

The Role of Indocyanine Green in Laparoscopic Low Anterior Resections for Rectal Cancer Previously Treated With Chemo-radiotherapy: A Single-center Retrospective Analysis

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Abstract. Aim: Anastomotic leakage represents the most fearful complication in colorectal surgery. Important risk factors for leakage are low anastomoses and preoperative radiotherapy. Many surgeons often unnecessarily perform a protective ileostomy, increasing costs and necessitating a second operation for recanalization. The aim of this study was to evaluate the role of indocyanine green in assessing bowel perfusion, even in cases of a low anastomosis on tissue treated with radiotherapy. Patients and Methods: Two groups of patients were selected: Group A (risky group) with only low extraperitoneal rectal tumors (<8 cm) previously treated with neoadjuvant chemo-radiotherapy; group B (no risk group) with only intraperitoneal rectal tumors (>8 cm), not previously treated with neoadjuvant therapy. Clinical postoperative outcome, morbidity, mortality and anastomotic leakage were compared between these two groups. Results: In group A, comprised of 35 patients, the overall complication rate was 8.6%, with two patients developing anastomotic leakage (5.7%). In group B, comprised of 53 patients, the overall complication rate was 17% with four cases with anastomotic leakage (7.5%). No statistical difference was observed for conversion rate, general complications, or anastomotic leakage. No statistical differences were observed in clinical variables except for American Society of Anesthesiologist score ($p=0.04$). Patients who developed complications during radiotherapy

had no significant differences in postoperative outcomes compared with other patients. Conclusion: Indocyanine green appears to be safe and effective in assessing the perfusion of colorectal anastomoses, even in the highest-risk cases, potentially reducing the rate of ileostomy. The main limitation remains the lack of a universally replicable standard assessment.

The incidence of rectal cancer in the European Union is 125,000 per year. Rectal cancer is classified according to the distance from the anal margin as low (up to 5 cm), middle (from 5 to 10 cm) and high (from 10 to 15 cm) (1). The standard treatment is surgery, often combined with radiotherapy and chemotherapy (2). There are two types of surgical approaches: Transanal and transabdominal resection, the latter consists of low anterior resection with total mesorectal excision (3). Nowadays, despite the improvement of these surgical techniques, anastomotic leakage (AL) represents one of the most fearful complications, with a frequency that reaches 30% (4). Spinelli *et al.*, through a national consensus, gave a clear definition of AL: A defect of the intestinal wall at the anastomotic site leading to a communication between the intra and extraluminal compartments. A pelvic abscess close to the anastomosis, even without any evident communication with the colonic lumen, should be considered as a leak. AL should be graded (A-B-C) according to the intervention required (5). The onset of AL has a significant impact on mortality and short and long-term morbidity; it also increases the incidence of local recurrence and leads to a reduced quality of life (4).

Many surgeons create a defunctioning protective ileostomy to avoid the risk and the severity of AL (6). On the other hand, some have noted that this procedure involves several risks for patients, including kidney failure, high stoma flow, prolapse, skin excoriation and also an increase in hospital stay (2). Furthermore, the creation of a temporary

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ileostomy requires a second surgical procedure for closure of the stoma, which consequently leads to a significant increase of hospitalization costs (7). In most cases, the utility of ileostomy in preventing AL is not justified. For these reasons, some surgeons prefer to reserve creating a defunctioning ileostomy only for high-risk patients (8).

The most important risk factors for AL are a low anastomosis, preoperative radiotherapy, high American Society of Anesthesiologists (ASA) score and perioperative blood loss (9). In the last few years, especially in colorectal surgery, the use of indocyanine green (ICG) has gained an important role in intraoperative angiography. This macromolecule, by binding to different serum globulins, allows surgeons to evaluate the perfusion of anastomotic stumps (10).

The aim of our study was to evaluate the efficacy and safety of ICG in assessing intestinal perfusion even in high-risk cases. Therefore, in terms of AL and general complications, we compared two groups of patients with rectal cancer undergoing intraoperative evaluation with ICG, with and without ileostomy.

Patients and Methods

From December 2014 to December 2020, 88 patients underwent elective rectal surgery for cancer at the Colon-Rectal Oncological Surgery Unit of the Sant'Andrea Hospital La Sapienza University of Rome and were retrospectively analyzed. All procedures were performed by the same surgical team, with experienced laparoscopic surgeons. For all patients, an Enhanced Recovery After Surgery protocol was adopted. ICG fluorescence was used in all patients to assess intestinal perfusion (11, 12).

Study population. For this study, we selected two groups of patients: Group A (risky group), with true extraperitoneal rectal adenocarcinoma (<8 cm from the anal verge) treated with neoadjuvant chemo-radiotherapy or only radiotherapy (CHT-RT/RT), where a protective ileostomy is usually performed; and group B (no risk group), with intraperitoneal rectal adenocarcinoma (between 8 and 15 cm from the anal verge), not treated with neoadjuvant CHT-RT, where usually an ileostomy is not performed. For both groups, perfusion with ICG was performed intraoperatively. Exclusion criteria were: cases in which anastomosis was not performed, cases in which fluorescence evaluation was not performed, and cases in which there was a lack of RT, oncological, or surgical data.

Surgical technique. Our technique consists of a laparoscopic four-trocar approach, with the patient in a supine position with legs separated. The surgical steps are those of typical total mesorectal excision. At our center, we usually start by finding the inferior mesenteric vein even if sometimes we started from the sacrum with the approach to the inferior mesenteric artery. Evaluation of colic perfusion with ICG was performed systematically before performing the service incision and the proximal colon resection, and the point chosen is marked with a clip. The standard ICG dose used was 0.25 mg/kg by peripheral access. A second check with ICG was then performed after anastomosis, along with hydro-pneumatics testing. We performed the mechanical end-to-end Knight-Griffen anastomosis.

Table I. General features of study patients.

Parameter	Category	Value
Gender, n (%)	Male	52 (59.1)
	Female	36 (40.9)
Age, years	Mean (range)	67.3 (36-93)
ASA score, n (%)	1	0 (0)
	2	42 (47.73)
	3	43 (49)
	4	3 (3.3)

ASA: American Society of Anesthesiologists.

Radiotherapy. From December 2014 to December 2020, 35 patients affected by rectal cancer were treated with neoadjuvant CHT-RT or RT only at the Radiotherapy Department of Sant'Andrea Hospital in Rome (13, 14). Thirty patients were assigned to long-course CHT-RT treatment. Of these, 22 underwent intensity-modulated radiotherapy and received 45 Gy in 1.8-Gy daily fractions to the pelvis, with a simultaneous integrated boost of 55 Gy in 2.2-Gy daily fractions to the tumor and positive lymph nodes. The remaining 8 patients underwent 3-dimensional conformal radiotherapy and received 45 Gy in 1.8-Gy daily fractions to the pelvis, with a concomitant boost of 10 Gy in 1-Gy biweekly fractions to the tumor and positive lymph nodes. Concurrent CHT was administered to all these patients, comprising 825 mg/m² oral capecitabine twice per day, 5 days per week (15). Five patients were assigned to short-course RT treatment. They underwent intensity-modulated radiotherapy and received 25 Gy in 5-Gy daily fractions to the pelvis, without CHT.

During treatment, acute toxicities were coded according to the Common Terminology Criteria for Adverse Events (version 5.0, 2017) for gastrointestinal, genitourinary and hematological events (16).

Statistical methods. Nominal continuous variables are expressed as averages with range (min to max), categorical variables are expressed in units and percentages. Descriptive statistics were used to summarize information relevant to the study. Associations between categorical variables were estimated using logistic regression and the univariate Cox regression model. Significance was accepted for $p < 0.05$. The licensed statistical programs SPSS (version 21.0; IBM, Armonk, NY, USA) and MedCalc (version 14.2.1; MedCalc software, Ostend, Belgium) were used for all analyses.

Results

From December 2014 to December 2020, 88 patients underwent minimally invasive anterior rectal resection with total mesorectal excision for malignant disease at the Colon-Rectal Oncological Surgery Unit of Sant'Andrea Hospital of La Sapienza University of Rome. In the whole population, 36 patients were female (40.9%) and 52 male (59.1%), with a mean ASA=2.51 (range=2-4), and a mean age at admission of 67.30 (range=36-93) years, as shown in Table I.

The laparoscopic approach was the predominant approach with a conversion rate of 5.7% (five patients). The median

Table II. Comparative analysis between the two groups.

Parameter	Category	Group A (n=35)	Group B (n=53)	p-Value
Age, years	Mean (range)	68 (36-89)	68 (44-93)	0.45
Gender, n (%)	Male	19 (54.3)	33 (62.3)	0.46
	Female	16 (45.7)	20 (37.7)	
ASA score	Mean (range)	3 (2-4)	2 (0-3)	0.042
Operative time, min	Mean (range)	240 (150-380)	215 (135-315)	0.058
Gas canalization, days	Mean (range)	2 (1-6)	2 (1-4)	0.82
Stool canalization, days	Mean (range)	3 (1-6)	3 (1-5)	0.87
Hospitalization, days	Mean (range)	4 (3-7)	4 (3-8)	0.98
Conversion, n (%)	Yes	3 (8.6%)	2 (3.8%)	0.38
	No	32 (91.4%)	51 (96.2%)	
Complications, n (%)	Yes	3 (8.6%)	9 (17%)	0.35
	No	32 (91.4%)	44 (83%)	
AL	Yes	2 (5.7)	4 (7.5)	0.99
	No	33 (94.3%)	49 (92.5%)	

AL: Anastomotic leakage; ASA: American Society of Anesthesiologists. Statistically significant *p*-values are shown in bold.

distance of tumor from the anal verge was 9.40 cm and 22 patients required temporary/permanent ostomy. Canalization was a median of 2 (range=1-6) days for gas and 3 (range=2-6) days for stool. The median day of discharge was 4 (range=3-8). The median operative time was 235 (range=135-380) min. The complication rate was 13.6% (12 patients). Six cases of AL were observed (6.8%). The 30-day mortality rate was 0%.

Group A (extraperitoneal rectal cancer treated with CHT-RT/RT) comprised 16 females (45.7%) and 19 males (54.3%), with a mean age of 68 years and mean ASA of 3. The mean operative time was 240 min, and the conversion rate was 8.6%. The mean distance from the anal verge was 4.87 cm. The mean time to gas canalization was 2 days and 3 days for stool, with a mean discharge on day 4. The overall surgical complication rate was 8.6% (three patients) with AL in two patients (5.7%) (Table II).

Group B (intraoperative rectal cancer, no CHT-RT) included 20 females (37.7%), 33 males (62.3%), with a mean age of 68 years and ASA of 2, undergoing laparoscopic rectal anterior resection with open conversion rate of 3.8% and mean operative time of 215 min. Complications were recorded in nine patients (17%), of these, four developed AL (7.5%).

When the groups were compared, the only significantly different variable was the ASA score, which was significantly higher for group A ($p=0.042$). There were no significant differences in terms of age, sex, operative time, day of gas and stool canalization and discharge. No statistical difference for rates of conversion, general complications, and AL were observed, as shown in Table II.

Regarding gastrointestinal toxicities, proctitis was observed in 18 patients (6 were grade 1, 11 grade 2, 1 grade 3), diarrhea in 1 (grade 3) and nausea in 1 (grade 2).

Table III. Features of the radiation therapy (RT) protocol in group A patients.

	Category	Frequency, n (%)
RT protocol	Short-course	5 (14.3)
	Long-course	30 (85.7)
Complications	Yes	20 (57.14)
	No	15 (42.86)
	Gastrointestinal	20 (100)
	Proctitis	18 (90)
	Diarrhea	1 (5)
	Nausea	1 (5)
	Genitourinary	5 (25)
	Dysuria	4 (80)
	Increased urinary frequency	1 (20)
Hematological		4 (20)
	Neutropenia	3 (80)
	Lymphocytopenia	1 (20)

Regarding genitourinary toxicities, dysuria was recorded in 4 patients (1 grade 1, 3 grade 2) and increased urinary frequency in 1 patient (grade 2). Hematological toxicities included neutropenia observed in 3 patients (grade 2) and lymphocyte count decrease in 1 patient (grade 3) (Table III).

In addition, results of selective analysis of the surgical outcomes of patients who had complications during RT compared with non-risk patients (group B), shown no significant differences in terms of general complications ($p>0.9$) and anastomotic leak ($p=0.66$) (Table IV). We chose to perform this comparison in order to highlight how the use of fluorescence can be useful even in patients who have developed local complications from RT and are consequently considered patients even more at risk of anastomotic leakage.

Table IV. Impact of radiotherapy (RT) complications on postoperative outcomes.

	Category	Patients with RT complications (n=20)	Group B (n=9)	p-Value
Postoperative complication, n (%)	Yes	3 (15)	9 (17)	>0.99
	No	17 (85)	44 (83)	
AL, n (%)	Yes	2 (10)	4 (7.5)	0.66
	No	18 (90)	49 (92.5)	

AL: Anastomotic leakage.

Discussion

AL has always been the major feared complication in colorectal surgery. Its frequency still remains high despite improvements in surgical techniques (4,17). In a recent consensus, a definition of colorectal AL was given, described as: A defect of the intestinal wall at the anastomotic site leading to a communication between the intra and extraluminal compartments. A pelvic abscess close to the anastomosis, even without any evident communication with the colonic lumen, should be considered as a leak. AL should be graded (A-B-C) according to the intervention required (5). This definition finally allows the complications of colorectal anastomoses to be standardized and classified according to severity and treatment required. Several risk factors for colorectal AL have been identified and are mainly the level of the anastomosis (low extraperitoneal have a higher risk), previous CHT-RT, malnutrition, cardiovascular comorbidities, age and alteration of the gut microbiome (4, 18). Neoadjuvant CHT-RT, which has become the gold standard in the treatment of rectal cancer, has always been identified as a risk factor for AL, mainly because of locoregional inflammation and the increased risk of tissue necrosis/ischemia (1, 19). Typically, most surgeons undertaking a low/ultra-low colorectal anastomosis on irradiated tissue are inclined to perform a protective ileostomy to mitigate the risk of AL (20). In addition, to avoid a particularly adverse surgical field in terms of fibrosis and inflammation, many Authors have recommended scheduling surgery between 8 and 12 weeks after the end of neoadjuvant treatment (21). This aspect is confirmed by our results, which show that in group A, 22 protective ileostomies were performed, and all the operations were performed between 8 and 12 weeks after the end of CHT-RT. In group B, no ileostomies were performed. However, our results do not show statistically significant differences in terms of AL between the two groups, despite group A theoretically being at higher risk of anastomotic complications. Our results showed that through use of ICG, a safe anastomosis can be achieved, even in irradiated patients (Table II). Furthermore, surgical outcomes for patients who had complications during RT were not worse.

Thus, our results showed that RT did not have a significant impact on post-surgical complications.

In contrast to these results, 22 ileostomies, performed with the aim of protecting previously irradiated anastomoses, were carried out in the risky group. However, this 'protective' strategy was not supported by the clinical data, the fistula rate being comparable in the two groups. On the contrary, an ileostomy entails greater discomfort for the patient, often requires nursing care at home, requires a second operation (with relative complications) and subsequent hospitalization that causes a greater expense for the hospital. In addition, although only in a few cases, there are patients in whom recanalization is not performed, with a consequent very low quality of life

In conclusion, from these preliminary results, the use of ICG seems to be a safe, effective and easily feasible method to assess the safety of colorectal anastomosis, even those defined as high risk, and can help surgeons in the decision-making path regarding the performance of a protective ileostomy. As already reported, the systematic use of ICG, appears to reduce the rate of AL <3% and a widening of the section line between 5 and 40%, reducing morbidity and consequently mortality in colorectal surgery (22). However, there are some pitfalls. In fact, it remains a subjective method for perfusion evaluation, which needs objective measurement tools (perfusion time, intensity) that provide real feedback on the correct vascularization of the bowels (23, 24). One of the major limitations of ICG angiography is the lack of intensity quantification. In fact, some authors have raised the criticism that the evaluation of perfusion may be influenced by the camera and therefore by the quality of the instrumentation (25). Some authors, report time-based intensity of fluorescence as a key value in objectively assessing perfusion and creating a suitable feasible cut-off (26). In addition, another major issue is the ideal injection dose and timing to achieve realistic and optimal visualization (26).

We can therefore conclude from our results that ICG appears to be a safe and effective method for assessing the safety of anastomosis. However, further evaluation is necessary to standardize this method more, looking for possible cut-offs assessable by all surgeons. This study has some limitations represented by its retrospective nature and

the small, although extremely selected, sample of patients. Further studies, prospective and randomized, are required to validate our results.

Conclusion

The use of ICG is assuming a role in colorectal surgery. Its use seems to reduce the rate of AL, even in particularly risky anastomoses, an advantage that may also lead to a consequent decrease in the rate of ostomies. The main limits are represented by the lack of standardization of perfusion assessment, which remains dependent on the surgeon.

Conflicts of Interest

The Authors declare that they do not have any conflicts of interest.

Authors' Contributions

Study conception and design were by Muttillio Edoardo Maria, Brescia Antonio and Mattia Falchetto Osti. Material preparation, data collection and analysis were performed by Angelicone Ilaria and Sperduti Isabella. The first draft of the article was written by Muttillio Edoardo Maria, Madaffari Isabella, Angelicone Ilaria and Federico Maggi. Mattia Falchetto Osti and Antonio Brescia made the final revision of the article. All Authors commented on previous versions of the article. All Authors read and approved the final article.

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