Applications of indocyanine green fluorescence imaging in colorectal surgery: a narrative review

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Background and Objective: The need to optimize visualization systems in minimally invasive surgery has given rise to a growing number of applications of indocyanine green (ICG) fluorescence. This narrative review aims to summarize the existing literature about the use of this fluorophore in colon and rectal surgery.

Methods: A literature search was performed using PubMed database to identify relevant articles on ICG fluorescence guided surgery and colorectal surgery.

Key Content and Findings: ICG fluorescent angiography has proved to be a useful tool to assess intestinal resection line perfusion, but study heterogeneity, low statistical power and confounding evidence have prevented demonstrating a decrease in anastomotic leak in colorectal surgery. Although the application of ICG near-infrared fluorescence is a safe and reliable technique for evaluating the lymphatic flow and detecting sentinel lymph nodes in colorectal surgery, especially in early cancer stage setting, current evidence does not allow to determine its use in routine clinical practice and it is far from being sufficient to establish ultra-selective colectomies programs. Endoscopic submucosal ICG injection allows intraoperative tumor site location when performed up to a week prior to surgery, but cost-effectiveness research need to define its advantage compared to traditional permanent dyes. Intraureteral ICG instillation may reduce ureteral iatrogenic lesions, but its invasive administration prevents its use in daily routine patients.

Conclusions: ICG fluorescence-based technology represents a niche of opportunities for improved visualization in the field of minimally invasive surgery. However, with the exception of angiography for the intraoperative evaluation of intestinal perfusion, the currently available evidence limits the indication for routine use of the rest of the applications. Future development of quantitative fluorescence measurement methods and established protocols may achieve better performance of this tool.

Keywords: Indocyanine green (ICG); colorectal; lymph node; ureter; tumor location

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Introduction

Colorectal cancer (CRC) remains a worldwide clinical problem as the third most common cancer for both men and women, and the second leading cause of cancer-related deaths (1). Although its management is based on a multidisciplinary approach, surgical resection remains the cornerstone of curative treatment (2). Related to its faster recovery, minimally invasive techniques are quickly becoming the standard of care. Technology innovations such as enhanced optic systems, robotic instruments, powered staplers and specialized operating platforms for natural orifice transluminal endoscopic surgery (NOTES) are being developed concurrently to support surgical outcomes. In this setting, fluorescence imaging is emerging as a major contributor to intraoperative decision making.

Indocyanine green (ICG) is the most commonly used fluorophore in fluorescence imaging, as it can be used in intravenous injections or local infiltration directly into tissues (3). Intravenously injected, the water-soluble dye rapidly binds to plasma lipoproteins and remains confined in the intravascular compartment with a half-life of 3–5 minutes, until biliary excretion starts. These pharmacokinetics makes ICG ideal for repeated applications. The long-standing safety and efficacy proved in classical clinical applications for several decades, such as establishment of cardiac output, liver function and ophthalmic angiography, has facilitated its introduction to new applications in the field of surgery. These advances could offer great value for surgeons and patients, by improving the visualization, accuracy and outcomes of colorectal resections.

The purpose of this narrative review was to summarize the existing literature about the use of ICG fluorescence imaging in colon and rectal surgery and emerging applications. We present the following article in accordance with the Narrative Review reporting checklist (available at https://ales.amegroups.com/article/view/10.21037/ales-22-38/rc).

Methods

The search strategy is summarized in *Table 1*. Literature review was performed between March and April 2022 using the PubMed database to identify relevant articles on ICG fluorescence guided surgery and colorectal surgery. Keywords searches included: "indocyanine green", "colorectal", "anastomotic leakage", "perfusion", "sentinel lymph nodes", "lymphatic mapping", "ureter", "tumor identification". Only English articles were included. After identification of relevant articles, the abstracts were read to select eligible article for full text revision. References of identified articles were searched for additional relevant articles. Case reports and editorial letters were excluded.

Fluorescence angiography (FA) for the assessment of anastomotic perfusion

Anastomotic leak (AL) represents the most unwanted complication of CRC surgery as it is associated with high morbidity and mortality, along with higher rates of reoperation, length hospital stay and hospitalization costs (4). Even more worrying, recent researches have shown a possible association between AL and an increased risk of cancer recurrence, as well as worse long-term oncological and functional outcomes (5,6). The incidence of AL after colorectal resections ranges between 3–20%, being highest in low anastomoses (7,8). The negative consequences of AL have led to constant research to develop prevention strategies in order to reduce its incidence. Evidence highlights many potential risk factors, most of them non-modifiable, including patient characteristics [age, body mass index (BMI), nutritional status, smoking, neoadjuvant treatment, high American Society of Anesthesiology (ASA) score] and surgical events like duration of surgery, intraoperative blood loss, surgical techniques and surgeon experience (9). Perhaps most important controllable risk factors are to ensure a free-tension anastomose and an adequate blood supply of the two transected bowel wall edges (10,11), which are the key to good anastomotic healing (9). With this in mind, colorectal surgeons have adopted standard intraoperative tests to assess blood perfusion of intestinal junction site. Traditionally, the blood supply of the anastomosis was assessed by the color of the intestinal mucosa, marginal bleeding and palpable arterial pulses in the mesentery (10,11). However, despite these different options to assess intestinal perfusion can be considered as principles of an anastomotic technique, for decades, it has not been possible to further reduce the incidence of AL. In the search for more useful methods, ICG FA has raised lately as a valuable tool to assess blood perfusion intraoperatively in real time. Multiple studies have been published to date on the usefulness of its application in colorectal surgery to prevent AL (12-18). Clinical trials data of impact of ICG FA on reducing AL is summarized on *Table 2*.

Table 1 The search strategy summary

Items	Specification
Date of search	March–April, 2022
Database(s) searched	PubMed
Search terms used	"Indocyanine green", "colorectal", "anastomotic leakage", "perfusion", "sentinel lymph nodes", "lymphatic mapping", "ureter", "tumor identification"
Timeframe	2005–2022
Inclusion criteria	Original articles, systematic reviews and meta-analysis
Exclusion criteria	Case reports, Editorial letters and non-English articles were excluded.
Selection process	Participating authors identified relevant articles based on content, clinical relevance and date of publication

Table 2 Clinical trials data summary of impact of ICG FA on reducing AL

Author and year	Study type	Number of patients and groups	Type of surgery	Transection line change	Anastomotic leak, ICG FA/control	P value
Kudszus *et al.* (12), 2010	Retrospective; single center	Total 402: ICG FA [201]; control [201]	Colorectal surgery	16.4%	3.5%/7.5%	0.04
Morales-Conde *et al.* (13), 2020	Prospective; single center	Total 192 (ICG FA): Group A [67)]; Group B [9]; Group C [81]; Group D [35]	Group A: right hemicolectomy; Group B: segmental resection of the splenic flexure; Group C: left hemicolectomy; Group D: rectal anterior resection	Group A: 6%; Group B: 11.1%; Group C: 25.9%; Group D: 25.7%	Group A: 3%; Group B: 0%; Group C: 1.2%; Group D: 5.7%	NA
Ohya *et al*. (14), 2020	Retrospective; multicenter (3 centers)	Total 400 (ICG FA)	Colon or appendiceal cancer	2.8%	1%	0.035
Jafari *et al.* (16), 2021.	RCT; multicenter (25 centers)	Total 347: ICG FA [178]; control [169]	Left-sided colectomy and rectal anterior resection	NA	9%/9.6%	0.37
Otero-Piñeiro *et al.* (15), 2021	Comparative prospective/ retrospective data; Single center	Total 284: ICG FA [80]; control [204]	TaTME	28.7%	2.5%/11.3%	0.02
De Nardi *et al.* (17), 2020	RCT; multicenter	Total 240: ICG FA [118]; control [122]	Left sided colectomy and rectal anterior resection	11%	5%/9%	NA
Alekseev *et al*. (19), 2020	RCT; single center	Total 377: ICG FA [187]; control [190]	Laparoscopic sigmoid and rectal anterior resection	19.2%	9.1%/16.3%	0.04

ICG FA, indocyanine green fluorescence angiography; AL, anastomotic leakage; RCT, randomized clinical trial; TaTME, transanal total mesorectal excision; NA, no-accessible.

Most of the articles consist on prospective and retrospective observational studies that evaluate the role of ICG intravascular bowel delivery and the intraoperative decision changes in the resection margin based on these results. On the one hand, Kudszus *et al.* (12) investigated the application of ICG FA in all anastomoses or resection margins in CRC resections performed in their center between 2003 and 2008. They reported that ICG FA suggested a change of the proximal colonic resection line location in 16.4% of the patients. In addition, ICG FA significantly reduced AL by 4% compared to the non ICG FA group. On the other hand, Morales-Conde *et al.* (13), assessed the utility of ICG FA in 192 patients who were grouped in 4 different categories based on the type of surgery: group A, right hemicolectomy (67 patients); group B, segmental resection of the splenic flexure (9 patients); group C, left hemicolectomy (81 patients); and group D, anterior resection of the rectum (35 patients). The change of section line based on ICG FA occurred in 35 cases of the included patients (18.2%): 4 in group A (6.0%), 1 in group B (11.1%), 21 in group C (25.9%), and 9 in group D (25.7%). AL occurred in 5 patients in total (2.6%): 2 in group A (3.0%), 1 in C (1.1%), and 2 in D (5.7%). They concluded that intraoperative ICG FA may lead to significantly greater changes in the resection line in left hemicolectomy, followed by low anterior resection, with decreased AL incidence. On the contrary, they reported ICG FA use may not be justified in right hemicolectomy. Similar results were encountered by Ohya *et al.* (14). They analyzed 400 patients with colon cancer who underwent laparoscopic surgery and evaluated the blood supply in anastomosis with ICG FA distinguishing three degrees of fluorescence around anastomosis: (I) good fluorescence acquired in the first 60 seconds of ICG injection, (II) delayed fluorescence beyond more than 60 seconds after injection, and (III) no fluorescence when minimal fluorescent signal was obtained. In 12 patients (2.8%), macroscopically normal anastomosis revealed delay (3 patients) or no fluorescence (9 patients), which led to changes in the bowel resection line. The overall percentage of AL was 1%, but a wide proportion of right colon cancers were included in the study group (58%) and, therefore, required an ileo-colonic anastomosis, which are less prone to leak. Again, authors concluded that the indication of ICG FA in ileo-colonic anastomosis is not clear yet (14). Focusing on the group of patients that seem to benefit the most, evaluation of bowel perfusion by ICG FA has also been performed exclusively during transanal total mesorectal excision (TaTME) by Otero-Piñeiro *et al.* in 2021 (15). With total of 284 cases in their retrospective cohort, 204 patients were assigned to control group (no ICG FA) and 80 patients to the study group (ICG FA). In 23 cases (28.7%) the impaired fluorescence made the surgeon to change the proximal resection line. In the study group only two patients (2.5%) suffered AL in contrast to the control group (11.3%). ICG FA was found as independent protective factor for AL in the multivariate analysis of the whole cohort (n=284) [odds ratio (OR) 0.142; 95% confidence interval (CI): 0.032–0.633; P=0.010].

All these promising data come from observational studies, which are characterized by known limitations. Up to date, 3 randomized controlled trials focusing on ICG FA have been published. On the one hand, the multicenter trial PILLAR III (16), published in 2021, recruited 347 patients who underwent left-sided/low anterior resection surgery with primary anastomoses within 10 cm of the anal verge, dividing them in 169 patients control group and a 178 patients study group undergoing ICG. Both groups were similar in demographics features, tumor size, and neoadjuvant chemoradiation prior to surgery. As the purpose of this trial was evaluate the impact of ICG FA on the incidence of AL, they reported 9.0% of incidence in ICG FA group compared with 9.6% in control group. Multivariate regression analysis ratified there was no difference in AL rates between both groups (OR 0.845; 95% CI: 0.375–1.905; P=0.37). On the other hand, De Nardi *et al.* (17) conducted a multicenter randomized controlled trial of 240 patients with CRC who underwent laparoscopic resections of the left colon or rectum. This study found similar results than in previous exposed randomized trial, presenting AL in 11 patients (9%) of the control group and in 6 patients (5%) when ICG FA was used [P= not significant (n.s)]. Nevertheless, authors had performed an initial power calculation assuming that the AL rate was 10%, so the study was overall underpowered to detect significant differences. For this reason, despite the lack of statistical confirmation, authors supported the utility of ICG FA in bowel blood supply assessment during low anterior resection or left colectomy (17,18). Finally, Alekseev *et al.* (19) performed a single-centre randomized controlled (1:1) clinical trial focused on the efficacy of ICG FA in reducing the incidence of AL following colorectal anastomoses in 377 patients who underwent to sigmoid or rectal resection. An AL (grade A, B or C) was developed in 48 patients: 17 (9.1%) in the ICG FA group and 31 (16.3%) in the non-ICG FA group (P=0.04). However, subgroup analysis of AL rates according to the level of the anastomosis from the anal verge demonstrated efficacy of ICG FA only in low anastomoses (4–8 cm), with an AL rate of 14.4% in ICG FA *vs.* 25.7% in the non-ICG FA group (P=0.04), while the rates of AL in high anastomoses (9–15 cm) were 1.3% in ICG FA group *vs.* 4.6%. non-ICG FA group. Authors concluded ICG FA is associated with a reduction in AL following low anterior resection.

In order to achieve larger samples of patients, several meta-analyses have been performed. A recent one, published in 2021, included 13 trials with 4,037 patients who underwent colorectal surgery: 1,806 patients corresponded to the ICG FA group, while 2,231 patients composed the control group (20). With an incidence of AL in the ICG FA group 3.8% *vs.* 7.8% in control group, they found significant differences in AL rate with or without using intraoperative ICG FA (OR 0.44; 95% CI: 0.33–0.59; P<0.00001) (19). Furthermore, Trastulli *et al.* (9) performed in 2021 a meta-analysis with 25 comparative studies that included overall 7,735 colorectal surgery procedures, whom 3,307 (42.8%) were in the ICG FA group *vs.* 4,428 (57.2%) in the standard intraoperative methods (SIMs) group. AL occurred in 435 patients in total (5.6%): 105 (24.1%) in the ICG FA group and 330 (75.9%) in the SIMs group (9). Their results indicated that the use of ICG FA significantly reduced the risk of AL in colorectal surgery (95% CI) (OR 0.39, P<0.001). Finally, in the meta-analysis performed by Arezzo *et al.* (21), 862 patients were considered to compare the evaluation of anastomotic perfusion during ICG FA in rectal cancer surgery, and compared with SIMs to prevent AL. They also concluded that ICG FA significantly reduced the incidence of AL (OR 0.341; 95% CI: 0.220–0.530), independently of age, gender, BMI, tumor and anastomotic distance from the anal verge and neoadjuvant therapy. However, it should be noted that there were a significant number of non-randomized trials and the heterogeneity in the definition and evaluation of AL (21).

One of the suggested limitations for verifying ICG angiography as an anastomotic failure predictor is because qualitative assessment may be limited in accurately distinguishing microcirculation changes. Perfusion time factors, including fluorescence slope, TMAX, T1/2MAX and time ratio, have been suggested as consistent predictor values of anastomotic complications (22). However, a number of conditions like the fluorescence light source, illumination of the operating room, color processing mode and the distance between the camera and the tissues are all crucial factors affecting the fluorescence intensity, which hinders the development and standardization of quantitative systems (22).

On the basis of the information available, ICG FA has demonstrated to be a viable and safe tool to optimize the proximal bowel transection line, to ensure adequate blood irrigation of the anastomoses, and probably to reduce the incidence of AL specially in left hemicolectomy, anterior resection and TaTME. Nevertheless, its routine use is still controversial, due the data from randomized trials and the lack of homogenous studies and confounding evidence. Nowadays, there is still no guidelines or generalized consensus for its use. Future development of a quantitative fluorescence measurements and established protocols may improve outcomes further.

Sentinel lymph node (SLN) identification and lymphatic mapping using ICG fluorescence

Lymph node status is a key prognosticator and a critical determinant of adjuvant treatment in CRC (23). Despite radical oncological techniques such as total mesorectal excision (TME), complete mesocolic excision (CME) and D3 colonic resections have improved survival in CRC patients, up to 20% of those with early-stage cancer and without lymph node metastases will develop local or distant recurrence within 5 years following surgery (2). SLN surgical protocols are born with an ultra-staging intention: they aim to improve the identification of lymph node metastases that escape from the *en bloc* resection, including the primary tumor and the regional lymph nodes (24). However, the applicability of the SLN in CRC has been limited by the low sensitivity reported in studies with blue dyes or radiocolloid injection (25).

Recently, ICG near-infrared (NIR) fluorescence has been proposed for SLN detection with promising results for breast (26), endometrial and cervical (27), gastric (28) and pancreatic carcinoma (29). The use of ICG for lymphatic mapping could improve the harvesting of lymph nodes, as it has proven to be superior for the detection of deeper lymphatic structures compared to traditional dyes such as methylene blue (30). Moreover, compared to radiotracers, it is cheaper, avoids the radiation exposure related risks, and is independent to the use of intraoperative gamma probe.

To date, more than 15 case series studies have been published concerning the role of ICG NIR in the detection of SLN in CRC surgery. Despite the volume of published papers, the absence of standardized protocols for the application of the fluorophore and the differences in the inclusion criteria of the studies have led to very heterogeneous outcomes. Overall, ICG has proved a detection rate of up to 90–95% assessing lymph flow and locating SLN in CRC, but clinical studies observed a wide range of sensitivity (from 0% to 85.6%) in the detection of lymph node metastases, when the harvested SLN are followed by histopathological examination (31).

When it comes to the ICG injection protocol, there is a wide range of possibilities described. Doses and concentrations reported are very variable, from a very low dose of 0.2 mL volume with 0.25 mg/mL concentration (32,33) to 2–5 mL volume with 5 mg/mL concentration (34-37). In one hand, this is related to the different ICG injection approach used, that can be either submucosal by endoscopic approach (38-42), subserosal by laparoscopic or open approach (34-36,43), both submucosal and subserosal (44) and even intravenous (32). On the other hand, besides the most reported timing of the injection is intraoperative, some authors apply it preoperative (38,40) or both pre- and intraoperative (42). Moreover, the time elapsed between ICG injection and detection of fluorescent lymph nodes ranges between 5–10 minutes (35,36,40) to 30 minutes (34,39,44), being mostly evaluated intraoperative, but also ex-vivo in some studies (32,33,36,40,44).

In the meta-analysis presented by Emile *et al.* in 2017 (45), authors reported better outcomes when ICG was administrated in a concentration dependent on the body weight (0.25 mg/kg) rather than a fixed concentration per milliliter, as it may be better distributed to the tissues in patients with higher BMI. On the contrary, some authors assert that the use of solutions with less concentration of ICG may diffuse too quick into the tissues, preferring the mixture of albumin with ICG to avert its dispersal; nevertheless, no superior results in terms of lymph node identification had been reported (43,46). Related to the ICG injection approach, Emile *et al.* (45) described that combined submucosal and subserosal injection achieve the highest sensitivity (100%), specificity (100%), and accuracy (100%), followed by the intravenous injection (89%, 87.7% and 88%, respectively). Instead, subserosal injection has the lowest sensitivity (55.7%), which they explain by the lack of tactile feedback in the setting of laparoscopic surgery that prevents the tip of the needle from reaching the submucosal plane, where the main lymphatic network is located, leading to an insufficient absorption of the dye. Besides, other authors reported the risk of spillage accidentally, and subsequent contamination of the surgical field with the fluorescent dye, when ICG is injected subserosal by laparoscopic approach (31). Finally, they did not suggest an optimal timing of ICG, as preoperative injection seems to have the highest sensitivity whereas intraoperative injection has the highest specificity in the meta-analysis performed (45).

Another justification in the despair results is the different proportion on early and advanced stages of CRC of the enrolled patients. Curie *et al.* (47) suggested that previous unfavorable outcomes in SLN in CRC were compromised not only by the application of non-effective dyes (48) but also the inclusion of advanced diseased patients, that can lead to an abnormal lymphatic drainage in context of the occlusion of the lymph channels by the spreading of the malignant cells (40,47). In accordance with this hypothesis, meta-analysis outcomes have reported better sensitivity (100%), specificity (76%) and accuracy (68.8%) in those studies that included more than 50% of early-stage patients (45). Moreover, lymph node mapping may be more beneficial in early CRC, as the identification of positive nodes would make the difference between receiving adjuvant chemotherapy or not. Based on these findings, a recent study performed by Carrara *et al.* (37) have modified the primary objective of sentinel node ultra-staging to propose limited colonic resections based on it. They have hypothesized the possibility of performing ultraconservative resection in low stages of colon and rectal cancers considering the basis of the negative predictive value of the SLN in combination with pathology assessment with one-step nucleic acid amplification (OSNA) technique. Nevertheless, although they obtained negative predictive value of 96.2%, they reported a limited sensitivity (73%), detecting in 27% of cases metastatic lymph nodes that were not the harvested SLN.

In conclusion, ICG NIR fluorescence is a safe and reliable technique for evaluating the lymphatic flow and detecting SLN in CRC. However, overall sensitivity, specificity, and accuracy of this technique vary according to a multitude of technical factors. Added to the low clinical significance for SLN concept in colon and rectal surgery when compared to skin and breast cancers, the use of this technique remains unclear in establishing suitable candidates for limited colonic resections. Optimization of ICG fluorescence SLN mapping requires further large, well-designed, randomized trials comparing different techniques of ICG injection to reach valid conclusions about its ultimate clinical utility and provide strong evidence before changing paradigm to ultra-selective colonic resection and introduction of SLN to the daily routine in colon and rectal surgery.

ICG marking for intraoperative tumor localization

Due to the lack of tactile perception in minimally invasive approach surgeries, especially in early stages of cancer with small size tumors, preoperative endoscopic tattooing of colorectal neoplasms methods was developed (49). Indian ink is the standard marking dye for endoscopic tumor site tattooing (49). Besides this technique results in permanent markings available to identify during the surgery, if the tattoo extends too wide outside the serosa, the accuracy of identifying the location of the tumor is lost and the operation is difficult to perform. Moreover, the use of Indian ink is associated with complications such as inflammation, local peritonitis, pseudotumors, abscesses and adhesions (50). ICG marking has emerged as an innovative technique that offers high visibility and precise identification of the tumor site during surgery, facilitating CME for colon cancer and TME for rectal cancer surgery, optimizing oncologic resection.

Despite several methods of local injection have been reported, such as subserosal laparoscopic injection (51) or preoperative endoscopic placement of marking clips equipped with ICG conjugated with resin (52), the preoperative endoscopic approach is considered the most appropriate, as the endoscope can precisely detect early cancer or scarring following local resection. Prior to surgery, endoscopy should be performed to inject the ICG solution into the submucosal layer adjacent the neoplasm, having up to 100% visibility when performed within 6 days prior to surgery (50). The most used site for marking has been the distal margin of the tumor (53). During laparoscopic surgery the tumor site marked with ICG is detected using a laparoscopic NIR camera system. This is an advantage over traditional dyes because it does not interfere with the field of view during tissue dissection in conventional viewing mode.

One of the main conflicts with ICG tattooing protocols, as dosage usually used is more than 25 mg, is its interference with intraoperative ICG angiography or fluorescence lymph node mapping (54). In order to assess multifunctional ICG protocols, Ahn *et al.* performed a prospective study including 192 patients who underwent endoscopic submucosal near the lesion ICG tattooing 12 to 18 hours before laparoscopic surgery for CRC (55). Five categories were divided depending on the amounts of injected ICG: >12, 1–12, 1–0.5, 0.5–0.3, and <0.3 mg. They concluded dose between 0.5–1 mg improved success rate of fluorescence lymph node mapping without compromising the fluorescent tumor localization and performing intraoperative ICG FA during anastomose assessment.

Although these are promising techniques, their usefulness and the protocol of ICG injection for this use in clinical practice need to be clarified in detail. Many questions remain about the time interval of administration before surgery, injection sites, dose of ICG to be administered. In addition, the cost-effectiveness of performing preoperative endoscopies close to surgery to perform ICG marking should be evaluated, since, unlike the classic dyes, this is not permanent. The detailed mechanisms by which the intestinal wall metabolizes and excretes the ICG molecules are not yet established. It is indispensable to further examine how simultaneous observation of ICG tumor site marking influence fluorescence in lymphatic mapping and its impact on CRC resection.

Ureteral visualization assisted with ICG fluorescence

Retroperitoneal location of the ureters may difficult its identification during colorectal surgery in patients with intra-abdominal obesity, diverticular disease, prior pelvic radiotherapy or retroperitoneal fibrosis (18). Although the incidence of iatrogenic injuries of the ureters is low (0.2–1.9%), it significantly affects postoperative morbidity, length hospital stay, and hospitalization costs (56). Furthermore, despite the known advantages of minimally invasive approach, this holds a loss of tactile feedback and an increased use of energy devices, rising the risk of devascularization, thermal injury or laceration of the ureters (57,58).

In order to reduce the incidence of iatrogenic injuries, the placement of preoperative ureteral catheters has been proposed. However, this technique has not been associated with a reduction of the risk of ureteral injury, instead it increases surgical time and length of hospital stay (59). Likewise, we must take into account the complications associated with the use of the catheter, such as mucosal edema, reflex anuria, ureteral perforation or obstruction (56). For this reason, it is necessary to explore new tools that allow optimal visualization and identification of the urinary tract, emerging ICG fluorescence imaging as an interesting alternative.

The technique described by Keller *et al.* (60) consists on the injection of 10–25 mg of ICG diluted in 10 mL of sterile water through a ureteral catheter previously placed, by bolus infusion or slow infusion over 5 minutes. Once in the urinary tract, ICG binds to the proteins of the urothelium, reversibly staining it and allowing visualization of the ureter illuminated with fluorescence when exposed to NIR light (60). The maximum fluorescence is obtained between 9 and 20 minutes after the administration of the dye, accomplishing this fluorescence in 100% of the ureters, as they reported. This technique has shown advantages over the conventional intraoperative use of a ureteral catheter without ICG, since fluorescent imaging allows early visualization on deeper fatty planes. However, as previously described, it is not a procedure exempt from the risks inherent to ureteral catheterization.

For this reason, the working group of Soriano *et al.* (56) proposed intraureteral retrograde ICG injection by cystoscopy. In their work, they evaluated the efficacy and safety of ICG injection in catheterized patients *vs.* non-catheterized patients. In their experience, intraureteral injection of ICG was ultimately the technique of choice in most patients, as it was simpler and more reliable. Thus, in the group of non-catheterized patients (n=63), the right ureter was identified in 97% of the cases and the left ureter in 100% of the cases. The reported results demonstrated that fluorescence persisted throughout the entire surgical procedure with a median time of 4.5 hours in catheterized patients *vs.* 4.2 hours in non-catheterized patients. Similarly, the study demonstrated the superiority of intraureteral injection insofar as it is faster, cheaper and also allows to eliminate the complications associated with the use of catheter. Additionally, the study demonstrated that ICG was safe since no adverse effects or complications derived from the use of the dye during it were recorded.

In conclusion, the use of intraureteral ICG for the identification of the ureters is feasible, providing not only a reduction of iatrogenic lesions, but also allowing the early identification of ureteral injury and its intraoperative repairment. Moreover, despite its invasive administration, using either a ureteral catheterization or cystoscopy, prevents its use in daily routine colorectal surgery, the cost of ICG and the time used to perform its administration is low compared to the potential risk of ureteral injury in selected patients (61).

Conclusions

The need to make up for the haptic deficiencies of minimally invasive surgery and the wide distribution and availability in current operating rooms of ICG fluorescence-based technology stimulates the exploration for new applications. Due to its initial development in the angiographic field, its application in the evaluation of intestinal perfusion is by far the most evaluated in colorectal surgery. The power of the studies carried out has not made it possible to establish statistically significant differences with respect to the decrease in anastomosis dehiscence, but the undeniable superiority with respect to traditional methods, accompanied by the absence of other modifiable factors to prevent this dreaded complication, has motivated the wide distribution in most operating rooms and the implementation of this tool in the daily life of many hospitals.

Regarding the other proposed applications presented, the currently available evidence shows promising results for selected situations but limits the indication for routine use yet. On one hand, the application of ICG NIR fluorescence for evaluating the lymphatic flow and detecting SLN in colorectal surgery is a safe and reliable technique. The drawback is that the published studies have not yet been able to determine its application framework, with very different scenarios coexisting. While some authors suggest using the intraoperative evaluation of SLN to limit colonic resection and *en bloc* lymphadenectomy, other surgeons propose its use to detect lymph nodes that would escape conventional dissection and, if they are malignant, to be able to offer adjuvant treatment to patients who had previously undergone classified as early stage. On the other hand, endoscopic submucosal ICG injection allows intraoperative tumor site location when performed up to a week prior to surgery, but cost-effectiveness research need to define its advantage compared to traditional permanent dyes. Probably, the development of joint protocols for SLN detection and tumor marking will define the application framework, although more studies are necessary to define the mode of application and timing from injection prior to surgery. Finally, intraureteral ICG instillation may reduce ureteral iatrogenic lesions, but its invasive administration prevents its use in daily routine, being able to be an extremely useful tool in selected patients with intra-abdominal obesity, diverticular disease, prior pelvic radiotherapy or retroperitoneal fibrosis.

In conclusion, ICG fluorescence-based technology represents a niche of opportunities for improved visualization in the field of minimally invasive surgery but, like all newly developed technologies, we must not lose the critical scientific perspective and guarantee that its application is represents an adequate cost-benefit profile and generates advantages over traditional approaches. Future development of quantitative fluorescence measurement methods and established protocols will achieve better performance of this tool.

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