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Real-time fluorescence image-guided gastrointestinal oncologic surgery: Towards a new era

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Abstract

Technological improvements are crucial in the evolution of surgery. Real-time fluorescence-guided surgery (FGS) has spread worldwide, mainly because of its usefulness during the intraoperative decision-making processes. The success of any gastrointestinal oncologic resection is based on the anatomical identification of the primary tumor and its regional lymph nodes. FGS allows also to evaluate the blood perfusion at the gastrointestinal stumps after colorectal or esophageal resections. Therefore, a reduction on the anastomotic leak rates has been postulated as one of the foreseeable benefits provided by the use of FGS in these procedures. Although the use of fluorescence in lymph node detection was initially described in breast cancer surgery, the technique is currently applied in gastric or splenic flexure cancers, as they both present complex and variable lymphatic drainages. FGS allows also to perform intraoperative lymphograms or sentinel lymph node biopsies. New applications of FGS are being developed to assist in the detection of peritoneal metastases or in the evaluation of the tumor resection margins. The present review aims to provide a general overview of the current status of real-time FGS in gastrointestinal oncologic surgery. We put a special focus on the different applications of FGS, discussing the main findings and limitations found in the contemporary literature and also the promising near

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future applications.

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Core Tip: The continuous improvements on the postoperative and the oncological outcomes of patients undergoing gastrointestinal cancer surgery has focused the efforts of the whole surgical community during the last decades. Fluorescence-guided surgery is currently being developed and implemented in many countries and centers with promising expectancies. Fluorescence-guided surgery has the potential to reduce anastomotic leak rates of colorectal or esophagogastric surgery. Moreover, this new technology provides intraoperative real-time lymph node mapping and detection of sentinel lymph nodes or occult peritoneal metastases.

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INTRODUCTION

Fluorescence-guided surgery (FGS) was first developed in 1947 with the introduction of fluorescein, a near-infrared (NIR) fluorescent dye, in brain tumor resections[1]. During the last decades, several authors have investigated the different applications of NIR as an intraoperative imaging tool in many gastrointestinal oncologic procedures. FGS is today considered a useful tool to complement the preoperative standard explorations and to assist in the intraoperative decision-making processes, contributing to improvements in both clinical and oncologic outcomes. Indocyanine green (ICG) is a NIR contrast agent that becomes fluorescent when excited by 800–900 nm wavelength light. In recent years, the intraoperative use of fluorescence with angiographic purposes has been expanded by surgeons and within centers worldwide. The objective is to assess the bowel's perfusion before and after the anastomosis confection to reduce the risk of anastomotic leakage[2]. This complication is the most dreadful after both upper and lower gastrointestinal resections and often relates to an inadequate blood supply in the intestinal stumps. Additionally, NIR imaging is currently used or under investigation in a growing number of applications in the field: To identify peritoneal implants or sentinel lymph nodes, to perform lymph mapping, to guide an oncologic tumor resection, or to visualize biliary and urinary structures preventing iatrogenic harms. Then, real-time NIR is becoming an important tool in the surgeon's armamentarium to perform safe and successful cancer resections, with the greatest future expectancies favored by the continuous technological improvements. We aimed to provide a complete and critical overview of the current evidence focusing on the different applications of FGS in gastrointestinal oncologic surgery.

ASSESSMENT OF THE ANASTOMOSIS PERFUSION AFTER COLORECTAL RESECTIONS

Colorectal cancer (CRC) is the third most common malignant tumor worldwide and the second cause of cancer-related death. CRC is responsible for 9.2% of the cancer deaths in the world[3]. Anastomotic leakage (AL) is the most feared complication after any colorectal resection[4]. AL is associated with increased mortality and poorer long-term oncological outcomes[5,6], especially in rectal cancer patients[7]. High rates of AL are still reported despite the successive improvements in the stapler devices and minimally-invasive techniques during the last years[8]. Several risk factors for AL

have been described. They include male gender, age, comorbidities, malnutrition, obesity, smoking, alcoholism, immunosuppression, neoadjuvant treatments, *etc.*[9,10]. The individual surgeon performance, which was systematically obviated in the literature, has been shown also to be an independent risk factor for AL[11,12]. However, there is a general agreement in considering the ischemia of the anastomotic stumps as a key factor in the development of the majority of AL[9,13,14].

AL can be defined as the separation between two bowel segments that were previously attached. The definition includes a wide spectrum of situations, from small leaks without systemic consequences, to severe peritonitis causing septic shock or death. The high clinical variability in such terms and its definition highly jeopardizes the comparisons within the multiple studies on the subject. To overcome those biases, research teams have attempted to unify the criteria to define and grade AL through the elaboration of different systems. The Colon and the Dutch leakage scores were created for this purpose[15-17]. In 2010, the International Study Group of Rectal Cancer (ISGRC) presented an extensive literature review and proposed a new definition and grading system for AL in rectal resections. AL was defined as any defect of the intestinal wall integrity at the colorectal or coloanal anastomotic site leading to a communication between the intra- and extra-luminal compartments[18]. This definition included leaks from suture and the staple lines of neo-rectal reservoirs or pelvic abscess close to the anastomosis. The ISGRC graded AL in a three-tiered system: Grade A reflects no need for therapeutic intervention; grade B if the AL requires therapeutic intervention but is manageable without re-laparotomy; and grade C when it requires re-laparotomy[18].

The assessment of the anastomosis perfusion is a crucial step during colorectal resections. Multiple methods have been described to assess the viability of the intestinal stumps, mainly implying different degrees of subjectivity[19]. The air leak test was proposed by Lazorthes *et al*[20] in the 1980s. Conventional inspection by the surgical team is based on the bowel appearance and coloration, bleeding on the edges of the intestinal stumps, or in the detection of the arterial pulse[6,21]. In the last years, the use of ICG fluorescence angiography (ICG-FA) has become widespread, especially within colorectal surgeons (Table 1). The first large clinical experience with ICG-FA was reported by Kudsus *et al*[22] in 2010. They used laser fluorescence angiography by injecting ICG to assess the bowel perfusion. They compared the study group with a matched historical cohort, 201 patients in each group. Overall, 3.5% of the patients in the laser fluorescence angiography group developed Grade C AL compared to 7.5% of the controls. The use of ICG reduced the risk of AL by 60% in elective surgery and changed the surgical plan in the 16% of the operations[22]. The safety and feasibility of ICG-FA were further confirmed in two phase-2 prospective clinical trials[23,24]. Moreover, in 2020 two randomized controlled trials (RCT) assessed the effectiveness of the new technique when compared with the conventional surgeon's judgment. The first was a multi-centric Italian superiority RCT. Two hundred fifty-two patients were referred for laparoscopic anterior rectal resection or left colectomy with a colorectal anastomosis, which was expected to be located between 2 and 15 cm from the anal verge. The primary outcome was the rate of AL defined by the ISGRC criteria within 30 d from surgery. In 13 patients, extended resections were performed according to the ICG-FA findings (11%). AL were developed in 6 (5%) patients in the ICG-FA group and in 11 patients (9%) in the control group ($P = \text{not significant}$)[25]. The second RCT enrolled 380 patients who underwent sigmoid or rectal resections between 2018 and 2019 in a single Russian institution. They observed that ICG-FA did not decrease the rate of AL in high (*i.e.* 9-15 cm from the anal verge) anastomoses: 1.3% *vs* 4.6% in the control group ($P = \text{not significant}$). In low colorectal anastomoses (*i.e.* 4-8 cm), the AL rate was significantly lower in ICG FA group: 14.4% *vs* 25.7%, respectively ($P = 0.04$). However, the difference was caused by the higher rate of Grade A leaks in the control group. The rates of clinically relevant AL (Grades B and C) were found to be similar between the two arms[26]. Arezzo *et al*[27] recently published an individual patient data meta-analysis including the two previous RCT and seven non-randomized studies. Pooled data from 1330 patients were analyzed, 862 in the ICG-FA group and 468 in the control group. The main outcome was the rate of AL during the first 30 d after surgery. The site of the anastomosis was modified after ICG-FA in 11.3% of the patients, whereas a new anastomosis was performed in 2% of the cases. ICG-FA reduced the odds of AL by 89.7%; indeed, the incidence of AL was significantly lower in the ICG-FA group than in the control group (4.2% *vs* 11.3%, respectively)[27].

Table 1 Summary of the outcomes of indocyanine green-fluorescence angiography to prevent anastomotic leakage after colorectal and esophageal resections

Ref.	Study design	Total <i>n</i>	ICG group	Non-ICG group	Anastomosis leak <i>n</i> (%)	<i>P</i> value	Surgical plan change (%)
Colorectal							
Kudszus <i>et al</i> [22], 2010	Retrospective-matched	402	201	201	ICG: 7 (3.5%); NICG: 15 (7.5%)	0.04	16%
Jafari <i>et al</i> [23], 2013	Case-control	38	16	22	ICG: 1 (6%); NICG: 4 (18%)	NS	19% cases 4.5% controls
Kim <i>et al</i> [55], 2015	Case-control	436	123	313	ICG: 1 (0.8%); NICG: 17 (5.4%)	NS	Not reported
De Nardi <i>et al</i> [25], 2020	Randomized controlled trial	240	118	122	ICG: 6 (5%); NICG: 11 (9%)	NS	11%
Alekseev <i>et al</i> [26], 2020	Randomized controlled trial	377	187	190	ICG: 17 (9.1%); NICG: 31 (16.3%)	0.04	Not reported
Arezzo <i>et al</i> [27], 2020	Meta-analysis	1330	862	468	ICG: 36 (4.2%); NICG: 53 (11.3%)	< 0.001	11.3%
Esophageal							
Zehetner <i>et al</i> [43], 2015	Prospective	150	150	N/A	4.6%	N/A	66%
Kumagai <i>et al</i> [47], 2018	Cohort series	70	70	N/A	1.4%	N/A	50%
Ladak <i>et al</i> [45], 2019	Meta-analysis	1067	631	436	Overall: 10.8%; ICG: 5.7%; NICG: 22.9%	NR	Not reported
Slooter <i>et al</i> [48], 2020	Cohort series	84	84	N/A	14.3%	N/A	2.4%

ICG: Indocyanine green; N/A: Not applicable; NICG: Non-indocyanine green; NR: Not reported; NS: Not significant.

ASSESSMENT OF GASTRIC TUBE PERFUSION FOLLOWING ESOPHAGECTOMY

The surgical resection of esophageal cancers is associated with high rates of postoperative morbidity and mortality. AL and respiratory complications are the most frequent severe adverse events following an esophagectomy[28,29]. The incidence of AL in the literature ranges between 5% and 20% and has been associated with mortality rates of 18% to 40%[30,31]. Remarkably, up to 40% of the long-term survivors after an AL will develop an anastomotic stricture and therefore may require additional interventions or permanent nutritional support[32,33]. The most frequent methods for intestinal reconstruction after an esophageal resection include the performance of a stapled gastric tube by using the greater curvature of the stomach. The gastropasty is then anastomosed with the cervical or the thoracic esophagus. The ischemia of the gastric tube is known to be the main predisposing factor for AL at esophagogastric anastomosis[34-36]. The tip of the gastric tube is the poorest perfused area[37]. Many other predictors for AL following esophagectomy have been described and include male gender, tobacco or alcohol abuse, obesity, the severity of comorbidities, corticoid therapy, emergency setting, and blood transfusions[30,35,36]. The conventional intraoperative methods to evaluate the perfusion of the gastric conduit are mainly based on the human visual inspection and therefore offer low accuracy. In recent years, different teams have experienced with ICG-IF intending to mitigate the burden of this deleterious complication, with variable results (Table 1). Some of them showed no effect of the ICG-IF to prevent an AL[28,38], while others did [29]. Other authors showed lower severity of AL but not a decrease in the AL rates[39-42].

Zehetner *et al*[43] presented in 2015 one of the earliest prospective studies using laser-assisted angiography with ICG. They enrolled 150 patients who underwent esophagectomy with a cervical reconstruction. Two-thirds of all anastomosis sites were changed due to the angiographic findings. There was one postoperative death, and 22% of the participants developed major complications. AL occurred in 16.7% of the cases, but most of them were successfully managed without a surgical reoperation.

The placement of the anastomosis and the precedent of arterial hypertension were significantly associated with AL[43]. Later, Koyanagi *et al*[42] evaluated 40 prospective patients with esophageal cancer to receive ICG-FA. They established four points in the gastric tube and determined the flow by calculating the time spent by the ICG to move between them. After they divided the flow into simultaneously or delayed. Morbidity was greater in the delayed group (60% *vs* 32%; $P = 0.055$). AL was observed in 7 patients, all belonging to the latest group. The same researchers designed an ancillary study recruiting 109 additional patients to confirm the findings of their first work. They also evaluated the calcifications in the aorta, celiac trunk, and superior mesenteric artery with computerized tomography scan. AL rate was 13.7% in the study. The blood flow at the gastric conduit and the calcifications in the superior mesenteric artery were significantly correlated with AL development[44]. Ladak *et al* [45] recently published a systematic review including 17 studies and 1067 patients. The pooled anastomotic leak rate was found to be 10% when ICG was used. They performed a meta-analysis including six non-RCTs that resulted in a risk reduction of 69% for ICG compared with the control group (odds ratio 0.31, 95% confidence interval: 0.15–0.63). However, there was high heterogeneity between the few studies published to date, and there is no prospective study comparing ICG and no-ICG for this indication. Therefore, the quality of the evidence regarding the real effectiveness of ICG-FA in esophagogastric anastomosis is still poor.

Recently, the quantification of the time-dependent change in the fluorescence signal has been postulated as a promising method to assess the future viability of the gastric conduit. New studies appeared recently with the aim to establish a standardized quantitative method for evaluation. One of the first was conducted by Kumagai *et al* [46] presenting the 90-s rule to find the best place to perform the anastomosis as the one enhancing within 90 s of the injection. They conducted a further prospective study including 70 patients. In 50% of the cases, the tip of the gastric tube was excised. Only a minor AL was diagnosed and developed into one of the 3 cases in which the enhancement time exceeded 60 s[47]. Slooter *et al*[48] recently presented a prospective study aiming to evaluate the time until the fluorescent enhancement of the gastric conduit as a quantitative fluorescent value for ICG-FA. They determined a threshold to predict anastomotic complications in 84 patients. The anastomosis site was changed in 2.4% of the cases as a result of ICG-FA. AL was observed in 14.3% of the included patients. When using the 90-s threshold, the time between ICG injection and the enhancement of the gastric conduit tip was a predictor for AL with a specificity of 98% but a sensitivity of 17% in the study.

LYMPH NODE DETECTION AND MAPPING

In 1992, Morton *et al*[49] introduced the sentinel lymph node (SLN) concept by injecting technetium-labeled dextran to 223 patients with non-advanced melanoma. Shortly after, Giuliano *et al*[50] applied this technique by using blue dye in 172 women with breast cancer. Both groups obtained excellent results, the SLN procedure expanded, and it is currently being implemented in the treatment of a growing number of cancers. The use of ICG for SLN was first reported in 2005, also in breast cancer[51]. Nowadays, the knowledge gained regarding SLN biopsy (SLNB) in breast cancer and melanoma has been extrapolated to gastrointestinal cancers, especially gastric and colorectal ones. The metastatic involvement of the lymph nodes is a major prognostic factor in those tumors. There is a permanent controversy regarding whether more extensive lymphadenectomies provide survival benefits in gastrointestinal malignancies[52,53]. It is noteworthy that greater lymphadenectomies are associated with higher morbidity and mortality rates[54].

The available preoperative radiologic examinations do not achieve enough accuracy to identify adequately the lymph node metastases. In this scenario, ICG emerged as a promising tool, allowing the performance of real-time intraoperative lymphograms (Table 2). Similar to the above mentioned applications of ICG in oncologic digestive surgery, the timing, dose, and technique presented high heterogeneity within the existing literature on the subject[55,56]. The latency time from the injection to the measurement was 40 min (range 3 to 152), which represents a non-despicable increase in the duration of the anesthesia[57–61]. Most authors prefer the intraoperative injection to perform LN mapping (LNM), while others the day before surgery looking for a more complete LNM in gastric cancers[62,63]. Peritumoral and subserosal seem to be the most widespread injection sites[60,61,64–66]. However, some authors have reported a series of submucosal injections obtaining favorable results[67–

Table 2 Summary of the studies on involving lymph node detection in gastrointestinal cancer

Ref.	Patients	Detection rate	Sensitivity	Specificity	Considerations
Kusano <i>et al</i> [76], 2008	26 CRC, 22 GC	CRC: 90.9%, GC: 88%	CRC: S: 25% ¹ , GS: 40% ¹	Sp: 100% ¹ , Sp: 100% ¹	CRC: PPV: 100% NPV: 81%, GC: PPV: 100% NPV: 62.5%
Cahill <i>et al</i> [78], 2009	891	NR	81%	93.2% ¹	PPV: 62% NPV: 95%. Lower FN if tumor size is less than 35 mm. IHC analysis increases sensitivity
Noura <i>et al</i> [58], 2010	25	92%	100%	100%	FNR: 0%. NPV: 100% Performed lateral pelvic dissection in order to increase SN detection accuracy
Kitagawa <i>et al</i> [80], 2013	397	97.5%	93.44% ¹	98.99% ¹	Uses dual technique (blue dye and ICG)
Kinami <i>et al</i> [82], 2015	72		90%	98% ¹	FN: 1.3%
Tummers <i>et al</i> [79], 2016	26	95%	75%	88.9%	Reduces second-tier nodes using nanocolloids
Lee <i>et al</i> [83], 2016	20	95%	100%	94.4%	FN: 0%
Villegas-Tovar <i>et al</i> [57], 2020	281	91%	64.3%	65%	AUC: 66.5%

¹Calculated using the data provided at the papers. AUC: Area under the curve; CRC: Colorectal cancer; FN: False negatives; FNR: False negative rate; GC: Gastric cancer; ICH: Immunohistochemistry; NPV: Negative predictive value; NR: Non reported; PPV: Positive predictive value; SN: Sentinel node.

69]. Xiong *et al*[70] showed that concentrations < 5 mg/mL and volumes injected ≥ 2 mL presented higher sensitivity and detection rates.

With the injection of ICG and a subsequent LNM, extra-anatomical routes of lymphatic spread can be evidenced in real-time. This is especially useful in gastric[71] or splenic flexure colonic cancers[65], both presenting complex lymphatic drainages. Likewise, ICG has demonstrated its usefulness to detect the lateral SLN in mid-low rectal cancer and to decrease the rate of complications[72]. Noura *et al*[58] reported a 92% detection rate of lateral SN in low rectal cancer in a pilot study with 25 patients. Moreover, ICG combined with NIR allows a deeper visualization of the lymphatic structures than the classical contrasts under conventional light[63,72]. This would increase the lymph node harvest and mitigate the risk for tumor downstaging and then suboptimal indications of adjuvant treatments[73-75]. This can be of particular interest in Western countries because of the high prevalence of obesity[63].

Kusano *et al*[76] reported the first experience of SLNB in gastrointestinal tumors with SLN detection rates of 90.9% in CRC and 88% in gastric cancer. Following them, many teams repeated the experience, and the detection rates ranged between 80% and 99%[57]. Those rates, as the accuracy of SLNB, are influenced by the tumor size, the T-stage, the body mass index, the tracer used, and the surgeon's experience[77]. Cahill *et al*[78] suggested that ICG-guided SLNB in CRC is more sensitive and has a lower tumor false negative (FN) rate if the tumor size is lesser than 35 mm. The SLNB could be useful in selected patients presenting cT1-2 gastric tumors where a routine D2 lymphadenectomy could lead to unacceptable morbidity. However, the main issue that limits the applicability of ICG to SLNB is caused by its diffusion towards the second-tier nodes. Tummers *et al*[79] addressed this problem by adding nanocolloids to the ICG. However, 9% of the patients were FN (*i.e.* macrometastatic nodes not stained), likely due to a tumoral blockage of the lymph flow. In a recent meta-analysis, the detection rate of SLN with ICG in CRC was 91%. Nevertheless, the accuracy in the prediction of nodal involvement was poor with an area under the curve of 66.5% and a sensitivity of 65%[57]. Other authors used dual-tracer techniques (*i.e.* blue dye + radiotracer) and reported an accuracy close to 99% in gastric cancer patients with stages cT1 and cT2 smaller than 4 cm but still with a high FN rate in the T2-stages[80]. The high FN rate is the most critical limitation in ICG-guided SLNB. The Japan Clinical Oncology Group multicenter trial (JCOG0302) was suspended due to a high proportion of FN in ICG-guided SLNB[81]. Although Kinami *et al*[82] and Lee *et al*[83] reported a 1.3% and 0% rate of FN, respectively, the majority of the studies have FN rates of approximately 20%, with small variations among them[60,67,79,84].

Last, by applying molecular biology techniques such as immunohistochemistry or one-step nucleic acid amplification it is possible to detect micrometastases and isolated

tumor cells in the lymph nodes. The meta-analysis by Ankersmit *et al*[73] reported an upstaging rate of 15% after immunohistochemistry analysis due to the detection of micrometastasis. Even higher upstaging rates have been reported with the combination of ICG and intraoperative one-step nucleic acid amplification analysis of the fluorescence nodes[85-87]. Although there is currently no recommendation to indicate adjuvant treatments in colorectal or esophageal cancers based on the presence of isolated tumor cells, in the foreseeable future the ICG-guided SLNB may contribute to offer more personalized and optimized options to treat the patients.

PERITONEAL METASTASIS DETECTION AND TUMOR RESECTION

Peritoneal metastases (PM) are a common evolution of gastrointestinal cancer, and they are strongly associated with a poor prognosis. Around 8%-25% of CRC patients will develop PM[88,89]. In the 1990s, the use of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy was proposed by Sugarbaker *et al*[90], showing a marked improvement in the patient's overall survival. Those aggressive procedures are associated with non-despicable rates of postoperative morbidity (16%-64%) and mortality (5%)[91]. Moreover, the completeness of tumor removal is still the most critical prognostic factor in patients with CRC and PM, as patients undergoing incomplete resections may expect only few oncologic benefits from the surgery. Thus, a careful patient selection in these complex scenarios is mandatory. Unfortunately, the available preoperative diagnostic imaging systems, as the intraoperative visual inspection, have shown a low sensitivity to detect PM nodules smaller than 5 mm[92,93]. The use of fluorescence *via* ICG for these purposes is based on an effect named "enhanced permeability and retention" (EPR). The EPR illustrates the affinity of ICG towards the tumoral and near-tumoral tissue due to neovascularization and impaired lymphatic drainage. ICG detection in PM nodules was described by Kosaka *et al*[94] in animal models. To date, only four groups have evaluated the role of ICG in the detection of PM from CRC. Liberale *et al*[95] published the proof-of-concept in 2016. They included 14 patients (63 evaluable nodules) after excluding patients with peritoneal carcinomatosis index (PCI) > 17. In the first procedure, 0.25 mg/kg of free ICG were injected intravenously 24 h before surgery, but no fluorescence was detected during the surgery. Thereafter, ICG was injected intraoperatively after a complete abdominal exposition. Nodules were classified *in vivo* as hyperfluorescent, moderately hyperfluorescent, or hypofluorescent. ICG detected additional PM in 3 patients (21.4%). All these PM were found in the abdominal flank regions and paracolic gutters. Sensitivity and specificity in patients with non-mucinous adenocarcinoma were 87.5% and 100%, respectively. In patients with mucinous tumors, ICG was poorly sensitive (0%). The authors attributed these findings to the correlation between the presence of mucinous material and the absence of vascularized tissue within tumor nodules[95].

Barabino *et al*[96] presented the same year a prospective study aiming to evaluate the detection of PM nodules *ex vivo* using NIR and ICG injected 24 h before surgery in 10 patients and 88 Lesions. During the surgery, only the tissues macroscopically suspicious were resected. The group presented their results in three different publications. In the first report, they showed that the overall sensitivity and specificity for CRC-PM detection were 72.4% and 77.3%, respectively, which were lower than initially expected. They also found a high false-positive rate of 40%[96]. The same team published an ancillary report over the same 10 patients to assess the impact of bevacizumab, an anti-angiogenic agent, on the extravasation of ICG. It was hypothesized that it may reduce the EPR effect and increase the FN rates. All the patients in the study received preoperative chemotherapy, 4 treated with bevacizumab and 6 without (4 cetuximab/2 no biotherapy) who were included as controls. Sensitivity and specificity were similar within groups[97]. In a further correspondence letter, the authors provided the data of 2 patients (22 nodules) presenting mucinous adenocarcinomas[98,99]. The analysis showed a sensitivity of 72.2% and specificity of 75%, which was similar than the whole population, and contrasted with the findings of the earlier study on the subject. In 2018, Lieto *et al*[100] reported 4 patients in which ICG was injected intraoperatively and then detected by the INR camera system. Sixty-nine specimens were analyzed *in vivo* and *ex vivo* with complete correspondence. The use of ICG added 25% of diagnostic improvement, as detected 16 nodules missed by conventional procedures. Sensitivity was 96.9% and specificity 75%, with a false positive rate of 25% and a FN rate of 3%[100].

There are currently alternative imaging systems to detect PM. Narrow-band imaging (NBI) appeared in 2005 and has been routinely used in gastrointestinal

Table 3 Summary of the studies evaluating the role of indocyanine green to detect peritoneal carcinomatosis

Ref.	Yr	Patients	Nodules	Additional nodules	Sensitivity	Specificity	Considerations
Liberale <i>et al</i> [95], 2020	2016	14	63	21.4%	87.5%	100%	
Barabino <i>et al</i> [96], 2020	2016	10	88		72.4%	77.3%	
Filippello <i>et al</i> [97], 2020	2016	10	29		65%	57.1%	Same patients than Barabino <i>et al</i> [96], but comparing the use of bevacizumab or not
Lieto <i>et al</i> [100], 2020	2018	4	69	16	96.9%	75%	ICG adds 25% of diagnostic improvement
Sluiter <i>et al</i> [104], 2020	2019	28	169		80%	74.8%	NBI increases sensitivity from 80% to 96% when compared with white light, with the same specificity

ICG: Indocyanine green; NBI: Narrow band imaging.

endoscopy[101]. The system consists of a camera filter that allows the identification of 415-540 nm wavelength light. They match with the two absorption peaks of the hemoglobin, then highlighting the microvascular architecture[102]. Previous studies have shown promising results during staging laparoscopy in advanced gastric cancer when compared with the standard white light imaging[103]. Recently, Sluiter *et al* [104] published the results from a prospective clinical trial over 28 patients comparing three advanced imaging techniques with the conventional white-light to detect PM from CRC: (1) NBI; (2) NIR-ICG administrated 3-12 h before surgery; and (3) Spray-dye chromoendoscopy. The use of the two latest was discontinued after 10 patients because the lesions were not fluorescent using NIR-ICG, and the spray-dye chromoendoscopy did not allow the entire visualization of the peritoneal cavity. The main finding of the study was that NBI increased the sensitivity in detecting PM to 96% when compared with the white light (Table 3).

We can consider that NIR-ICG imaging is a feasible tool to assist in the detection of the PM of CRC. The main advantages of ICG are its safety and its commercial availability. However, ICG is a non-specific molecule to detect the neoplastic tissue, therefore its specificity is limited. The standard dosage or timing of ICG injection are still to be determined. Moreover, its effectiveness may be limited in patients with mucinous neoplasms or already treated with antiangiogenics. The next step may be the detection of tumor tissue by molecular-FGS. The first clinical study evaluating the safety and feasibility of molecular-FGS using bevacizumab-800CW to detect PM from CRC reported a sensitivity of 100% and a specificity of 54%. The study involved 7 patients; in 2 of them additional tumor deposits were detected. There were no serious adverse events related to the administration of the tracer[105]. A multicenter pilot study has been recently published including 14 patients diagnosed with PM from colorectal origin in which SGM-101, a carcinoembryonic antigen-specific tumor-targeted fluorescent agent, was administrated to identify peritoneal malignant tissue. There was no adverse effect. Sensitivity was 98.5% and specificity 62.2%. The positive predictive value was 82.3% and the negative predictive value was 95.8%[106].

The bevacizumab-800CW fluorescent tracer has been also recently used for back-table evaluation of the circumferential resection margin in eight fresh surgical resection specimens of locally-advanced rectal cancer[107]. The future development of these techniques towards its intraoperative application could drive surgical decision-making in the case of positive circumferential resection margin to extend resections or to indicate concomitant intraoperative radiation therapy.

CONCLUSION

The use of fluorescence imaging in gastrointestinal oncologic surgery has expanded in the last years. The technology has demonstrated to be safe and has the potential to improve both the clinical and the oncologic outcomes. Preliminary studies showed that ICG-FA may reduce the risk to develop ALs after esophageal or colorectal resections. ICG has been found to be successful to perform lymphographies or to detect sentinel nodes, with acceptable accuracy rates. Few studies recently addressed

the applicability of fluorescence to identify occult peritoneal disease, also with promising returns. However, there is a notorious heterogeneity regarding the dosage, timing, and imaging systems used in the different studies. This heterogeneity is also noted in the outcomes they have evaluated. Future standardization is mandatory to elucidate the real role of FGS in these scenarios.

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