



Applications of indocyanine green-enhanced fluorescence in laparoscopic colorectal resections

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Abstract

Recently, Indocyanine Green (ICG)-enhanced fluorescence has been introduced in laparoscopic colorectal surgery to provide detailed anatomical informations. The aim of our study is the application of ICG imaging during laparoscopic colorectal resections: to assess anastomotic perfusion to reduce the risk of anastomotic leak, to facilitate vascular dissection when vascular anatomy of tumor site is unclear, and to identify ureter to prevent iatrogenic injury. After the transection, 5 ml of ICG solution is intravenously injected. A Full HD IMAGE1S camera, switching to NIR mode, in few seconds provides a real-time angiography of colonic perfusion. After anastomosis, another bolus is injected to confirm the anastomotic perfusion. When the tumor is localized in difficult site, the fluorescence provides a real-time angiography of tumor area vascularization to perform the vascular dissection. When the tumor is tightly attached to the ureter, the ICG solution injection through the catheter allows ureter identification. From November 2016, 38 patients were enrolled: ten left colectomies, 22 right colectomies, three transverse resections, and three splenic flexure resections. In five cases, intraoperative angiography led to the identification of vascular anatomy. In one case the surgical strategy was changed. In one procedure, ureter identification allowed to prevent injury. Three postoperative complications that required surgical reoperation occurred, of which one anastomotic leak, due to a mechanical problem. ICG-enhanced fluorescence imaging is a safe, cheap and effective tool to increase visualization during surgery. It can be employed also in small hospitals without learning curve. It is recommended to obtain additional information on anatomy and perfusion in colorectal surgery.

Keywords Laparoscopic colorectal resections · ICG · Enhanced fluorescence · Indocyanine

Introduction

Major developments in minimal surgery video imaging have been achieved during the last few years: the use of high-definition (HD) as well as 3-dimensional (3-D) systems has proved to be able to improve surgeon performance and patient safety. Recently, indocyanine green-enhanced fluorescence was introduced in laparoscopic surgery to improve the view and provide detailed anatomical information during surgery [1].

Anastomotic leakage is the most dreaded post-operative complication in colorectal surgery with often devastating clinical results for the patient and considerable economic consequence for healthcare provider. The reported leak rate ranges from 1 to 30% and increases as the anastomosis is more distal [2]. This incidence has persisted despite widespread and increasing uptake of laparoscopic approach that has made a significant and positive impact on postoperative complication rates. Although several factors like surgical

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techniques, patient risk factors, suture material or devices have been identified as possible causes of anastomotic leakage, the complete pathogenesis is still unclear. Poor local tissue oxygenation secondary to inadequate anastomotic vascular perfusion seems to be the most important factor in the determination of anastomotic viability. Nowadays, common practice used to evaluate anastomotic perfusion is surgeon intraoperative visual judgment based on clinical findings, such as color, bleeding edges of resected margins, pulsation and temperature. However some studies suggested that the clinical judgement of the operating surgeon underestimated the risk of anastomotic leakage in colorectal surgery [3].

Based on the ability of ICG to become fluorescent when excited by near-infrared light, when intravenously injected, we obtain a real-time angiography that can be used to evaluate the bowel perfusion prior and after colorectal anastomosis.

Furthermore, there are some anatomical regions, like splenic or hepatic flexure, where the vascular anatomy is unclear, because they are on the border between different vascular districts. The ICG real-time angiography allows to identify the vascularization of the tumor site to perform an oncological correct resection.

Sometimes, the tumor is tightly attached to the Toldt-Gerota plane and ureter identification is difficult. When it happens on injecting ICG solution through the catheter, the fluorescence allows ureter identification to prevent injury during the dissection.

Methods

ICG

ICG dye is a sterile, anionic, water-soluble but relatively hydrophobic, tricarbocyanine molecule; it was developed for near infra-red photography by the Kodak research laboratories in 1955 and was approved for clinical use in 1959 by the FDA [4]. It has been used in medicine to measure cardiac output, to study the anatomy of the retinal vessels, and to measure liver functional reserve before hepatic resection in cirrhotic livers. When ICG solution is injected through the catheter via the intravenous route binds the plasma proteins, especially lipoproteins, with minimal leakage into the interstitium. There are no known metabolites. ICG is rapidly extracted by the liver without modifications and nearly exclusively excreted by the liver appearing unconjugated in the bile about 8 min after injection, depending on liver vascularization and function. When injected through the catheter, it binds to the proteins on the urothelial layer.

ICG becomes fluorescent once excited with specific wavelength light in the near infra-red (NIR) spectrum (approximately 820 nm) or a laser beam. The fluorescence can be

detected using specific scopes and cameras, and then transmitted to a standard monitor allowing identification of anatomical structures where the dye is present (i.e., biliary ducts, vessels, lymph nodes.)

Laparoscopic system

In all cases, a laparoscopic system (Karl Storz GmbH & co KG, Tuttlingen, Germany) was used. The imaging is generated by a high-end full HD camera system IMAGE1 S that can be operated in dual mode for both white light and fluorescence imaging. The video camera is connected to an ICG laparoscope with 30° field of direction and 10 mm diameter equipped with a special filter for optimal reproduction during ICG-enhanced fluorescence and standard white light imaging. The Xenon light source (D-LIGHT P SCB, Karl Storz) provides both visible and NIR excitation light. Switching from standard white light mode to near infrared mode is simply done via foot-pedal control. Visualization in both modes is improved by the IMAGE1 SPIES System (Karl Storz GmbH & co KG, Tuttlingen, Germany) which comes with various imaging modules that can be selected according to surgeon's preferences.

Patients

From November 2016 to December 2017, 38 patients with colorectal cancer candidates for a standard surgical treatment of laparoscopic colorectal resection at the Hospital of Fidenza, Ausl Parma, were enrolled.

Patients with advanced colorectal cancer (clinical stage IV according to the AJCC classification [5]), patients with a history of adverse reaction to ICG or to iodine, pregnant and lactating women were excluded.

Preoperative risk factors including age, sex, ASA score, obesity comorbidities, steroid therapy, preoperative radiation and preoperative transfusions were recorded (Table 1).

All patients signed informed consent which showed all information about the characteristics of the study, the aim

Table 1 Patient characteristics

Patient characteristics	
<i>N</i>	38
Gender (M/F)	18/20
Age (years)	61 (47–80)
BMI (kg/m ²)	26 (19–32)
Anesthetic risk	
ASA I	2
ASA II	31
ASA III	5
ASA IV	0

and the potential risks and that inclusion in the study was voluntary and simply additive to routine care.

Colorectal resections were performed in a standardized method by multiport laparoscopy for every case, performing an intra-corporeal anastomosis for left-side resections and a hand-sewn, side to side extra-corporeal anastomosis for right-side resections. A medial–lateral dissection technique was used and the splenic flexure was mobilized routinely for left-side resections.

After transection, 5 ml of ICG solution diluted in saline solution at a concentration of 0.3 mg/Kg was injected intravenously by the anesthesiologist through a peripheral vein. A Full HD IMAGE1 S camera, switching to NIR mode, in about 30–50 s displayed fluorescence: it provided a real-time angiography of colonic perfusion. If there was an ischemic area, a new transection was performed within an area of better perfusion. In left colectomy or anterior rectal resection, the ICG injection was performed after anvil introduction in the proximal stump.

Another bolus of 5 ml ICG solution was injected once the colorectal mechanical anastomosis was performed, to confirm the adequate vascularization [6] (Fig. 1). If there was an ischemic area, a new anastomosis was performed.

Due to the lack of any objective technique to measure the intensity of the fluorescence, bowel perfusion was subjectively assessed by the surgical team who also indicated the perfusion level as adequate (meaning uniform to that of proximal colon) or insufficient. If poor perfusion was demonstrated, we waited 300 s prior to resect the bowel.

When the tumor was in difficult site (hepatic, splenic flexure or transverse colon), after tumor or endoscopic tattoo identification, 5 ml of ICG solution was intravenously injected: a real-time angiography of tumor area was obtained. On the angiographic guide, the vascular dissection and pedicle ligation were performed (Fig. 2).

During the dissection of the Toldt-Gerota plane, when the tumor was tightly attached to the ureter, 5 ml of ICG solution was injected through the catheter: by binding to proteins on the urothelial layer, the fluorescence allowed ureter identification (Fig. 3).

Perfusion images were recorded and assessed in real time. Any information or change in timing and/or quantity of injection as well as any change in the transection line after ICG-enhanced fluorescence injection was recorded.

All intraoperative data as the type of procedure, timing of the procedure, conversion, were collected (Table 2).

All post-operative data (length of stay, complications evaluated according to Clavien-Dindo classification, treatment of complications and mortality) were collected [7].

Fig. 1 Anastomotic perfusion in left hemicolectomy in white light (a) and NIR one (b) (Color figure online)

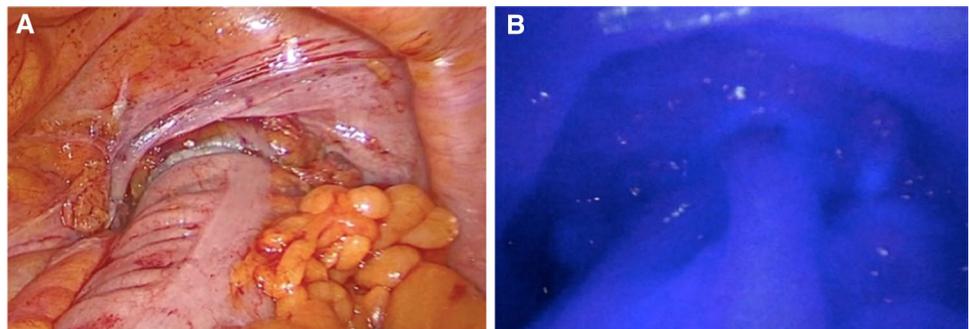


Fig. 2 Vascular anatomy identification in transverse resection. Identification of the vascular pedicle of tumor in white light (a) and NIR one (b) (Color figure online)

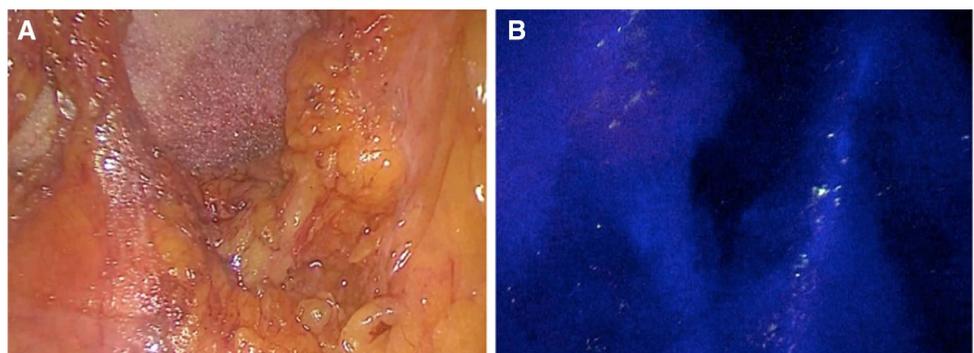


Fig. 3 Ureter identification in right colectomy during the dissection of Toldt-Gerota plane in white light (a) and NIR one (b) (Color figure online)

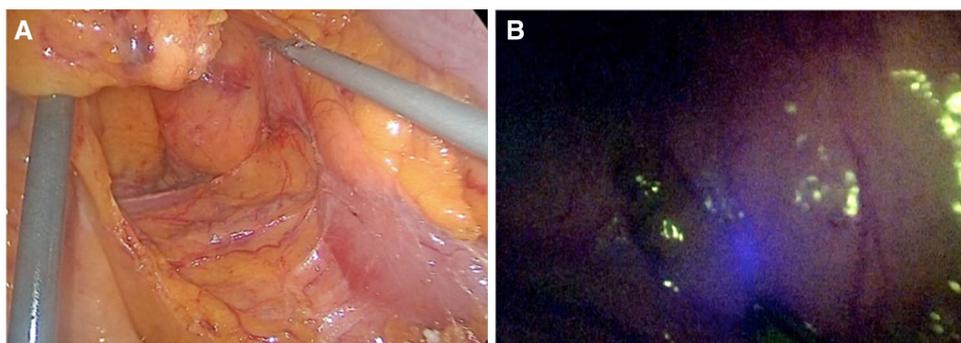


Table 2 Perioperative parameters

Perioperative data	Procedure	Good anastomotic perfusion	Change of surgical strategy	Vascular anatomy identification	Ureter identification	P.O.C.	A. L.
Right colectomy	22	22	0	1	1	2	1
Left colectomy/R.A.R.	10	9	1	0	0	0	0
Atypical resections	6	6	0	5	0	0	0

R.A.R. rectal anterior resection, P.O.C. post-operative complications, A.L. anastomotic leak

Results

From November 2016, 38 patients were enrolled: ten left colectomies, 22 right colectomies, three transverse resections, and three splenic flexure resections. They were 18 males and 20 females, the median age was 61 (range: 47–80); the median BMI was 26 (range: 19–32). The ASA score was II for 31 of them, I for 2 of them and III for 5 of them.

No changes in surgical plane were decided before fluorescence angiography. In all cases, the surgical team judged the perfusion of the colon adequate on standard white light, according to the color of the bowel, and no visible sign of ischemia was evident at visual inspection. Based on the fluorescence intensity recorded under NIR light, after injection of ICG, the distal part of the proximal bowel to be anastomosed was judged to be insufficiently perfused in one left colectomy. The complete lack of fluorescence in comparison with the proximal portion of bowel was used as criteria to detect the poor perfusion. So the surgical team opted for a change in the surgical strategy and the dissection of the colonic stump was extended into an area of better perfusion. After the new transection, the angiography showed a good perfusion of the stumps. Then, the anastomosis was performed and the new angiographic check showed a good anastomotic perfusion. In this patient, there was a conversion to open surgery because there was also a bleeding from the vessels for the splenic

flexure that was difficult to control in laparoscopy but it was well controlled in open surgery. In this patient, a protective ileostomy was carried out and no anastomotic leak occurred in the post-operative period. Reversal of ileostomy was performed in this patient; the anastomotic evaluation prior to reversal was made by means of endoscopy and no sign of leak or stenosis was reported.

In all the other cases, the anastomotic perfusion was good.

In six cases, three splenic resections and three transverse resections, the intraoperative angiography led to the identification of vascular anatomy and of the vessels to be dissected: switching from white light to NIR one, vascular dissection was performed on the angiographic guide and vascular pedicle was ligated at its origin carrying out an oncological resection.

In one right colectomy, the ureter was tightly attached to the tumor; so, we used the fluorescence to identify the ureter: the possibility to switch from white light to NIR one was very useful to perform the dissection on the Toldt-Gerota plane to prevent ureteral injury. There were no side effects related to the injection of ICG.

Three postoperative complications that required surgical reoperation occurred, in three right hemicolectomies of which one anastomotic leak, in the first post-operative day, due to a mechanical problem of the stapler. The other two complications were one intra-abdominal abscess that was drained laparoscopically and a hemoperitoneum that was treated by hemostasis through a laparoscopic approach.

Discussion

Although improved minimal access techniques and optimized perioperative care protocols have greatly impacted short and intermediate postoperative outcomes, anastomotic complications, especially early postoperative anastomotic leaks, remain unpredictable and are often devastating. Anastomotic breakdown can be due to mechanically faulty or perfusion problems [2]. Furthermore, aside from acute dehiscence or breakdown, impaired perfusion can also contribute to intermediate or late stricture formation [8]. Among different risk factors for anastomotic leakage, adequate perfusion is a well-recognized prerequisite for complete healing of anastomosis. The risk of anastomotic leak is higher in low colorectal anastomosis and it is associated with a higher risk of local recurrence. Any means of minimizing or even avoiding anastomotic complications would justify considerable investment in time, effort, and direct investment. Intraoperative checking of mechanical integrity of anastomosis can be carried out by testing for air-tightness with air or methylene blue or with endoscopy. Intraoperative assessment of intestinal perfusion and viability usually relies on subjective judgement based on visual inspection of the intestinal color, palpable pulsation and bleeding from the cut edge. However, it has been shown that surgeon's subjective evaluation and prediction of anastomotic leakage are poor [9]. Intraoperative perfusion assessment techniques such as transabdominal Doppler ultrasound, transabdominal laser Doppler flowmetry and oxygen spectroscopy have not been widely accepted because such techniques cannot be easily applied in routine clinical practice or have not proven reliable. Many surgeons perform a proximal defunctioning stoma to mitigate the consequences of anastomotic dehiscence. However, diversion also can negatively impact the patient in terms of psychological and physical functioning and with regard to actual complications in their formation and closure [10].

Indocyanine green-enhanced fluorescence is an innovative technique to evaluate the anastomotic perfusion during laparoscopic colorectal surgery that allows to evaluate the vascular microcirculation of the bowel [11].

In the review of Degget et al. [12] are presented small case studies where the application of ICG-enhanced fluorescence allowed to show ischemic anastomosis that on the clinical evaluation seemed to be well perfused and in some studies, the evaluation of anastomotic perfusion with angiography was associated with a reduced risk of anastomotic leak. However, the studies presented are conducted on small cases with the evaluation of the anastomotic perfusion only after anastomosis was performed, and with laser fluorescence.

In our experience, according to the literature [13], the images obtained with real-time angiography using ICG appear compelling and seem at least to document technical sufficiency with regard to in situ vascularization of the stumps at the time of anastomotic construction. The evaluation of stumps perfusion before anastomosis allows to identify an ischemic area in the proximal or distal stump and, even, to resect only the ischemic stump reducing the risk to perform an ischemic anastomosis. It is also important to highlight that perfusion should be tested also with the distal segment of colon in its definitive position after anastomosis to be sure that the perfusion does not change due to any tension or anatomic factor occurring after anastomosis.

Real-time ICG angiography is a cheap technique. In agreement with published data, patients who experienced leakage had an increased requirement for reoperation, intensive care support and hospital length of stay (30.3 days vs 9.2 days) [14]. The majority of the cost comes from the utilization of these resources, as well as the need for further imaging and radiological or surgical interventions. Interestingly, Koperna [15] estimated that the actual cost of significant leakage increased fivefold (from €8400 to €42 250). This is in agreement with an American study which found that severe complications after surgery increased the cost by a factor of five (\$30 000–\$159 000) [16].

On the other hand, the economic impact of the routine use of indocyanine green-enhanced fluorescence to evaluate the vascular assessment of the anastomosis to prevent anastomotic leak is negligible, as the cost of a single ICG phial does not exceed 100€.

The real-time angiography is also a safe technique. No complications occurred in our experience and the only contraindications are allergy and hyperthyroidism.

Furthermore, the routine application of enhanced fluorescence is possible without learning curve as it consists in the intravenous injection of ICG solution and in the evaluation of the appearance of fluorescence on the monitor. So, it can also be used in small hospitals using laparoscopic technology that is ordinarily used in surgical procedures.

Real-time NIR fluorescence angiography using ICG during laparoscopic colorectal surgery was proved feasible and reproducible with a minimum of added complexity.

It is a rapid technique that provides informations in few seconds. On comparison, more than 10 min is required to obtain an ischemic demarcation of the bowel visible to standard light after vessel division, while ischemia of the colon is immediately evident using fluorescence [13].

In addition, the real-time angiography is useful to perform a vascular dissection angiography guided for cancer localized in site where the vascular anatomy is unclear through the possibility of switching rapidly from white light to NIR one.

In the same way, the fluorescence allows to identify anatomical structures as ureter during surgery to prevent injury.

A disadvantage of ICG-enhanced fluorescence is that the assessment of fluorescence intensity is subjective. Analytic measures to objectively quantify signal intensity are already evolving; they are based on time to peak intensity and they require investment for their development and correlation with clinically important outcomes [17].

Conclusions

ICG-enhanced fluorescence imaging is a safe and effective tool to increase visualization during laparoscopic surgery. It is cheap, easy to replicate, and it can be employed also in small hospitals without learning curve. If our results will be confirmed by larger prospective studies, ICG fluorescent angiography might offer the possibility to facilitate the assessment of vascularization during colorectal resections to perform oncological resections and to reduce the incidence of anastomotic leak. We also expect that it will lead in some cases to a change of surgical strategy as a demonstrable reduction in the incidence of anastomotic leak could favor a reduction of the number of defunctioning stoma performed.

It could be also recommended to identify anatomical structures as ureter to prevent iatrogenic injury.

Compliance with ethical standards

Conflict of interest All the authors has no conflicts of interest.

Research involving human participants and/or animals The project has been submitted for the approval by Ethical Committee.

Informed consent All the patients sign the informed consent.

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