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Indocyanine green fluorescence angiography during laparoscopic low anterior resection: results of a case-matched study

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Abstract
Introduction Colorectal anastomoses after anterior resection for cancer carry a high risk of leakage. Different factors might influence the correct healing of anastomosis, but adequate perfusion of the bowel is highlighted as one of the most important elements. Fluorescence angiography (FA) is a new technique that allows the surgeon to perform real-time intraoperative angiography to evaluate the perfusion of the anastomosis and hence, potentially, reduce leak rate.
Aim The aim of this study was to evaluate the impact of FA of the bowel on postoperative complications and anastomotic leakage after laparoscopic anterior resection with total mesorectal excision (TME).
Methods FA was performed in all patients undergoing laparoscopic anterior resection with TME for cancer followed by colorectal or coloanal anastomosis. Results were compared to a historical controls group of 38 patients previously operated by the same surgeon for the same indication but without the use of FA.
Results From October 2014 to November 2015, 42 patients underwent laparoscopic anterior resection with TME and FA of the bowel. The surgeon subjectively decided to change the planned anastomotic level of the descending colon due to hypoperfused distal segment in two out of 42 patients in the FA group (4.7 %). Anastomotic leakage, confirmed by postoperative CT scan and water-soluble contrast enema, was found in two cases of a historical controls group and none in the FA group. No adverse events (side effects or allergic reaction) related to FA were recorded. All the other postoperative complications were comparable between the two groups.
Conclusion In our experience, ICG FA was safe and effective in low rectal cancer resection, possibly leading to a reduction in the anastomotic leakage rate after TME.

Keywords ICG · Anastomotic leaks · Bowel perfusion · Rectal cancer · Fluorescence · Indocyanine green

Colorectal anastomoses after anterior resection for cancer carry a high risk of leakage (2–24 %) [1, 2].

Insufficient blood perfusion, undue tension on the anastomosis, steroid use as well as technical failure of staplers have been highlighted as potential risk factors for the development of anastomotic leakage [1–4].

Although it is difficult, if not impossible, to identify which of these factors is the most important for correct anastomotic healing, adequate bowel perfusion has been stressed as one of the key elements [1, 3–5].

Intraoperative assessment of bowel perfusion is usually subjectively estimated by the surgeon according to the color of the bowel as well as by a visual evaluation of pulsatile bleeding coming from the edge of the bowel to be used for anastomosis [6–8].

Different techniques to assess the optimal gastrointestinal perfusion have been proposed, including pulse

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oximetry, polarographic measurement of oxygen tension, near-infrared and visible light spectrophotometry, intravital microscopy, Doppler ultrasound, hydrogen gas clearance, and radioisotope studies [6]. Fluorescence angiography (FA) is based on direct visualization of the fluorescence emitted by a specific fluorophore (indocyanine green, ICG) under near-infrared (NIR) light that can be identified using dedicated cameras and scopes [9, 10]. This technique can be used to perform a real-time angiography during surgery to evaluate the perfusion of the anastomosis [11–14].

The aim of this study is to present our results on the use of FA during laparoscopic low anterior rectal resection (LAR) for cancer. The clinical outcomes and in particular anastomotic leakage were compared to a case-matched historical series of LAR, performed without FA by the same surgeon (LB).

Methods

FA was performed in all patients undergoing LAR for cancer with total mesorectal excision (TME) followed by colorectal or coloanal anastomosis at the Minimally Invasive Surgery Research Center of the University of Insubria in Varese, Italy, between October 2014 and November 2015.

These patients were matched to a historical series of LAR with TME without the use of FA. All demographic data came from a prospective database including age, sex, American Society of Anaesthesiologists (ASA) score, body mass index (BMI), tobacco use, comorbidities, preoperative steroid use, preoperative radiation, and preoperative transfusions. Approval from the ethical committee was not required due to the retrospective nature of the study.

In order to reduce the bias related to surgical technique and experience, the comparison was made only among those patients operated by one of the senior authors of this paper (LB) (Table 1).

Patients undergoing transanal TME, with iodine allergy, as well as pregnant and/or lactating women were excluded.

The Karl Storz image1 fluorescence system (Karl Storz, Tuttlingen, Germany) was used to perform FA before and after the anastomosis.

The technique and dosage regimen have been described by the authors elsewhere [14]: In brief, 5 cc of 0.2 mg/kg of indocyanine green (Pulsion Medical System, Feldkirchen, Germany) is injected intravenously after the division of the mesentery at the level of planned transection. Usually 30–45 s after the injection, fluorescence is visible on the colonic wall confirming bowel perfusion.

Once completed, the anastomosis was evaluated for airtightness and the donuts were checked for integrity. A protective ileostomy was performed in all cases.

Routine CT scan plus water-soluble contrast enemas were performed postoperatively whenever anastomotic leakage was clinically suspected.

Patient outcomes, including postoperative complications classed according to the Dindo–Clavien classification [15], were recorded.

Table 1 Demographic and preoperative patient's characteristics

	FA group	Control	*p*
Age (mean)	69 ± 8	67 ± 7	NS
Sex (M/F)	28/14	22/16	NS
BMI (mean)	27 ± 11	29 ± 15	NS
Cardiovascular disease	28/42 (66 %)	11/38 (28 %)	$P < 0,05$
Steroid therapy	1/42 (2 %)	0/38 (0 %)	NS
Tobacco use	18/42 (42 %)	23/38 (60 %)	$P < 0,05$
Distance from anal verge (mean cm)	6.3 ± 2	7.2 ± 3	NS
Type of anastomosis			
End-to-end circular anastomosis	30/42 (71 %)	31/38 (81 %)	NS
Coloanal manual anastomosis	12/42 (29 %)	7/38 (19 %)	NS
Change in the surgical strategy	2/42 (5 %)	NA	
pT stage			
pT1	2	0	NS
pT2	11	12	NS
pT3	25	22	NS
pT4	4	3	NS
pN +	24	18	NS
pM+	0	1	NS
Neoadjuvant chemoradiotherapy	33/42 (78 %)	23/38 (60 %)	NS

Continuous variables were expressed as means with standard deviations (±SD). Comparisons were performed with the Person's Chi-square test, and a P value of 0.05 or lower was considered as statistically significant.

Results

From October 2014 to November 2015, 42 patients (28 females, 14 males, mean age: 69 ± 8 years) underwent laparoscopic LAR for rectal cancer and intraoperative FA.

The historical control group was composed of 38 patients (22 females, 16 males, mean age 67 ± 7 years) undergoing LAR for the same indication between October 2012 and September 2013, by the same surgeon, with the same technique (except performance of FA).

Patient preoperative demographics were comparable except for statistically significantly higher incidence of cardiovascular medical history in the FA group while in the historical control group, tobacco use was significantly higher than FA group (Table 1).

The mean operative time for the FA group was 165 ± 25 versus 172 ± 18 min in the historical control group. This difference was not statistically significant (NS).

There were no side effects or allergic reaction related to the injection of ICG.

In two out of 42 patients in FA (4.7 %), the surgeon decided to change the planned anastomotic level of the descending colon due to hypoperfusion of the distal part of proximal colonic limb. The mean length of resected bowel was 4 ± 3 cm.

Postoperative outcomes and complications are described in Table 2.

Two clinically relevant anastomotic leakages, (Dindo–Clavien grades II and III), confirmed by postoperative CT scan and water-soluble contrast enema, occurred in the historical control group, while there was none in the FA group. One of these patients was treated with re-laparoscopy and drainage; the second was treated conservatively (both had protective ileostomy during the first surgical procedure). Both patients had an uneventful recovery.

Table 2 Postoperative outcomes

Postoperative morbidity	FA group	Control group	p
Ileus	3/42 (7 %)	2/38 (5 %)	NS
Blood transfusion	5/42 (12 %)	2/38 (5 %)	NS
Pulmonary complications	11/42 (26 %)	6/38 (15 %)	NS
Wound infections	2/42 (5 %)	0/38 (0 %)	NS
Urinary tract infections	6/42 (14 %)	5/38(13 %)	NS
Urinary retention	3/42 (7 %)	1/38(3 %)	NS
Postoperative leak	0/42 (0 %)	2/38 (5 %)	NS
Others	7/42 (17 %)	5/38 (13 %)	NS
Re-operation	0/42 (0 %)	1/38 (3 %)	NS
Mortality	0/42 (0 %)	0/38 (0 %)	NS

The prevalence of all other postoperative complications did not differ statistically significantly between the two groups. The mean postoperative stay was 7 ± 2 days in FA group versus 8 ± 7 days in the no FA assessment group (difference NS). There were no deaths in either group.

Discussion

This short series confirms that fluorescent angiography during laparoscopic colectomy is feasible and safe. Although this was a historical comparison, ICG FA did not require extra time (165 ± 25 vs 172 ± 18 min in the historical control group) (difference NS) as it can be performed during the operation and visualization is almost immediate as reported by other studies [9–11, 13, 14].

No clinically relevant leaks were observed in the FA group, whereas two AL were reported in the case-matched group: This difference is not statistically significant likely due to the limited number of patients analyzed. Two patients in the FA group required changes in the planned resection margin due to hypoperfusion.

Hypoperfusion is a well-recognized cause of anastomotic leakage [1]. In clinical practice, adequate perfusion is often evaluated by the surgeon who checks for colonic viability based on color, the presence of bleeding from bowel edges, or the observation of vessel pulsations [6]. However, this type of evaluation has been reported to be very subjective and unreliable with very low sensitivity and specificity [7].

Other intraoperative techniques including oxygen spectroscopy, transabdominal laser Doppler flowmetry, and Doppler ultrasound have been proposed with controversial results. Moreover, clinical application of these other techniques, especially in laparoscopic surgery, is unpractical [1, 6–8].

FA allows performing a real-time angiographic control of bowel perfusion that can be evaluated or not according to the intensity of the fluorescence emitted by ICG [12]. The technique is easily reproducible, with relatively low added costs and time, and considering the limited side effects reported for ICG (none in our series), safe [11–14].

The use of FA to assess the bowel perfusion during surgery has been already reported in several non-randomized studies, mainly focusing on esophageal and colorectal surgery [11–14, 16].

Due to the design of most of these studies, the majority concentrated on the change of surgical strategy due to the subjective recording of hypoperfusion while only one

retrospective study reported a significant reduction in anastomotic leakage rate compared to historical controls [17].

To date, there are very few articles focused on the use of FA during LAR with TME, where the risk of anastomotic leakage is higher than in other large bowel resections and the rate of protective ileostomy is high.

In our study, the anastomotic leak rate was 0 and 5.2 %, respectively, in the FA and historical controls group. Although it is impossible to prove that the change in the surgical strategy according to FA (5 %) was directly responsible for the absence of anastomotic leakage, the fact that the time frame between the two group was short (only 2 years) and that the operative technique and the surgeon were identical in both groups might have reduced the role of other technical factors related to AL.

Sherwinter et al. [18] performed FA in 22 patients undergoing LAR after completion of the anastomosis and reported four cases of abnormal perfusion. In two out of the four patients, they decided to perform a protective ileostomy and no leakage was observed, while in the remaining two patients no protection was performed and both developed a clinically and radiologically proven leakage.

Jafari et al. [13] recently published the results of a multicentre prospective study on the change of anastomotic level according to FA in left-sided colorectal resections. Although this study did not specifically focus on TME (only 21 % of patients had colonic resection for cancer), all the participants were experienced colorectal surgeons. In this study, FA led to change the resection margin in 11 (8 %) of 139 patients. The overall anastomotic leak rate was 1.4 %, and no anastomotic leaks were reported in the 11 patients who had a change in surgical plan based on intraoperative perfusion assessment with FA.

The only controversial results on the positive effect of FA in colorectal resections have been reported in a retrospective case-matched study by Kin et al. [19]. In their experience, the proximal resection margin was changed in 4.6 % of patients, but no statistically significant reduction in the leak rate was found in comparison with the historical group. The authors acknowledged several limitations of their study such as the retrospective nature, the different period of time where the two groups were compared and, in particular, the small sample size. The probability of falsely concluding that there was no difference (type II error) was high.

One of the main limitations of FA evaluation is that the surgeon assesses the quality of perfusion subjectively and it might be influenced by several factors such as ICG dosage and timing, distance between the tip of the endoscope and the bowel, light cable quality, near-infrared light intensity, and patient characteristics such as blood pressure, arteriosclerosis of marginal vessels, and perhaps also BMI [20]. Some experimental studies have been published in order to quantify the intensity level with the final aim of identifying cutoff values and minimizing the intra- and inter-observational variability, but they are mainly based on the measurement of the "time to peak" of fluorescence that requires standard conditions difficult to achieve in clinical practice and specifically designated software [12].

Conclusion

In our series, we found that ICG fluorescence angiography was safe and effective in LAR with TME, possibly leading to a reduction in the anastomotic leakage rate. However, because our study was retrospective and non-randomized, large randomized controlled trials are needed to confirm the utility of ICG FA in assessing the vascularity and reducing the AL rate. Further studies are also required to identify a standard technique to measure the minimal value of fluorescence intensity, below which, anastomotic leakage due to hypoperfusion might occur.

Compliance with ethical standards

Disclosures Luigi Boni, Abe Fingerhut, Alessandro Marzorati, Stefano Rausei, Gianlorenzo Dionigi, and Elisa Cassinotti have no conflicts of interest or financial ties to disclose.

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