Fluorescence imaging in colorectal surgery: an updated review and future trends

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Abstract

Fluorescence imaging in colorectal surgery is considered a novel predominantly intraoperative method of ensuring a greater surgical success. The use of fluorescence is linked to advanced tumor visualization and projection of its lymphatics, both vessels and nodes, which results in a higher chance of achieving a total excision. Additionally, iatrogenic complications prove to be reduced using fluorescence during the surgical excision. The combination of fluorescence and artificial intelligence to better facilitate oncological surgery will soon become an established approach in operating rooms worldwide.

Key words

Colorectal surgery, fluorescence imaging, indocyanine green, near infrared light, fluorophore

Introduction

Advances in colorectal surgery (CRS) are rapidly growing with fluorescence imaging (FI) taking the lead in establishing current research trends and in ongoing clinical trials due to a high prevalence of colorectal cancer (CRC) in the global population. FI is widely used intraoperatively to detect tumor growth patterns, lymphatic networks, and to visualize pathways of bowel perfusion to help ensure complete resection. FI gives surgeons an incomparable advantage in visualizing anatomical structures during laparoscopic, robotic, and open procedures with an illuminated view into the complex vascular structures at both macrocirculatory and microcirculatory levels. The detection of sentinel lymph nodes (SLN), the tumor itself, and potential intraperitoneal metastases before establishing a surgical strategy provides a clearer idea of the extent of resection. Additionally, the identification of vital structures such as the ureters or the urethra helps to minimize the risks of iatrogenic intraoperative damage.

The use of artificial intelligence (AI) to guide the surgical strategy, predominantly intraoperatively, is one of the future directions in surgery, which is currently widely explored. Combining the use of FI with AI opens up countless opportunities of innovation and development in the treatment of CRC by perfected algorithms giving guidance to surgeon can improve the overall resection of the tumor and shorten the procedure duration.
In the absence of prospective randomized controlled studies, there are no satisfactory standards or guidelines for injection dosage, site, and observation periods. All the proofs shows that the techniques are safe, cost effective and easy to repeat. So far, only the consensus conference statement on the general use of near-infrared fluorescence imaging (NIR) and indocyanine green (ICG) guided surgery aimed to describe and compare the four areas of practice and strongly stated that considerable deep research and standard operating procedures are required to optimize its use [1]. The use of NIR-ICG can reduce significantly risk of AL by providing real-time evaluation of perfusion of the anastomosis in everyday surgical practice.

Methods

The aim of this article was to review the available literature in the clinical setting of FI in CRS. PubMed, Google Scholar, and Web of Science databases were used to search original articles concerning the use of FI in CRS. The following articles were included, namely articles related to tumor visualization, articles related to the ureter, articles related to intraperitoneal metastasis identification, articles related to the visualization and biopsy of SLN, articles related to lymphography, articled related to vascular imaging, and articles related to AI guided fluorescence imaging, and enhanced reality techniques. We focused on studies reporting FI in CRS. The search terms used in PubMed were the following: “colorectal OR rectal” AND “Indocyanine OR ICG” AND “surgery OR surgical” AND “fluorescence imaging OR FI” AND “ureter” AND “intraperitoneal metastasis OR metastasis” AND “sentinel lymph node OR lymph node” AND “lymphography” AND “vascular OR vascularization” “artificial intelligence or AI” AND “angiography”. The search was performed for publications reported between 1999 and 2021. Full-text articles in English were retained. In addition, reference lists of the retained articles were further analysed looking for articles which matched the criteria for the present review. All data concerning patient characteristics and technical modalities used in studies were retained.

Tumor visualization

In CRS, ICG is used for a spectrum of purposes with tumor visualization as the initial target of researchers. Injection of ICG into the submucosal plane at the distal aspect of the lesion to localize the tumor during robotic stereotactic total mesorectal excision (TME) was explored by Atallah *et al.* ICG in combination with stereotactic navigation and robotic surgery is safe, feasible, and can improve surgical precision [2].
Preoperative tumor markings are required to determine the exact location of the lesion. Watanabe *et al.* described patients who underwent preoperative colonoscopy with ICG injection through the mucosa into the submucosal space of the bowel wall only at the distal side of the tumor [3]. The intraoperative visibility rate of the tumor site on a PINPOINT image was 93.8%. Lee *et al.* in his study injected a dye into the serosal layer on the opposite sites of the tumor, where 93.5% of the tattoos were seen intraoperatively during laparoscopic CRS [4]. In the study by Ahn *et al.*, 199 CRC patients underwent a submucosal ICG injection [5]. In a laparoscopic NIR camera, the dilution allowed fluorescent tumor localization to be easily distinguished from its surroundings. Therefore, the injection with a high volume and concentration of dye (i.e., a 10mL solution containing 25mg of ICG) in 4 different locations near the tumor was recommended.

Fluorescent dye-coated clips used as tumor markings can solve tattooing-related issues. Case report described in 2019 used ZEOCLIPS FS clips and cameras that are easily detected throughout the translucent intestinal wall using a fluorescent laparoscope [6]. They can highly reduce the possibility of accidental intestinal wall puncture which can be problematic, especially in low rectal cancers when resection areas are determined intraoperatively.

In visualization, we can also distinguish tumor-targeted compounds with fluorescence properties. In CRC, the carcinoembryonic antigen is overexpressed in almost 95% of cases, making it an optimal target for agents such as SGM-101 [7]. Boogerd *et al.* in his pilot study showed that more than 33% of patients had their therapeutic strategy changed detected by FI and that were not clinically suspected before [8]. De Valk *et al.* conducted a study in which 24% of patients had a surgical plan changed based on FI with additional malignant lesions detected in 6 patients [9]. De Valk *et al.* also published their study performed in humans of a NIR fluorescent peptide called cRGD-ZW800-1, that can lower background fluorescent signal allowing FI of CRC [10]. De Gooyer *et al.* worked on the dual-labelled carcinoembryonic antigen-targeting tracer In-DTPA-SGM-101 that allows preoperative CT imaging and FI resection with the higher intensity signal in tumor area [11]. Additionally, fluorescence-labelled antibodies such as EGFR, VEGR, and small molecules such as c-Met, glutathione S-transferase, cathepsin or endothelin A receptor often expressed on the tumor cell surface accumulated at very high levels in the colorectal tumor cell [12].

Ureter, urethra, and transanal tube identification

The incidence of ureteral injuries (UI) may be a serious complication of CRS, and it is estimated to occur at a rate comprised between 0.3 and 1.5%, with 9% of all UI occurring during CRS [13]. In colorectal procedures, the lower third of the left ureter is most prone to damage [14]. Nowadays, UI are significantly increased by the introduction of transanal TME which can result in a substantial morbidity [2, 15]. The fluorescence-guided detection of the ureters provides a safe and non-invasive means of identification which can prevent any iatrogenic injuries.

ICG offers a visualization of the ureters during laparoscopic pelvic surgery. In Mandovra *et al.* study 33% of patients the detection of ureters by cystoscope guided injection of ICG was difficult due to an extensive amount of surrounding adipose tissue [16]. In Atallah *et al.* study ICG was injected retrogradely via cystoscopy allowing to clearly localize both ureters during TME [2]. Left ureter can be protected by using the transileal conduit ureteral catheter when it is located near the sigmoid tumor while using an ICG-FI laparoscopy [17]. White *et al.* administered ICG intraureterally using cystoscopy with a successful identification in 94% of patients who underwent adjunctive ureteral identification during robot-assisted CRS [18]. The identification of ureters is considered sensitive, safe, and cost–effective, especially when the technique to merely insert the tip of the ureteral catheter up to 1cm into the vesicoureteric junctions, helps to reduce the complications related to ureteral catheterization [16].

Other dyes such as methylene blue (MB) can also be used for NIR fluorescence administered intravenously. Due to its good safety profile, it may be used for colorectal procedures. Because of its renal excretion, it should be applied cautiously in patients with kidney disease or supported with diuretics [19]. Verbeek *et al.* reported the use of NIR fluorescence-guided surgery to visualize the ureters with an intravenous injection of MB [20]. Barnes *et al.* described an experiment with 40 patients in whom 14 ureters could be seen only under FI [21].

New fluorescent compounds considered in the identification of the ureters such as CW 800 - CA, Fluorescein, Liposomal ICG, UL - 766, and Ureteral glow are worth mentioning [22, 23, 24]. De Valk *et al.* studied ZW800-1 compound which provides visualization of the ureter and its motility but allows also a real-time assessment of ureteral function [25]. In Barnes *et al*. study, the new near-infrared fluorophore (the IRDye800BK) demonstrated a very good penetration and visualization of the urethra under fluorescence at an estimated tissue depth of around 2cm [26]. Simultaneously, the use of an ICG silicone catheter also demonstrated excellent fluorescence without leaving any residual solution behind in the urethra after its removal.

Identification of the transanal tube introduced to reduce the intraluminal pressure is another means to protect anastomosis in CRS. It is considered to be effective in decreasing the rate of anastomotic leakage (AL) after anterior resection (AR) (15 vs. 8.3%, odds ratio [OR]: 2.02, 95% confidence interval [CI] 1.01-4.06) [27]. In Ryu *et al.* study 3 of the patients underwent a transanal tube insertion with fluorescence guidance in order to prevent any AL [28].

Intraperitoneal metastasis identification

Detecting the presence of peritoneal metastasis at an early stage with the use of ICG could well improve oncological results, in both therapeutic pathways and possibilities of surgical treatment [29].

Barabino *et al.* prospective study analysed 88 peritoneal carcinomatosis of colorectal origin after injection of ICG, from which 58 were classified as cancerous among which 42 were correctly classified using an intraoperative NIR camera [30]. Among the 30 non-cancerous lesions, 18 were correctly classified using the intraoperative NIR camera. Liberale *et al.* study aimed to detect metastases to the peritoneum [31]. In 29% of cases, the CRS procedure was extended to include additional foci invisible to the naked eye, and 84% of the foci were cancerous and 16% were benign.

Fillippello et al. described the fluorescence sensitivity of the carcinomatosis nodule after administration of bevacizumab [32]. The sensitivity was higher in patients who did not receive bevacizumab as compared to those who received the drug (76.3 and 65.0% respectively). The rate of false negative results was higher in the bevacizumab group than in the group that did not receive the drug (53.8 and 42.9% respectively). Bevacizumab is suspected to enhance permeability and retention effect causing ICG accumulation in peritoneal carcinomatosis resulting from CRS.

Baiocchi *et al.* meta-analysis screened over 192 articles from which 6 series of 71 patients were retrieved, reporting ICG-guided detection of 28 cases with peritoneal carcinomatosis for a total of 71 patients and 353 peritoneal nodules [33]. The investigated tumors were CRC in 28 cases. Sensitivity varied from 72.4 to 100%, and specificity from 54.2 to 100%. Colorectal carcinomas were studied in relation to the mucinous component, concluding that this type of cancer has a poor affinity for ICG [31].

In van der Vorst *et al.* study, 71 superficially located colorectal liver metastases (CRLM) from 40 patients were identified and resected using the FLARE image-guided surgery system with the NIR-ICG [34]. In 5 out of 40 patients the metastases were undetectable before.

Achterberg et al. study described a 5-step surgical workflow documenting that the NIR signal was used to assess the resection tumor margins in patients with CRLM in vivo for future clinical studies which help surgeons to achieve a tumor-negative margin in minimally invasive liver metastasectomies, with effective margin-negative(>1mm) resections during laparoscopic or robot-assisted operations [35].

Visualization and biopsy of sentinel lymph nodes

Kitai was first to admit that SLN visualisation is a promising technique for further clinical exploration [36]. In CRC, SLN detection (SLND) techniques are still controversial as the sensitivity reported in the literature varies from one study to another [37, 38].

Nagata et al. study shows limitations of SLND, dependent on the stage of the tumor [39]. Locally advanced tumors like pT3 CRC and palpable nodes may result in high false negative rate (46,2%), where in T1 or T2 no false negative results are found. Emile *et al.* review and meta-analysis described an upstaging of 12.3% for fluorescently stained SLN metastases [40].

Chand *et al.* study evaluated 10 patients for lymphatic drainage in CRC [41]. The ICG localization was consistent with preoperative imaging in 8 of the 10 patients. Two had additional LN located outside of the proposed resection margins. In those patients the resection was extended resulting in positive LN on the histopathology. This shows a potential value for localization, especially in laparoscopic cases where there is no tactile sense.

Carrara *et al.* collected samples from 95 patients with non-metastatic CRC who were treated with laparoscopic colonic resection and complete mesocolic excision (CME) after peritumoral ICG injection [42]. The detection rate was 96.8% and the negative predictive value and accuracy rates were 96.2 and 93.4% respectively. An ultra-conservative treatment can be offered to patients with a limited disease, and as a result, an SL biopsy should be considered as the standard approach.

Apart from resecting SLN in CRS, we should not forget about lateral pelvic lymph node (LPLN), that plays a crucial role for local recurrence, as approximately 8.6 to 21.0% of patients with middle-low CRC have associated LPLN metastasis [43]. In Zhou *et al.* study, 42 patients who underwent TME with LPLN excision were assessed and divided into two groups with ICG and non-ICG [44]. The ICG group had a significantly larger number of LPLNs harvested as compared to non-ICG. The technical difficulties and the complicated anatomy of the pelvic sidewall along with the tissue oedema and fibrosis induced by chemoradiotherapy further increase the difficulty of the surgery and have subsequently reduced the number of lymph node dissections.

Kim *et al.* study intraoperatively identified metastatic LPLN under the dual control of FI and 3D lymphovascular reconstruction with simultaneous resection [45]. A bilateral LPLN dissection was performed in 50% of patients. All metastatic LPNs were identified among index LPLN.

Liberale *et al.* established a protocol where they validated the concept of SLN identified with FI after an intravenous injection of ICG in order to compare SLN identified via FI with SLN detected by the standard MB [46]. In CRS, it is essential to identify the first tumor draining node and focus on more advanced techniques during the histopathological analysis to improve the accuracy of nodal staging.

Lymph flow supply imaging: lymphography

The determination of a suitable mesenteric division and the appropriate degree of lymphadenectomy by tracing the blood supply is crucial when deciding on the extent of intestinal resection in laparoscopic CRS. A visualization of the lymph and blood flow is possible to achieve via an ICG injection into the submucosa near the tumor via colonoscopy and with an intravenous intraoperative administration. Nishigori *et al.* study determined ICG changes in the surgical lymphadenectomy plan in 23.5% of cases [47]. The metastatic rate of ICG positive nodes was at 10% and the metastatic rate of ICG negative nodes was at 5.3%. Interestingly, there were no metastatic nodes which were ICG negative more than 5cm away from the tumor.

Watanabe *et al.* study demonstrated ICG LN labelling in CRC of the transverse or splenic fold where the lymphatic drainage may vary and the precise site of lymphatic dissection is uncertain [48]. ICG was injected into a submucosal layer around the tumor at 2 points before LN dissection. In 19 out of 20 patients, the lymph flow was visualized. Five patients required alteration of surgical excision margins.

Factors such as inadequate ICG concentrations, excess India ink blocking the drainage, and inflammation from tattoo placement were found to have a detrimental effect on the lymphangiography [41, 47]. Peritumoral injection of ICG along with FI lymphangiography helps to demonstrate the intraoperative localization of the primary tumor, its lymphatic drainage, and SLN in CRC.

Park *et al.* assessed the extent of D3 lymphadenectomy with and without ICG in laparoscopic right-sided hemicolectomy [49]. The ICG solution was injected into the submucosa in the peritumoral area at 1 or 2 points. The numbers of central LN compartments and total harvested LN were significantly higher in the fluorescence group than in the conventional group, whereases the number of metastatic LN was not significantly different between the 2 groups. The extent of lymphadenectomy was changed in 1/3 of patients.

Vascular imaging

The quality of blood supply is currently examined with the naked eye, together with the assessment of vascular pulsation. It depends on the surgeon's experience and is difficult to repeat. ICG FI has been extensively used to evaluate blood flow in the anastomotic site in CRS to reduce the incidence of AL. The incidence of AL after AR has been reported to range between 6.3 and 13.3% [50].

One of the most important studies PILLAR II analysed left-sided hemicolectomy and AR [51]. One hundred and forty-seven patients were taken, of whom 139 qualified for the analysis. The mean level of anastomosis was 10±4cm away from the anal verge. Splenic flexure mobilization was performed in 81% of patients and a high ligation of the inferior mesenteric artery (IMA) in 61.9% of patients. There was a 99% success rate for fluoresce angiography (FA), and FA changed surgical plans in 11 patients, with the majority of changes occurring at the time of the transection of the proximal margin. The AL rate was 1.4% (n=2). There was no AL in the 11 patients who had surgical plan altered based on intraoperative perfusion assessment with FA.

In Ris et al. study NIR-ICG perfusion was assessed before and after anastomosis construction in comparison to operator visual assessment [52]. From 220 patients, 43.7% of them underwent a high AR or reversal of Hartmann's operation, and 17.9% of patients had a low AR. NIR-ICG assessment resulted in a change in the site of bowel division in 5.8% with no further leaks in these patients. Leak rates were 2.4% overall, 2.6% for colorectal anastomoses,

Son *et al.* proposed a step-by-step flow chart using perfusion factors to predict anastomotic complications after laparoscopic CRS [53]. ICG was slowly injected into peripheral blood vessels, and the fluorescence intensity of colonic flow was measured sequentially, producing perfusion graphs using a video analysis and modelling tool. The incidence of anastomotic complications was 7%.

In 2020, 2 randomized trials were conducted separately in Italy and Russia. De Nardi *et al.* included 240 patients who underwent randomized laparoscopic left-sided hemicolectomy and rectal resection [54]. Authors compared intraoperative ICG and subjective visual evaluation of bowel perfusion without ICG. ICG-FA showed insufficient perfusion of the colonic stump, which led to an extended bowel resection in 13 cases. No statistically significant reduction in the AL rate using ICG was noticed. An AL developed in 11 patients in the control group, and 6 patients in the study group (p=0.2). Alekseev *et al.* conducted a FLAG trial with 377 patients who underwent sigmoid and rectal resection [55]. ICG-FA identified impaired blood perfusion of the colon in 36 cases. An AL developed in 17 patients in the ICG-FA group and in 31 in the non-ICG-FA group. ICG-FA did not decrease the rate of AL of high anastomoses (9-15cm from the anal verge), at 1.3 vs. 4.6% in the non-ICG-FA group (P = 0.37). In contrast, a decrease in the AL rate was found for low (4-8cm) colorectal anastomoses (14.4% in the ICG FA group vs. 25.7% in the non-ICG FA group), that can be beneficial for this group.

Arezzo *et al.* developed a meta-analysis in nearly 1,330 patients with AL at 4.2% with ICG vs. 11.3% without ICG [56]. They concluded that the greatest benefit from ICG can be found in men, ≥65 years of age, BMI ≥25, ≤6cm from the anal edge.

Nowadays, quantification of ICG perfusion propose the use of factor T0 (time between injection and appearance of fluorescence). Iwamoto *et al.* reported the efficiency of predicting AL in CRS by observing median T0, from when ICG was injected and ICG disappeared from the injection track to the rise of the histogram of intensity in 25 cases of AR of CRC [50]. It was significantly longer in the AL group than the one in the non-AL group (P=.03). If a prolonged T0 could be recognized intraoperatively, it would be possible to construct a diverting stoma only in appropriate patients.

Frank *et al.* compared intra-arterial infusion of ICG selectively through the IMA and negative ICG imaging via systemic intravenous ICG infusion after the complete ligation of the IMA and of the inferior mesenteric vein (IMV) in an experimental study in a porcine model [57]. Clear resection margins were defined after intra-arterial infusion, and all tissues in the IMA basin were colored. In the model of intravenous application of ICG, all organs and tissues were colored except the rectum, urinary bladder, and ductus deferens. Negative staining via intravenous ICG application is easier to conduct, but the intra-arterial selective ICG perfusion leads to better image results.

Currently, there are numerous performed reconstructions of cloaca or anorectal malformations (ARM), which require intestinal flaps on vascular pedicles for vaginal reconstruction and/or colonic pull-throughs [58]. The visual assessment of tissue perfusion is usually the only method used. Rentea *et al.* investigated the use of intraoperative ICG-FA to be more precise than the surgeon's eye. ICG-FA resulted in an alteration of surgical plan in 4 out of the 13 cases. In 3 cases, ICG-FA resulted in the distal bowel being transected at a level (>10cm) higher than planned, and in 1 case the distal bowel was resected, and the colostomy used for pull-through. ICG-FA correctly identified patients who might have developed a complication from poor tissue perfusion.

Spota *et al.* study analysed the current practices and results of NIR of the anastomosis in digestive tract surgery through the EURO-FIGS registry [59]. A total of 1,240 patients were included in the study, and 74.8% of these patients were operated on for cancer. In 83.8% of cases, a pre-anastomotic ICG dose was administered, and in 60.1% of cases, a post-anastomotic ICG dose was administered. A significant difference ($p<0.001$) was found in the ICG dose given in the 4 pathology groups registered and a significant ($p<0.001$) negative correlation was found between the ICG dose and the BMI. In 27.3% of the procedures, the choice of the anastomotic level was guided by means of NIR imaging. In 98.7% of the procedures, the use of ICG provided a sense of confidence about the anastomosis. A total of 133 complications occurred, without significance in the incidence of complications in the anastomoses, whether they were ICG-guided or not.

Forgione *et al.* proposed a 3D preoperative resection modeling and intraoperative fluorescence vascular imaging which better defines optical dissection planes on porcine model [60]. Laparoscopic surgery was performed with selective arterial catheterization performed on the branches of the SMA and IMA with ICG administered intraoperatively in boluses or through a continuous infusion that clearly marked pre-identified vessels and the target colonic segment helping to achieve precise resection margins based on the visible vascular anatomy. The fluorescence was assessed using specific software at several regions of interest in the colon. Quantitative software analysis indicted the optimal resection margins and allowed for the tailoring of the amount of colon resected to ensure adequate anastomotic perfusion.

Slooter et al. investigated the intraoperative use of FA with ICG to assess omental perfusion [61]. During the creation of a pedicled omentoplasty, blood flow to segments of the omentum may become compromised. If unrecognized, this can lead to its necrosis. Fifteen patients had pelvic surgery with omentoplasty and FA. FA of a pedicled omentoplasty allows for an assessment of omental perfusion and leads to change in management in 80% of cases.

Artificial intelligence-guided fluorescence imaging and enhanced reality techniques

The computer modeling of ICG perfusion patterns, based on tissue tracking, has been used to develop an intraoperative surgical decision support tool [62]. In study conducted by Cahill, 19 out of 20 patients were diagnosed with cancer. Sensitivity was 100% and specificity was 92%. An approach to combine biophysical inspired model and artificial intelligence (AI) was developed via the intraoperative analysis of NIR, which intensities in heterogeneous tissues over time.

Developed computer algorithms distinguish the varying patterns of ICG perfusion through cancerous and normal tissues. A video tracking algorithm was developed to compensate for external factors which could have impaired the final results. This tool differentiate between malignant, metastatic, and normal tissues helps to identify early cancer or its metastasis due to their disorganized vascular structure.

Colonic vascular are varied and difficult to visualize preoperatively. Artificial intelligence-based real-time analysis microperfusion (AIRAM) is a proposed tool to predict the risk of anastomotic complications in laparoscopic colorectal tumor excisions [63]. The analysis of ICG-FA was used to predict an advancement of ischemia in the region of the anastomosis. Real-time processing was developed to establish the circulatory patterns allowing an intraoperative visualization of vessels and reducing the probability of post-laparoscopic anastomotic complications.

Analysis of quantitative parameters and organisation into patterns by AI allows the surgeon to accurately evaluate perfusion at a microcirculatory level, in addition to the currently used method of ICG angiography. The drawbacks of this method are environmental factors, that can be reversed with the AIRAM system. The AI-based classification of microcirculation had a more accurate and consistent performance than the conventional parameter-based method.

Fluorescence-based enhanced reality (FLER) is proposed to be an alternative method to visualize real-time laparoscopic images by using a virtual perfusion cartogram [64]. Simultaneous quantitative mucosal and serosal FI was obtained via intravenous ICG administration and FLER analysis. The mucosal ischemic zone was significantly larger than the serosal one, which potentially suggests that surgeons perform a larger resection when only the serosal perfusion is analyzed with FA.

The FLER method has also been used to create a perfusion map during hybrid esophageal surgery to improve anastomotic perfusion [65]. ICG-FA was performed using a laparoscope, and the fluorescent signal was quantified using a specifically developed ER-PERFUSION software. The images were overlaid onto a real-time video creating a more accurate localization of the perfusion information at the site on the gastric fundus. This ischemic gastric preconditioning method might reduce the anastomotic leak rate of patients undergoing esophagectomy.

Future studies using FLER in FA have a crucial role in analyzing bowel perfusion, leading to a more accurate assessment of the extent of ischemia and of the subsequent alteration of surgical excision margins.

Conclusions

The application of ICG FI can offer unprecedented value for surgery through an improvement in the accuracy and outcomes of oncologic resections. It can be used to localize structures of interest, which provide surgeons with better understanding of anatomical structures. Fluorescence-guided surgery remains an area of ongoing research with promising results for tumors which exhibit affinity for organic dyes. All newly developed and introduced technologies in science, NIR-assisted surgery should meet unfulfilled clinical needs, be safe and cost effective, and provide an advantage over traditional methods.

Fluorescence guided detection may provide a safe and non-invasive means for identification of ureters and prevent them from iatrogenic injuries.

Intraoperative ICG-FI may allow to detect peritoneal metastasis, contributing to the completeness of the surgical resection. Further investigations are required to better characterize the optimal timing to improve the sensitivity of the technique and to evaluate its real impact on long-term results. From this perspective, tolerability, and availability of ICG make it a good candidate for the design of a larger clinical trial.

SLN mapping with fluorescent dyes has a key role in the future of CRS and should be explored further in multicenter studies. FI may allow to detect metastatic LN after intravenous dye administration that would be more representative of cancer invasion than classical SLND after local peritumoral injection. A visualization of the lymph flow may be achieved with ICG injection into the submucosa near the tumor through colonoscopy or via an intravenous intraoperative administration.

Intra-arterial fluorescence mapping allows to visualize segmental colonic perfusion and helps to prevent intraoperative complications. Augmented intraoperative imaging using selective arterial FI of colorectal targets is a promising approach, which requires further trials and research to maximize its potential in CRS.

FI is considered to be both effective and safe across a broad range of clinical settings. Further research is needed to optimize the dose and concentration of ICG, as well as the route and timing of ICG administration. Intraoperative bowel perfusion assessment planned for primary anastomosis with FA may decrease the rates of AL and thereby improve patient outcomes. A randomized controlled clinical trial is planned to further evaluate the true clinical significance of this novel technology as compared to the standard assessment of the proximal transection line. NIR is a noninvasive technique used on a daily basis in surgical practice that permits the real-time perfusion evaluation of organs and tissue during surgery, following intravenous admission of ICG to verify planned resection area, by the identification of tissues that are well-perfused and non-perfused.

A new surgical era is unfolding where computer-assisted systems including navigation are merged with minimally invasive and robotic instrumentation. Globally, it is a step towards the further development of comprehensive and integrated surgical systems, which will include usable source data from a variety of inputs.

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