Updates in Surgery (2020) 72:477–482
https://doi.org/10.1007/s13304-020-00725-6

ORIGINAL ARTICLE

Indocyanine green-enhanced fluorangiography (ICGf) in laparoscopic extraperitoneal rectal cancer resection

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Received: 8 October 2019 / Accepted: 12 February 2020 / Published online: 18 February 2020

Abstract
Anastomotic leak (AL) is one of the worst complications of rectal anterior resection (RAR) and its incidence varies according to the anatomical site, increasing in lower anastomoses. Many etiological factors have been evaluated and most of these are related to bowel perfusion. Indocyanine green-enhanced fluorangiography (ICGf) has been proposed to help surgeons assess colonic perfusion with higher reliability than subjective clinical judgment. The aim of the study was to evaluate the efficacy of this tool in patients subjected to elective laparoscopic RAR for extraperitoneal rectal cancer. All the patients subjected to elective laparoscopic RAR for extraperitoneal rectal cancer between May 2015 and January 2017 were considered. In all of them, ICGf was performed to evaluate bowel perfusion. The control group included an equal number of patients subjected to the same procedure from January 2014 to April 2015, before the start of routine use of this tool at our institution. The endpoint of the study was to compare the incidence of AL between the two groups. A total of 33 patients were included in both groups. Relying on fluorescence intensity in the indocyanine green (ICG) group, we changed the level of resection in 6/33 patients (18.2%). An AL developed in 2/33 patients (6%) in the ICG group versus in 7/33 patients (21.2%) in the control group. The routine use of this technique may help surgeons in selecting the best level of proximal bowel resection during RAR.

Keywords ICG · RAR · Fluorescence · Anastomotic leak · Colorectal anastomoses · Fluorangiography

Introduction

An anastomotic leak (AL) is defined as 'a communication between the intra- and extra-luminal compartments owing to a defect of the integrity of the intestinal wall at the anastomotic site' [1]. It represents one of the most serious complications following rectal anterior resection (RAR), worsening postoperative outcomes in both the short and the long term. Indeed, it increases in-hospital stay, mortality rate and secondary complications [2–4], which prove particularly detrimental in oncological patients, since it is associated with reduced long-term cancer-specific survival and a greater risk of recurrence [5].

Its etiology is multi-factorial and there is still a lack of consensus regarding all the factors that may predispose to AL. It is well known that its incidence varies according to the anatomical site, increasing in lower anastomoses [6, 7]. Other factors influencing the risk of AL include individual characteristics (e.g., male sex, age, comorbidities, stage of disease) and technical aspects (e.g., level of vascular ligation, number of EndoGIA™ staple fires, operative time, blood loss) [8]. An adequate local tissue oxygenation has been proven to play a key role in the determination of anastomotic viability and many of the above-mentioned factors are shown to impair vascular perfusion [6, 9, 10].

Indocyanine green (ICG) is a fluorescent dye that binds to plasma proteins, is confined to the vascular compartment and is rapidly metabolized by the liver with no known metabolites. It absorbs nearly infrared (NIR) light between 790 and 805 nm and re-emits electromagnetic energy at 835 nm, which can be visualized by its fluorescence,

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allowing real-time evaluation of tissue perfusion. Its circulatory half-life is 3–5 min and the rate of allergic reaction is 1 per 333,000 [11, 12].

Indocyanine green is currently employed to assess bowel micro-perfusion in real time and to show lymphatic drainage and bile duct anatomy [13, 14]. Several studies have demonstrated its efficacy and feasibility in numerous medical fields including colorectal surgery, to provide a more reliable colonic perfusion assessment than a subjective clinical one.

Many studies in literature have focused on the value of ICGf in colorectal surgery [7, 10, 12, 14–18]. However, to the best of our knowledge, only a few have analyzed exclusively high-risk anastomoses, as for extraperitoneal rectal cancers [17]. The aim of this study was to evaluate the efficacy of ICGf in patients subjected to elective laparoscopic RAR for extraperitoneal rectal cancer only. The endpoint was the incidence rate of AL between this group of patients and a control group including patients subjected to the same procedure before the start of routine use of ICGf at our institution.

Methods

This is a retrospective single-center cohort analysis conducted on prospectively recorded data extracted from the database of Clinica Chirurgica of Trieste University Hospital, Italy. All the patients subjected to elective laparoscopic RAR for extraperitoneal rectal cancer in the period from January 2014 to January 2017 were considered. The distance of the cancer from the anal verge was evaluated on preoperatory sagittal magnetic resonance imaging. All patients operated on in an emergency setting or with open technique were excluded. Patients were divided into two groups: an ICGf group (May 2015–January 2017), including the first 33 patients on whom ICGf was used to assess bowel viability, and a control group (January 2014–April 2015), including the last 33 patients subjected to the procedure before we started to use ICGf.

Preoperative factors were recorded, including sex, age, American Society of Anesthesiologists (ASA) score, body mass index (BMI), comorbidities (diabetes, renal failure, cardiovascular disease), previous pelvic radiotherapy, serum albumin levels, and American Joint Committee on Cancer (AJCC) stage. Intra-operative details included blood loss, level of anastomosis (higher versus lower than 5 cm from the anal verge), type of anastomosis (stapled colorectal versus hand-sewn coloanal), number of EndoGIA™ staple fires, air leak test, operative time and diverting ileostomy.

Anastomotic leaks were diagnosed on the basis of clinical and/or radiological signs as defined by the International Study Group on Rectal Cancer [1]. AL was stratified according to the grade of severity. All patients were followed up for at least 30 days postoperatively. Those with diverting ileostomy were systematically assessed by means of a double contrast barium enema performed between the 3rd and 4th postoperative week.

Laparoscopic equipment

Indocyanine green-enhanced fluorangiography (ICGf) was performed using a laparoscopic SPIES system (KARL STORZ GmbH&Co. KG, Tuttlingen, Germany) and a full high-definition camera system (IMAGE 1 SPIESTM, KARL STORZ). A xenon light source was employed (D-LIGHT P SCB, KARL STORZ), providing both visible and NIR excitation light. The surgeon controlled the switch from standard light to NIR by means of a foot switch. The fluorescence angiogram of the bowel wall showed the area of good perfusion with blue color and no perfusion with the absence of color (dark), allowing a subjective evaluation.

Surgical technique

A standardized technique was used, with a routine mobilization of splenic flexure of the colon and high ligation of the inferior mesenteric artery, leaving the marginal artery of Drummond untouched. After distal resection of the rectum (EndoGIA™ with Tri-staple™ technology), the left colon was exteriorized through a Pfannenstiel incision for visual perfusion assessment. The surgeon established the level of proximal resection, evaluating color changes of the bowel wall and pulsation of blood vessels, and marked it with a clip, or forceps. A bolus of 0.2 mg/kg ICG was injected intravenously and the angiography was performed by switching from white light to NIR light.

The fluorescence angiogram of the proximal stump showed the perfusion in a maximum lagtime of 90 s. The site of resection was changed whenever the vascularization at ICGf was deemed to be inadequate (absence of color) (Fig. 1); ICGf was no longer performed before the completion of the anastomosis. For colorectal anastomosis, the proximal stump was divided with a diathermy and the top anvil of the circular stapler (CEEA™) was put in place and fixed with a prolene purse string. An intra-corporeal stapled colorectal anastomosis was performed, with its integrity being confirmed by an air leak test. For very low rectal cancers, a double approach was chosen, with a transanal extraction of the specimen and a hand-sewn coloanal anastomosis. A second bolus of ICG was then administered and both proximal and distal stump were assessed in their definitive setting, laparoscopically or transanally. The control group underwent the same standardized procedure, with the exception of ICGf use.

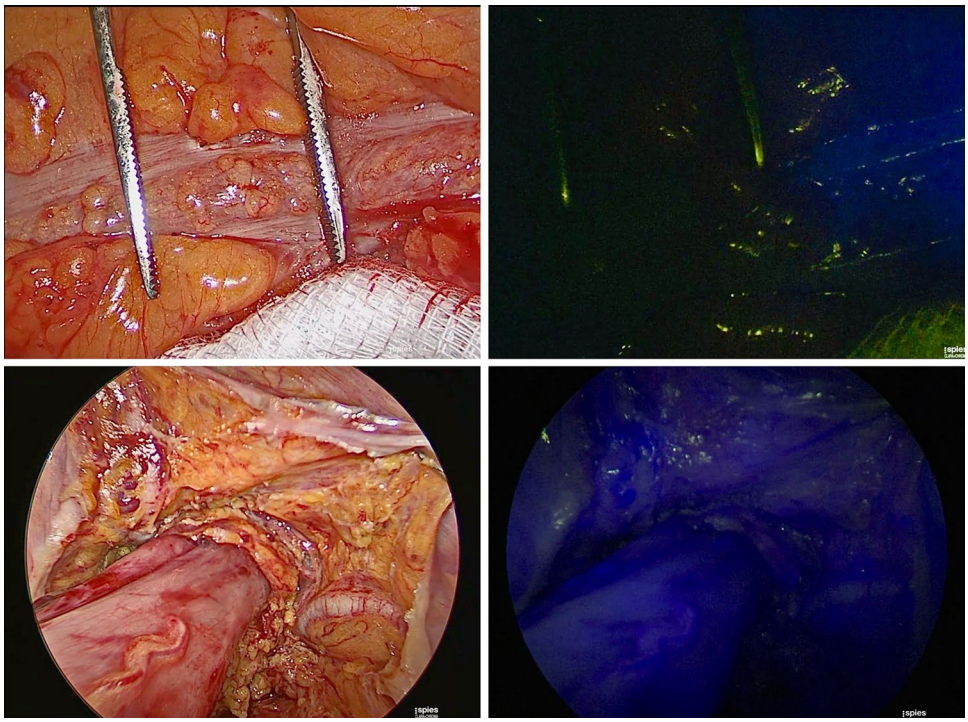

Fig. 1 Example of indocyanine green-enhanced fluorangiography (ICGf) performed before the transection: the forceps show the chosen point of transection, which corresponds to the limit of adequate vascularization during ICGf (upper image). Example of ICGf performed after the completion of anastomosis, which confirms the adequate perfusion of the whole bowel (lower image)

Statistical analysis

Quantitative variables were expressed as mean ± standard deviation or median [25° percentile–75° percentile], whereas qualitative variables were expressed as absolute frequencies and percentages. Differences between categorical variables were tested using Pearson's Chi square test (Fischer exact test when appropriate) or proportion test. Differences between continuous variables were tested with *t* test for independent data or the Mann–Whitney *U* test, according to the normal distribution or not of variables. All statistical analyses were performed using R software, version 3.5.0-2018 (http://www.r-project.org). A *p* value of less than 0.05 was considered to indicate a statistically significant difference.

Results

A total of 66 patients were enrolled in the study. Both the ICGf group and the control group consisted of 33 patients, 21 males and 12 females (mean age 71.85 ± 11.1) in the ICGf group, 15 males and 18 females (mean age 69.03 ± 11.3) in the control group. Preoperative data are reported in Table 1. These variables were homogeneous in the two groups,

Table 1 Pre-operatory variables

Variables	ICGf group (33 patients)	Control group (33 patients)	*p* value
Age (years), mean ± SD	71.85. ± 11.1	69.03 ± 11.3	0.31
Male (%)	21 (63.6%)	15 (45.5%)	0.14
ASA score			
1	0 (%)	4 (12.1%)	**0.03**
2	19 (57.6%)	22 (66.7%)	
> 2	14 (42.4%)	7 (21.2%)	
Serum albumin level, mean ± SD	4.14 ± 0.37	3.83 ± 0.38	**0.001**
Previous pelvic radiotherapy	16 (48.5%)	14 (42.4%)	0.62
Renal insufficiency	3 (9.1%)	1 (3%)	0.61
Diabetes	6 (18.2%)	2 (6.1%)	0.26
Cardiovascular disease	3 (9.1%)	1 (3%)	0.61
BMI (kg/m^2), mean ± SD	25.6 ± 4.0	25.7 ± 4.1	0.68

p values < 0.05 are shown in bold

except for the ASA score, which proved higher in the ICGf group, and serum albumin level, significantly lower in the control group.

Intra-operative data and AL rate are reported in Table 2. The intra-operative data were homogeneous in the two groups. In particular, the site of anastomosis was higher than 5 cm from the anal verge in 19 patients (57.57%) and lower in 14 patients (42.43%) in each group. There were no statistically significant differences either in AJCC staging, type of anastomosis, ileostomy, operative time, and number of EndoGIA staple fires. Air leak test was positive in 3/26 (11.54%) patients of the ICGf group, versus none in the control group, but the difference was still not statistically significant. There were no intra-operative adverse events or conversions to open surgery. Relying on fluorescence intensity in the ICGf group, the level of resection was changed in 6/33 patients (18.2%). In the control group, no change in resection was recorded for vascular reasons, but we reported one change in resection to obtain safety margins for oncologic purposes. The mean time between ICG injection and fluorescence detection was 40.0 ± 15.9 s. AL developed in 2/33 patients (6%) in the ICG group versus 7/33 patients (21.2%) in the control group ($p = 0.15$). In the ICGf group, we had one grade A leak and one grade B leak, while in the control group we noted 3 grade A leaks, one grade B and 3 grade C. Considering only the clinically significant AL, in the ICGf group there was only one late AL [in the 15th postoperative day (POD)], whereas in the control group there were one AL (grade B and C) and they were clinically evident earlier (two in 6th POD, one in 7th POD, one in 9th).

None of the patients developed side effects related to the injection of ICG.

Discussion

In the last 2 decades, technological advancement, as well as improvements in surgical skills, has enhanced the surgeon's ability to perform low and ultra-low anastomoses [19]. However, AL remains a challenging and feared complication after colorectal surgery. Its prevalence ranges from 5 to 20% in colorectal and coloanal anastomoses [2, 5, 20]. This postoperative complication increases mortality (1.9% versus 15.9%) and in-hospital length of stay (7 days versus

Table 2 Cancer-related and intra-operatory variables

Variables	ICGf group (33 patients)	Control group (33 patients)	*p* value
Site of anastomosis			
>5 cm	19 (57.57%)	19 (57.57%)	1.00
<5 cm	14 (42.43%)	14 (42.43%)	
AJCC stage			0.28
0	4 (12.12%)	4 (12.12%)	1.00
1	17 (51.51%)	15 (45.5%)	0.81
2	6 (18.18)	2 (6.06%)	0.26
3	3 (9.09%)	9 (27.7%)	0.11
4	3 (9.09%)	3 (9.09%)	1.00
Ileostomy	19 (57.57%)	14 (42.42%)	0.32
Type of anastomosis			
Mechanical colorectal	25 (75.76%)	27 (81.82%)	0.55
Hand-sewn coloanal	8 (24.4%)	6 (18.18%)	
Change in resection of proximal stump[a]	6 (18.18%)	0 (0.0%)[a]	**0.03**
Blood loss > 250 ml	2 (6.06%)	NA	//
Air leak test	3/26 (11.54%)	0/28(0%)	0.21
Number of EndoGIA staple fires			
≤T2	27 (81.8%)	29 (87.9%)	0.49
>2	6 (18.2%)	4 (12.1%)	
Operative time (min), median [25°p–75°p]	217 [185–240]	201 [165–290]	0.90
Anastomotic leak	2 (6.06%)	7 (21.21%)	0.15
Grade A	1 (3.03%)	3 (9.09%)	
Grade B	1 (3.03%)	1 (3.03%)	
Grade C	0 (0%)	3 (9.09%)	

p value < 0.05 is shown in bold

[a]Only change in resection for vascular reasons were considered

23 days). It is associated with reduced long-term cancer-specific survival and greater risk of recurrence [5].

Since vascularization and sufficient oxygenation of bowel stumps are fundamental to the healing of the anastomosis, assessment of adequate perfusion seemed to be essential in reducing AL rates even in a pre-ICG era [21, 22].

In our study, the preoperatory, cancer-related and intra-operatory variables were homogeneous in both groups of patients and all the surgical procedures were performed or tutored by two colorectal senior surgeons following the same standardized technique. This guaranteed a more accurate comparison in our sample between performing an RAR using ICGf or not.

The most common and traditional way to evaluate bowel perfusion is to observe color changes of the bowel wall and pulsation of blood vessels. Nevertheless, visual observation even by experienced surgeons cannot accurately evaluate minute changes in the microcirculation of the bowel, especially in more challenging situations such as abnormal anatomy or visceral obesity. ICG fluorangiography can be used to easily observe the perfusion status of the bowel stumps. In previous studies, the effects of using ICGf to reduce the rate of AL have not been clearly demonstrated [15].

The main limitation of the perfusion assessment with ICGf is that qualitative evaluation alone can be limited in distinguishing changes in the microcirculation of the bowel and the results of the analysis can be influenced by the characteristics and reliability of camera system and video shooting conditions, as well as the cardiac output of the patient at the moment of ICG injection. Moreover, the surgeon assesses the quality of perfusion subjectively, while the ideal colonic viability test should be objective and reproducible. Quantitative blood flow analysis would be important to measure changes in microcirculation and recent research on this topic has been undertaken. For example, Sherwinter et al. used a fluorescence score based on a sequence of ICG uptake and time of excitation [15, 23]. It should also be taken into account that a postoperative reduction in blood supply or outflow/venous return could occur, leading to late AL.

Given the above, the preliminary results of our study seem consistent with what is already reported in the literature [16, 17, 24]. When compared to mere clinical assessment, ICGf appears to be more specific in determining the most suitable point of bowel resection. In our case, the planned point of resection was modified after fluorescence evaluation in 18.18% of the cases, which is comparable to what is reported by Jafari et al. (19%) and by the PILLAR II multicentre study, where the surgical plan was changed in 7.5% of < 10 cm from the anal verge rectal cancers and 5.8% of > 10 cm from the anal verge ones [16, 17].

In our study, no AL was reported in the patients who underwent a change of resection point after fluoroangiography assessment. In addition, the second round of fluorescence evaluation, performed after completion of the anastomosis, did not determine any intra-operative change, which is similar to what is described by Boni et al. [18].

Compared to the control group, AL rates showed a downward trend in the ICGf set, decreasing from 21 to 6% ($p = 0.15$), although this was not statistically significant probably due to the small size of our sample. This incidence is even lower than reported in the literature by randomized and controlled trials regarding robot-assisted low anterior resections (12%) and our findings are consistent with what is reported by Jafari et al., who demonstrated a similar downward trend in AL incidence (18% versus 6%) when an extraperitoneal anastomosis was performed [17, 25, 26].

It is interesting to note that in the event of leakage, our ICGf patients did not develop any grade C leaks, suggesting at least its usefulness in avoiding gross damage to the anastomosis and severe complications. Moreover, the ICGf group developed only one late clinically significant AL, in the 15th POD, whereas in the control group AL was clinically evident earlier (median POD 8). The fact that AL occurred later in the IGCf group compared to the control group may be explained by other factors beyond arterial perfusion (e.g., reduced blood outflow). Therefore, ICG seems to protect patients from AL due to arterial issues, but not from all the other factors involved in the development of AL.

In fact, both patients who developed AL in the ICGf group were high-risk patients ab initio: the first was on elderly diabetic ASA III female, with a positive intra-operative air leak test (staple line was reinforced with stitches), the second was an elderly obese ASA III male who underwent an ultra-low anterior resection; both of them had received preoperative radiotherapy, and, in view of the high risk of developing a postoperative AL, a diverting ileostomy was performed.

The use of ICGf seems to have great potential for reducing AL rates in rectal surgery. Our experience showed a downward trend in AL rates in the ICGf setting, thus confirming the possible benefits and safety of this new technology. However, further research should find reliable analyses to objectively assess microcirculation.

Funding The authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Ethical standards All procedures performed in this study were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. For this type of study formal consent by the institutional research committee is not required in Italy.

Informed consent Informed consent was obtained from all individual participants included in this study.

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