *vs* 321.2 ± 77.8 harvested lymph nodes: *vs* 50.8 ± 17	NA
Ushimaru *et al*[52], 2019	Japan	Retrospective, PSM	ICG: 84; non-ICG: 84	NIR, Karl storz	Endoscopic submucosal 0.05 mg/mL, 10 mL, 4 sites	Laparoscopic distal gastrectomy	Operative time mean ± SD: 206.1 ± 5.0 *vs* 237.0 ± 5.0, harvested lymph nodes: 47.5 *vs* 42.6	NA

ICG: Indocyanine green; PSM: Propensity score matching; PFS: Progression free survival; HAS: Human albumin solution; ESCC: Esophageal squamous cell carcinoma; EAC: Esophageal adenocarcinoma; DNIR: Near infra-red; DFS: Disease free survival; OS: Overall survival; NA: Not available.

to thoracic duct identification, ICG lymphangiography facilitates the identification of aberrant ducts, thereby preventing iatrogenic injury and postoperative chylothorax.

ICG FLUORESCENCE IN GASTRIC SURGERY

In gastric surgery, ICG fluorescence is used to detect sentinel lymph nodes in early gastric cancer patients and guide lymphadenectomy in patients with advanced gastric cancer. Also, ICG is utilized for tattooing tumor sites in early gastric cancer patients, facilitating intraoperative identification.

Sentinel node mapping for early gastric cancer

The aim of sentinel lymph node sampling in early gastric cancer patients is to avoid unnecessary lymphadenectomy. Traditionally radioisotopes are used for sentinel node detection. Compared to other techniques, low cost and easy avai-lability are the main advantages of ICG lymphangiography. Both submucosal and subserosal ICG injections have been used to detect sentinel nodes. However, most studies used the endoscopic peritumoral submucosal injection of 2 mL ICG (5 mg/mL). Subserosal injection requires tumor visualization or palpation, which may not be feasible in many patients with early gastric cancer. Also, the intraoperative subserosal injection might result in leakage of ICG into the surgical field. The timing of injection has been variable in different studies. However, preoperative injection a day before surgery has better accuracy and fewer false negative results than intraoperative injection before skin incision. Park *et al*[51] reported the utilization of ICG in the dissection of infrapyloric nodes in patients undergoing laparoscopic distal gastrectomy for gastric cancer. The mean time taken for the exposure of the right gastroepiploic vein was significantly shorter in the ICG group compared to non ICG group (P = 0.001). In a retrospective study, ICG guided laparoscopic lymphadenectomy resulted in a significantly increased number of retrieved lymph nodes (47.5 ± 1.7 *vs* 42.6 ± 1.7, P = 0.046)[52]. Similar results were reported by Cianchi *et al*[53] in robotic gastrectomy for gastric cancer. A Korean multi-centre randomized trial reported that a dual tracer that combines Te99- labelled Human serum albumin and ICG improved the overall detection rate of sentinel nodes. Also, the Korean study showed that sentinel basin dissection has better lymph node yield than the pick-up method used in other studies[54]. A reliable intraoperative diagnostic technique to detect
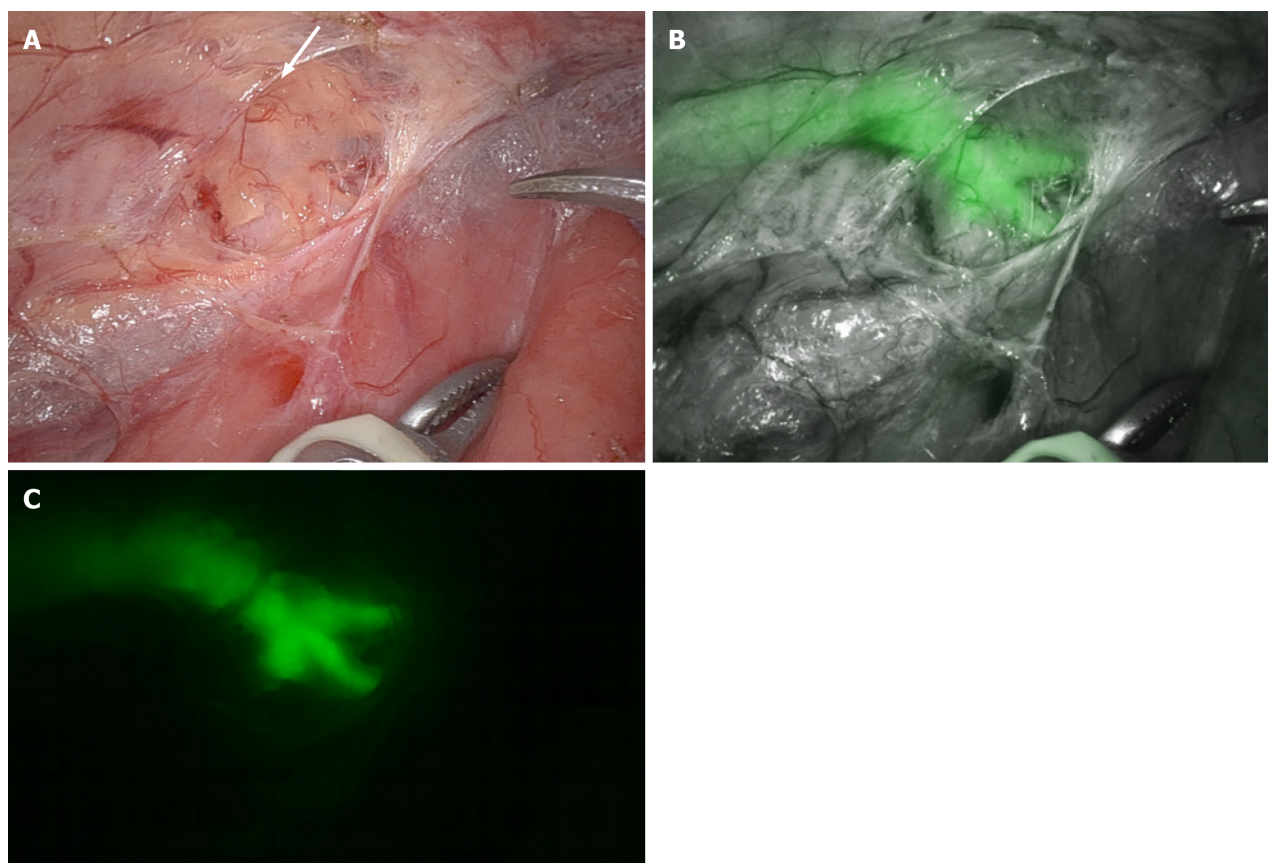
Figure 5 Visualization of the thoracic duct. A and B: Visualization of the thoracic duct during robotic esophagectomy in normal mode (A) is enhanced by indocyanine green fluorescence (B); C: The branching pattern of the thoracic duct is well visualized in fluorescence mode.

metastatic tumor cells is an essential component of sentinel node navigation surgery. However, as highlighted in the JCOG0302 trial frozen section investigation with only one plane has a high false negative rate of 46%[55]. Hence, all lymph nodes retrieved from the sentinel basins were evaluated in the SENORITA trial. Also, for nodes larger than 4 mm, serial sections at 2 mm intervals were taken for examination. Further, rapid molecular diagnostic techniques like one-step nucleic acid amplification assay might improve the sensitivity of intraoperative evaluation (Table 5). Isozaki *et al*[56] reported an excellent gastric cancer-specific cumulative 5-year survival rate of 98.5% for ICG sentinel lymph node mapping in early gastric cancer.

Improving the performance of D2 lymphadenectomy

Studies comparing the ICG and non-ICG-guided lymphadenectomy have shown significantly better lymph node yield, less blood loss, and operative time in the ICG group. A meta-analysis of 13 studies with 1882 patients also showed significantly better lymph node yield in the ICG group (40.33 *vs* 33.40 nodes)[57]. In the RCT, Chen *et al*[58] reported a significantly higher mean number of retrieved nodes (50.5 *vs* 42, $P < 0.001$) and a lower noncompliance rate (31.8% *vs* 57.4%, $P < 0.001$) with the ICG arm (Table 4). Each lymph node station in gastric cancer has well-defined anatomical boundaries (Figure 6). ICG fluorescence complements proper surgical technique in achieving D2 lymphadenectomy. Improvement in compliance to D2 lymphadenectomy with ICG fluorescence is primarily seen in patients undergoing total gastrectomy. Also, patients in the ICG arm had better 3-year overall and progression-free survival[59]. Another potential utility of ICG-guided lymphangiography in patients with advanced gastric cancer is identifying metastatic lymph nodes beyond D2. However, the clinical utility of identifying and dissecting the nodes beyond D2 needs to be further studied.

ICG FLUORESCENCE IN COLORECTAL SURGERY

In large bowel surgery, ICG fluorescence is used to evaluate intraoperative bowel perfusion at the anastomotic site, identification of ureter, detection of metastases, lymphatic mapping, and tattooing of early colonic malignancy.

Assessment of bowel perfusion and anastomosis

The blood supply of the large bowel is variable in critical watershed areas due to diminished or absent collateral vessels. For satisfactory anastomosis healing, the bowel should be tension free and have sufficient vascular perfusion. Perfusion

Table 5 Studies on sentinel nodal navigation in early gastric cancer

Ref.	Country	Study type	Patient	ICG dose	Surgery	Mean SN yield	Results	Long term outcome
Isozaki *et al* [56], 2019	Japan	Multicenter retrospective cohort	100	Intraop endoscopic submucosal 1 mL 2.5% ICG 4 sites wait 15 min. Sentinel node biopsy followed by frozen	Open SNNS/DiG WDG: 3; 1/2 DG: 18; PPG: 19; SG: 31; LR: 29	3.8	Sensitivity: 85.7%. Specificity: 98.9%. Accuracy: 98%	5-yr OS: 89.6%. Gastric cancer specific survival: 98.5%
An *et al* [54], 2020	Korea	Multicenter RCT	580 patients; LSG: 292; LSNNS: 245	Dual tracer, ICG 2.5 mg/mL, 2 ml, and 99mTc-HSA, 2 mL	LSG group: Open: 3; LSG: 266. LSNNS group: LSNNS: 210	9	SBD: SB nodes: 59.7%; hot nodes: 23.4%; hot and green: 12%; green nodes: 4.9%. Operative time: LSG: 180 min; LSNNS: 192.5 min. Upstaging: 7.4%	NA
Miyashiro *et al*[55], 2014	Japan	Multicenter RCT	440 patients suspended	Serosal injection 4-5 mL, 25 mg/5 mL ICG	Sentinel node biopsy followed by gastrectomy with lymphadenectomy	4	False negative: 46.4%	NA

RCT: Randomized controlled trial; ICG: Indocyanine green; SNSS: Sentinel node navigation surgery; WDG: Wide-extent distal gastrectomy; LR: Local resection of stomach; SG: Segmental gastrectomy; PPG: Pylorus preserving gastrectomy; OS: Overall survival; DiG: Diminished gastrectomy; SBD: Sentinel basin dissection; HN: Hot nodes; SB: Sentinel basin; LSG: Laparoscopic standard gastrectomy; LSNNS: Laparoscopic sentinel node navigation surgery.
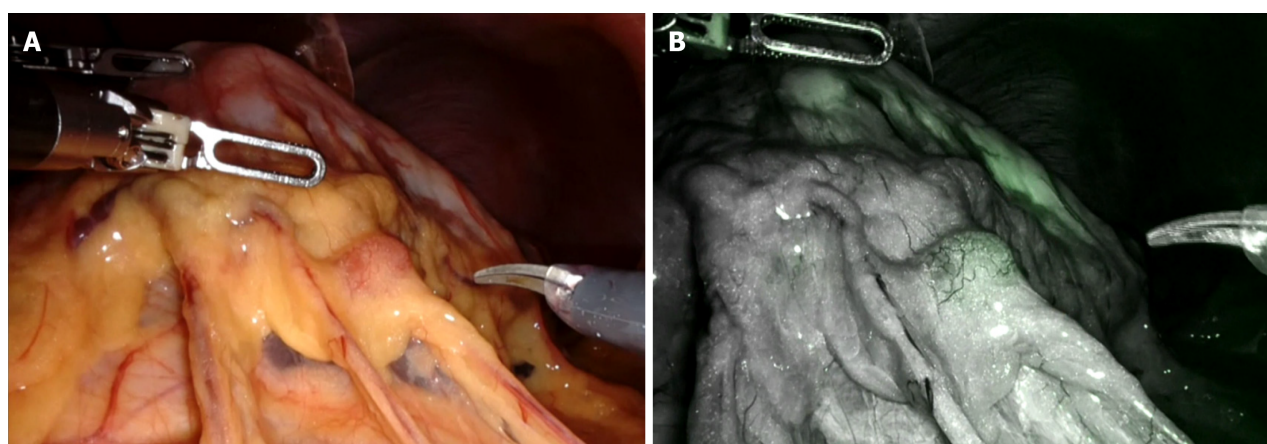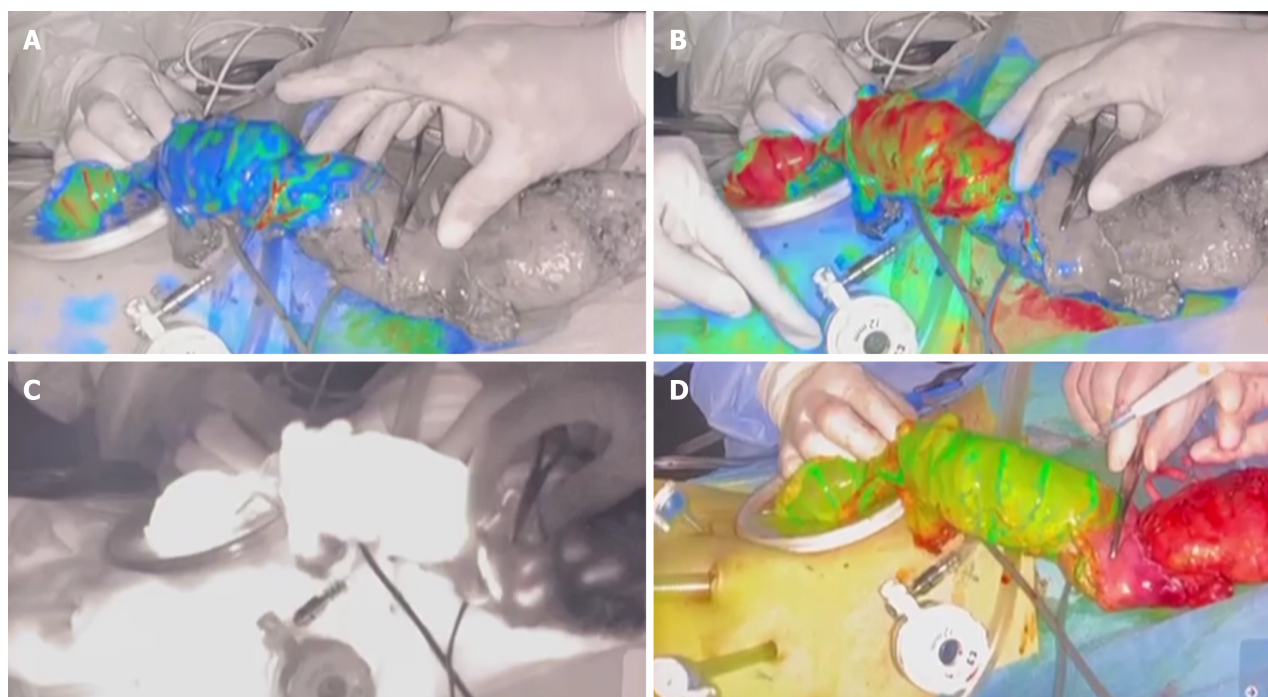

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Figure 6 Visualization of perigastric lymph node during robotic D2 gastrectomy in normal mode and fluorescence mode. A: In normal mode; B: In fluorescence mode.

assessment is done before the bowel transection to identify the demarcation line and after anastomosis to decide for diversion in low rectal anastomosis (Figure 7). Multiple meta-analyses had reported lower anastomotic leak and complication rates with ICG fluorescence angiography. A recent meta-analysis reported a lower pooled anastomotic leak rate (4.3% *vs* 9.43%, $P < 0.00001$) with ICG use[60]. Emile *et al*[61] reported that ICG-guided vascular assessment resulted in the revision of the transection point in 9.6% of patients. The main pitfall with using ICG for vascular assessment is the inability to assess mucosal perfusion. Sherwinter[62] first described the feasibility of assessing mucosal perfusion using a rigid sigmoidoscope and 12 mm laparoscopic trocar to introduce a laparoscopic ICG camera to assess staple line. Another limitation of the current technique is subjective perfusion assessment. Wada *et al*[63] reviewed the prospectively maintained video recordings of 112 patients undergoing left colonic resection with ICG fluorescence and used computer-based analysis to create fluorescent intensity to time curve and used parameters like Fmax, T_{max}, and slope (F_{max}/T_{max}) to quantitatively assess the vascular perfusion. Further studies to validate its application in surgery are awaited.

Ureter identification

Ureteral injury is reported in up to 0.6% of patients undergoing colorectal procedures. Preoperative ureteral stenting is done in high-risk patients with inflammatory disorders and advanced malignancy to aid ureteral identification and prevent injury. Meta-analysis of retrospective studies showed that stenting does not significantly reduce the chance of injury. However, it may help in the intraoperative identification of the damage[64]. Currently, many colorectal proce-

Figure 7 Objective evaluation of colonic perfusion using indocyanine green fluorescence during low anterior resection. A and B: Increasing fluorescence levels show the transition from blue (A) to red (B) and guide the selection of the line of bowel division; C: Fluorescence is displayed on a Grayscale; D: Fluorescence displayed in overlay mode.

dures are done using a minimally invasive approach. To identify the ureter, ICG is instilled along with ureteral stenting to aid in visual identification and preservation.

Lymphatic mapping and lymph nodal assessment

Colorectal malignancy spreads through the periarteriolar lymphatics to principal lymph nodes; hence, complete mesocolic excision and central vascular ligation is suggested. The Japanese also recommend D3 lymphadenectomy for clinical stage II and III colorectal malignancies based on a similar model. However, the regional lymph node zone varies and depends on the location of the tumor and its relationship to the feeding vessel. Nishigori *et al*[65] initially studied ICG fluorescence imaging in 21 patients undergoing colectomy with perioperative submucosal injection and observed lymph flow in 18 patients. Also, the principle lymph nodal basin was observed in 4 patients (23.5%), which changed the line of vascular ligation and extent of lymphadenectomy. Similarly, Watanabe *et al*[66] did lymphatic mapping in 31 patients undergoing colectomy for splenic flexure malignancy. Splenic flexure, the watershed area between the superior and inferior mesenteric artery territory, is classically treated with complete mesocolic excision of the middle and left colic regions. However, the study showed no bidirectional lymph flow. Hence the study hypothesized CME with middle colic ligation of distal third transverse colon cancer and CME with left colic ligation for proximal descending colon cancer. The study, which evaluated the histopathological examination of the fluorescent and non-fluorescent metastatic lymph nodes, showed no uptake of ICG in lymph nodes with complete tumor infiltration. Also, it revealed no ICG uptake in cancerous areas within partially fluorescent nodes. Thus ICG fluorescence-guided lymphatic mapping is primarily suited for early malignancy with no bulky node. Meta-analysis on sentinel lymph nodal biopsy showed higher pooled accuracy in T_1-T_2 (98%) compared to T_3-T_4 (77%)[67].

Tattooing

Colorectal polyps are treated with colonoscopic polypectomy, and submucosal invasion on pathological examination mandates completion segmental colectomy. Conventionally India ink and radioactive colloids are used for tattooing these early lesions. However, both are associated with limitations like short levelling time, radiation exposure, and surgical plane diminution. Preoperative endoscopic ICG injection to the polypectomy region or early colonic malignancy helps identify the tumor site promptly with a near-infrared camera. The addition of albumin to the ICG injection increases the levelling time to up to 10 d[68].

FUTURE PERSPECTIVES

ICG and its fluorescence property have created a new era of navigation surgery with the potential for better postoperative outcomes. Currently, ICG fluorescence employs angiography and cholangiography features for tumor-to-background

differentiation. Experimental studies of binding tumor-specific ligands with fluorophore have improved the detection of primary and metastatic tumors[69]. Boogerd *et al*[70] reported improved colorectal malignancy (primary, recurrent and metastatic) detection using fluorescent anti-carcinoembryonic antigen antibodies in 26 patients. This enhanced detection led to a change in surgical management in about one-third of the patients.

The use of ICG angiography in liver segmentation and mapping improves precision and R0 resection rate. However, its impact on oncological outcomes has not been well studied. Gon *et al*[71] have published their study protocol to evaluate long-term outcomes like recurrence-free survival following ICG fluorescence-guided liver resection. The study has completed patient recruitment, and clinical results are awaited.

Novel routes and formulations of ICG are being explored to widen its application. Thammineedi *et al*[72] reported the feasibility of administering ICG in an aerosol form *via* nebulization to visualise the tracheobronchial tree. Tracheo-bronchial fluorescence could minimize the incidence of airway injury in patients undergoing minimally invasive salvage esophagectomy and those with extensive periesophageal fibrosis following neoadjuvant chemoradiotherapy. Tokumaru *et al*[73] reported that subcutaneous injection of ICG in the inguinal region is as effective as ultrasound-guided injection into inguinal nodes to visualize the thoracic duct. The median time from the simple subcutaneous injection technique to the observation of ICG fluorescence of the thoracic duct was 119 min.

Experimental studies using ICG as a dual tracer that is detectable by radiography and fluorescent devices have increased its applicability as a marker for *in-vivo* mapping[74]. The results of future clinical trials to establish the usage of ICG as a marker are anticipated. He *et al*[75] in their clinical report regarding the fusion of lipiodol and Nano-ICG formulation, revealed its potential to enhance the photostability and fluorescence intensity of ICG. The growing trend of navigation surgeries using ICG fluorescence implies the impending need for research studies to explore, validate and develop this arena. Future studies would expand the research scope, increase the application of ICG fluorescence and overcome limitations.

CONCLUSION

The use of ICG as a guiding tool for dissection in gastrointestinal cancer surgery seems extremely promising. Further evidence from high-quality studies on larger sample sizes is needed to include ICG-guided surgery in standard practice. Our review has examined the contribution of prior research in multiple disciplines of hepato-biliary-pancreatic and gastrointestinal surgery. This study provides a comprehensive and contemporary representation of the literature and enhances understanding of the current affairs of this domain. This may serve as a practical guide for researchers in developing their study to be highly relevant to both research and practice.

FOOTNOTES

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