Techniques in Coloproctology (2018) 22:535–540
https://doi.org/10.1007/s10151-018-1832-z

ORIGINAL ARTICLE

Indocyanine green fluorescence angiography during low anterior resection for low rectal cancer: results of a comparative cohort study

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Received: 6 June 2018 / Accepted: 31 July 2018 / Published online: 10 August 2018

Abstract

Background Anastomotic leak (AL) after low anterior resection (LAR) is associated with increased morbidity, mortality, cost and cancer recurrence rates. The aim of this study was to evaluate the impact of fluorescence angiography (FA) on AL following LAR for low rectal cancer.

Methods This is a single surgeon retrospective cohort study with a historical, consecutively sampled case matched control group. The institution's prospectively maintained institutional review board (IRB)-approved database was queried for all patients who underwent a laparoscopic LAR for rectal neoplasia with a colorectal or coloanal anastomosis < 5 cm from the anal verge between 2013 and 2016. Patients were divided into two groups: patients in whom FA was employed (study group, 2015–2016) and those patients in whom it was not (control group, 2013–2015). All patients were diverted with a loop ileostomy. The primary outcome measured was the AL rate and the secondary outcome measured was change in surgical plan following FA.

Results Sixty patients were included in the study: 30 patients in the FA group and 30 patients in the control group. Patients' demographics, the use of neoadjuvant chemoradiation, tumor stage, and mean height of anastomosis were comparable between the study groups. FA led to a change in surgical plan in four patients (13.3%) none of who suffered an AL. Two patients in the control group had a clinically and radiologically confirmed AL, whereas there were no leaks in the FA group (6.7% vs. 0%, $p = 0.49$).

Conclusions FA changed the surgical plan in 13.3% of LAR's, potentially reducing the incidence of AL in these high-risk patients.

Keywords Indocyanine green fluorescence angiography · Low anterior resection · Low rectal cancer

Introduction

Anastomotic leak (AL) is a devastating postoperative complication after low anterior resection (LAR). Leak rates may reach 10–20% in 'high-risk' anastomoses (< 10 cm from anal verge and/or following neoadjuvant radiation therapy) [1, 2]. Rectal cancer patients suffering from an AL are at risk of increased morbidity and mortality, prolonged length of stay, impaired functional outcomes, and increased local recurrence rates [3]. These unfavorable outcomes translate into a substantial economic burden on health systems worldwide [4].

Various patient, surgeon, and procedure related variables have been implicated as risk factors for AL [1, 2, 5]. Potential surgeon and procedure related variables include surgeon's experience, tension-free anastomotic technique via splenic flexure mobilization and high ligation of the inferior mesenteric artery (IMA) and vein (IMV), and endoscopic evaluation of the anastomosis with an air leak test. Assuring perfusion to both ends of the anastomosis is crucial as adequate blood supply seems to play a major role in anastomotic healing.

Poster presentation at 2017 annual meeting of the American Society of Colon and Rectal Surgeons (ASCRS), Seattle, WA, June 10–14, 2017, poster # P630 and poster presentation at the annual meeting of the Association of Coloproctology of Great Britain and Ireland (ACPGBI), July 3–5, 2017, Bournemouth, UK, poster # P121.

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During LAR the surgeon should evaluate perfusion of colonic mucosa and serosa prior to proximal resection and after construction of the anastomosis. Such verification is traditionally performed by a variety of means such as adequate tissue color, palpable pulses within supplying mesentery, and bleeding edges of transected margins. However, studies have shown that, unfortunately, the surgeon's subjective perfusion assessment does not correlate with the risk of AL [6, 7]. Several technologies have been proposed to evaluate colonic perfusion. Scanning laser Doppler flowmetry, visible light spectroscopy, near-infrared (NIR) spectroscopy, and even on-table angiography have all been described; however, none of these modalities have been embraced by surgeons as they are difficult to use, time consuming, not reproducible, and/or expensive [8–10].

Fluorescence angiography (FA) utilizing the fluorophore indocyanine green (ICG) allows for real-time intraoperative evaluation of bowel perfusion [11, 12]. It was first approved by the US Food and Drug Administration (FDA) in 1959 and has been used in other fields of surgery such as hepatobiliary, foregut, transplant, and plastic surgery. After intravenous injection, ICG rapidly binds to plasma proteins and is confined to the intravascular compartment. Under NIR light, it becomes fluorescent, providing a real-time evaluation of intestinal perfusion [13].

Previous studies have shown that ICG enhanced FA is technically feasible and safe in colorectal surgery and that it may lead to a change in the resection margin and alter surgical strategy potentially effecting AL rates [14]. However, most of these studies are heterogenous with regard to the indication for surgery, surgical approach, and surgeon's experience. The purpose of this study was to evaluate the impact of FA on AL following LAR for low rectal cancer performed by a single surgeon.

Materials and methods

This is a retrospective cohort study with a historical, consecutively sampled case matched control group. The institution's prospectively maintained institutional review board (IRB)-approved database was retrospectively queried for all patients who underwent an elective laparoscopic LAR for a rectal neoplasm with a colorectal or coloanal anastomosis < 5 cm from the anal verge between 2013 and 2016 by a single surgeon (SDW). Exclusion criteria were a planned laparotomy, a redo coloanal anastomosis, an urgent or emergent operation, and/or anastomosis > 5 cm from the anal verge, or a planned abdominoperineal resection. Patients were divided into 2 groups:patients in whom FA was employed (study group; 2015–2016) and patients in whom it was not (control group ; 2013–2015). All patients were diverted with a loop ileostomy.

During the surgical procedure, the PINPOINT™ Endoscopic Fluorescence Imaging System (Novadaq, Toronto, Ontario, Canada) was used to assess colonic perfusion at two critical steps of the operation: (1) the planned point of proximal resection just before bowel resection and (2) after completion of the anastomosis, when the integrity of the serosal and mucosal aspects of the completed anastomosis were assessed via laparoscopy and proctoscopy, respectively. In the application of bowel perfusion, ICG was used in the range of 0.1–0.3 mg/kg. A canister containing 25 mg of ICG was diluted with 10 ml of sterile normal saline (NS) resulting in a concentration of 2.5 mg per 1 ml.

For the initial assessment, the planned point of proximal colon resection was marked by the surgeon with an instrument under white or visible light before imaging with FA. This step was performed after full mobilization of the splenic flexure, high ligation of the inferior mesenteric artery (IMA) and ligation of the inferior mesenteric vein (IMV) at the lateral border of the 4th portion of the duodenum, transection of the rectum, and division of the rectal and colonic mesentery up to the intended transection point at the bowel wall. The colon was then extra-corporealized through a wound protector. The proposed site of proximal resection was selected by the surgeon using clinical judgment based on tissue color, palpation, and the extent of the colonic mesentery. The clinical evaluation did not include inspecting the cut edges for bleeding since resection of the bowel had not yet been performed. After this selection, the anesthesiologist administered a bolus of 3.5 ml of ICG intravenously followed by a 10-ml flush of sterile NS. Perfusion of the colon was visualized and assessed via FA and the line of demarcation between perfused and non-perfused tissue was noted and compared with the initial planned resection point. The colon was then divided within an area of well-perfused tissue.

After completion of the anastomosis, a standard air leak test was performed after which perfusion of the completed anastomosis was assessed with FA. A second bolus of 3.5 ml of ICG was followed by a 10-ml flush of sterile NS. FA was employed via laparoscopy to assess the serosal aspects of both ends of the anastomosis. The PINPOINT™ endoscope was then inserted into a custom designed rigid proctoscope and advanced to the anastomosis under visible or white light guidance. A third bolus of 3.5 ml of ICG was followed by a 10-ml flush of sterile NS. Perfusion of both proximal and distal anastomotic mucosal appearance was assessed and the distance of the anastomosis from the anal verge was determined.

All patients followed an enhanced recovery after surgery protocol. Imaging in the postoperative period was performed only when an AL was clinically suspected. The imaging modality used was a computed tomography (CT) scan including rectal contrast.

The primary outcome measured was AL occurring within 60 days of the initial operation. AL was defined according to the previously published grading system by the International Study Group of Rectal Cancer [15, 16] as a defect at the anastomotic site leading to a communication between the intra- and extra-luminal compartments as proven by the following: (1) anastomotic defect noted on digital rectal examination, (2) endoscopic evidence of an anastomotic defect, (3) radiologic evidence of extravasation of rectal contrast, (4) radiologic evidence of a peri-anastomotic fluid collection with pus or feculent aspirate. Thus, pelvic fluid collections that were diagnosed on CT imaging and drained revealing serous or serosanguinous fluid with sterile cultures were not considered as an AL. The secondary outcome measured was the change in surgical plan following FA. A change in plan was recorded as one of the following: (1) changing the previously marked proximal resection margin, (2) redoing the anastomosis, (3) avoiding an anastomosis and instead performing an end colostomy.

Statistical analysis

Statistical analysis was performed using statistical software SPSS version 20 (SPSS, Inc., Chicago, Il, USA). Chi–square test and *t* test were used to identify differences between the study groups and a p value < 0.05 was considered to represent statistical significance for all comparisons. Data are presented as the mean ± standard deviation.

Results

Between July 2015 and October 2016, 30 consecutive patients (16 males, mean age: 58 ± 12 years) underwent elective laparoscopic LAR for rectal cancer with a colorectal or coloanal anastomosis < 5 cm from the anal verge and intraoperative FA by a single surgeon (SDW). The historical control group consisted of 30 patients (18 males, mean age 58 ± 13 years) that underwent LAR for rectal cancer between July 2013 and June 2015, performed by the same surgeon, without FA. Patients' demographics, the use of neoadjuvant chemoradiation, comorbidities, and tumor stage were compared between the study groups (Table 1).

Operative data are presented in Table 2. The groups were comparable for operative time and the distance of the anastomosis from the anal verge. More patients in the FA group had a straight anastomotic configuration (51.7% vs. 26.7%, $p = 0.04$) and underwent transanal total mesorectal excision (taTME) (43.3% vs. 13.3%, $p = 0.01$). Eleven of the 13 patients who underwent taTME had a hand-sewn anastomosis. Five patients in the FA group underwent a synchronous resection: liver ($n = 2$), prostate and seminal vesicle ($n = 1$), colon ($n = 1$), and small bowel ($n = 1$). In the control group, one patient had a synchronous partial bladder resection and another required preemptive conversion from a laparoscopic to an open approach for technical difficulties due to morbid obesity (Table 3).

Four patients (13.3%) in the FA group required a change in the planned proximal resection margin based on FA evaluation. In these four patients, no change in resection margin was noted based upon clinical judgement alone. In three of these patients the surgeon was required to choose a more proximal point of resection due to the lack of adequate fluorescence at the point previously selected. The fourth patient was morbidly obese with Eaton Lambert syndrome and was noted to have ischemia of the entire left colon after FA. The surgeon used FA to select the site of transverse colon resection and construct an end colostomy. Three of these patients received intraoperative vasopressors. In the control group, the surgeon opted to change the surgical plan

Table 1 Patients' characteristics

	CG $N = 30$	FA $N = 30$	p value
Age, years, (SD)	58 (13)	58 (12)	0.879
Male, *n* (%)	18 (60.0)	16 (53.3)	0.602
BMI (SD)	27.2 (6.2)	25.9 (5.7)	0.376
Neoadjuvant CRT, *n* (%)	14 (46.7)	17 (56.7)	0.438
Comorbidities			
Ischemic heart disease, *n* (%)	1 (3.3)	5 (16.7)	0.052
Peripheral vascular disease, *n* (%)	11 (36.7)	6 (20.0)	0.152
Diabetes	3 (10)	2 (6.7)	1
Current smoker, *n* (%)	0	2 (6.7)	0.492
Former smoker	2 (6.7)	2 (6.7)	1
Pre-op hematocrit, %	36.7 ± 4	38.3 ± 4	0.15
Pre-op albumin, g/dL, mean ± SD	4.2 ± 0.4	4.1 ± 0.4	0.8
T Stage, *n* (%)			0.197
High grade dysplasia	0 (0.0)	2 (6.7)	
Unresectable polyp	0 (0.0)	1 (3.3)	
0	5 (16.7)	11 (36.7)	
Is	1 (3.3)	0 (0.0)	
1	6 (20.0)	2 (6.7)	
2	7 (23.3)	3 (10.0)	
3	10 (33.3)	10 (33.3)	
4	1 (3.3)	1 (3.3)	
N Stage, *n* (%)			0.175
0	19 (63.3)	25 (83.3)	
1	10 (33.3)	5 (16.7)	
2	1 (3.3)	0 (0.0)	
M Stage, *n* (%)			1.000
0	30 (100.0)	29 (96.7)	
1	0 (0.0)	1 (3.3)	

CG control group, *FA* Flourescence angiography, *SD* standard deviation, *BMI* body mass index, *CRT* chemoradiation therapy

Table 2 Operative data

	CG $N=30$	FA $N=30$	p value
Operative time, min (SD)	347 (84)	347 (91)	0.994
Intra-op vasopressors, *n* (%)	14 (46.7)	4 (13.3)	0.005
Intra-op transfusion, *n* (%)	2 (6.7)	2 (6.7)	1.000
Distance from anal verge cm (SD)	2.9 (1.2)	2.7 (1.1)	0.488
Anastomosis type, *n* (%)			0.153
Hand-sewn	12 (40.0)	17 (58.6)	
Stapled	18 (60.0)	12 (41.4)	
Anastomosis configuration, *n* (%)			0.049
Straight	8 (26.7)	15 (51.7)	
Colonic J pouch	22 (73.3)	14 (48.3)	
Intersphincteric dissection	6 (20%)	3 (10%)	0.472
Synchronous resection, *n* (%)	1 (3.3)	5 (16.7)	0.052
taTME, *n* (%)	4 (13.3)	13 (43.3)	0.01
Conversion	1 (3.3)	0	1
Change in surgical plan based on FA	N/A	4 (13.3)	1.000

SD standard deviation, *taTME* transanal total mesorecal excision, *FA* fluorescence angiography

Table 3 Postoperative outcomes

	CG $N=30$	FA $N=30$	p value
Anastomotic leak	2 (6.7)	0 (0.0)	0.492
Pelvic fluid collection	0	2 (6.7)	0.492
Ileus	2 (6.7)	7 (23)	0.145
Urinary retention	2 (6.7)	1 (3.3)	1
Urethral injury	0	1 (3.3)	1
Superficial surgical site infection	1 (3.3)	1 (3.3)	1
Fever	1 (3.3)	1 (3.3)	1
Deep vein thrombosis	0	2 (6.7)	0.492
Myocardial infarction	1 (3.3)	0	1
Mortality	0	1 (3.3)	1

CG control group, *FA* fluorescence angiography

in three patients due to inadequate perfusion. In the first patient, there was a questionable transition point in the left colon, therefore the entire left colon was again extra-corporealized and the distal aspect was re-resected verifying healthy pink mucosa and an appropriately bleeding cut edge. The second patient had a colonic J pouch anal anastomosis, however the pouch appeared ischemic. The incision was reopened, the J pouch was resected and a straight anastomosis was constructed. This patient had an AL on postoperative day 7. In the third patient, after construction of a colonic J pouch anal anastomosis, the abdomen was re-insufflated and it was noted that the efferent limb of the colonic J pouch was ischemic. Accordingly, the surgeon opted to resect the pouch and a straight, stapled coloanal anastomosis was performed. Only one of these three patients received intraoperative vasopressors.

Two patients in the control group had an AL on postoperative day 4 and 7, while no leaks were recorded in the FA group (6.7% vs. 0%, $p=0.49$). Both leaks were diagnosed by CT scan after the patients presented with sepsis. The patients were successfully treated non-operatively with intravenous antibiotics and placement of drains via interventional radiology. Two patients in the FA group had a pelvic fluid collection on CT scan performed due to abdominal pain. The collections were drained revealing serosanguinous fluid with no evidence of extraluminal contrast extravasation and thus were not defined as ALs. One patient in the FA group who underwent taTME with transanal prostatectomy for a locally advanced T4 cancer had a postoperative urethral leak that was successfully treated conservatively.

There were no side effects or allergic reactions related to the injection of ICG. One death was recorded in the FA group on postoperative day 10 due to massive aspiration.

Discussion

This study reports the impact of FA on the operative outcomes, specifically AL and change in surgical margin, of patients with rectal cancer who underwent laparoscopic LAR with an anastomosis at 2.8 cm (average) from the anal verge. Our results show that FA changed the surgical plan in 13.3% (4/30) of patients, none of whom developed an AL, while in the historical control group, two patients developed an AL (0% vs. 6.7%, $p=0.49$).

Several retrospective case–control studies have reported similar results. Kudzus et al. reported a 16.4% change in surgical plan in 201 patients having colorectal surgery [17]. The level of anastomosis was not specified. FA reduced the risk of surgical reintervention due to AL by 4.6% (FA: 3.1% vs. control: 7.7%; $p=0.04$). Another study using FA in robotic LAR by Kim et al. [18] included 123 and 313 patients in the study and control groups, respectively. They reported a 4.6% overall reduction in the AL rate (FA: 0.8% vs. control: 5.4%, $p=0.03$) using ICG angiography. With a study design similar to ours, Boni et al. compared the operative outcomes of LAR performed by a single surgeon for rectal cancer with ($n=42$) and without ($n=38$) FA [12]. They showed a 4.7% change in surgical plan possibly accounting for the 5% overall reduction in the AL rate (FA: 0% vs. control: 5%, $p=$NS). The average height of the anastomosis from the anal verge was 6.3 cm and 7.2 cm in the FA and control groups, respectively. Contrary to these findings is a recent publication by Kin et al. including 173 patients in each arm, who had laparoscopic and open left colectomy and LAR for benign and cancer indications [19]. The authors showed no difference

in the AL rate between patients who were evaluated by FA (7.5%) and those who were not (6.4%). The average height of the anastomosis in this study was 11 cm. Eight patients (5%) had a change in the proximal resection margin after using FA, one of whom developed AL.

The PILLAR II multicenter study by Jafari et al. is the largest published prospective case series to date ($n=139$) [1]. This study included patients who had FA during left-sided colonic resection, with the anastomosis 5–15 cm from the anal verge. Importantly, this study is the only one in which FA of both serosa (laparoscopic) and mucosa (intraluminally) was performed in the same fashion, similar to our study. The reported AL rate was exceptionally low at 1.4% and FA changed the surgical plan in 11 patients (7.9%), none of whom had AL. Of note, only 25.9% of patients in this study had an anastomosis < 8 cm from the anal verge. Another prospective case series by Boni et al. included 107 patients undergoing laparoscopic right ($n=40$) and left colectomy or LAR ($n=67$) for benign and cancer indications [20]. FA led the surgeon to re-resect to a well-perfused proximal margin in four patients (3.7%), none of whom developed an AL. Only one AL was recorded after a right colectomy and was probably unrelated to ischemia. Finally, Watanabe et al. published a prospective series of 119 patients following laparoscopic and open left colectomy and LAR showing no change in the surgical plan following FA and a low AL rate of 5.9% [21].

To minimize potential bias, our study was designed to include a more homogenous cohort of patients. Patients were included only if they were laparoscopically and electively operated upon by the same surgeon (SDW). Unlike the studies presented above, in our study, patients were included only if the indication for surgery was rectal neoplasia and only if the anastomosis was recorded as up to 5 cm from the anal verge. There was a short interval period (1 month) between the historical control group and the FA group, which minimizes potential bias resulting from the surgeon's experience. Furthermore, FA was used to assess both mucosa and serosa in a standardized fashion as described in only one other study (PILLAR II). The authors find mucosal assessment with FA through the custom made rigid proctoscope as technically feasible, supplying excellent images of both the proximal and distal ends of the anastomosis, even in a very low anastomosis.

Perfusion assessment to the anastomosis is a true technical challenge, especially in the case of a low rectal cancer, as depicted by the 11.6% overall rate of change in surgical plan in the entire cohort (FA group:13.3% vs. control group:10%). Our study shows that FA resulted in a 13.3% change in surgical margin. One can surmise that had the margin not been changed because of FA, the leak rate would have been 13.3% for the FA group and 10% for the entire cohort, figures consistent with the current expected incidence.

The retrospective nature of the study has its obvious inherent limitations regarding selection bias. Another limitation is our small sample size limiting conclusions from the statistical analysis, particularly regarding the AL rate (FA-0% vs. CG-6.7%, $p=0.4$). Perhaps with a larger cohort we would have reached statistical significance. Lastly, a limitation was that on only LARS with anastomoses < 5 cm from the anal verge were included in this analysis.

Conclusions

Based on our results we conclude that FA may potentially reduce the AL rate after LAR, through safe and accurate colonic perfusion assessment. Future studies focusing on lymph node assessment and ureteric identification are currently underway and will further substantiate the importance of this tool in the surgeons' armamentarium.

Funding None.

Compliance with ethical standards

Conflict of interest Steven D. Wexner is a paid consultant for NOVADAQ and for Karl Storz Endoscopy, Medtronic, and Novodaq, and is entitled to royalty payments from Intuitive Surgical, Karl Storz Endoscopy and Medtronic. The other authors declare that they have no conflict of interest.

Ethical approval The institution's prospectively maintained institutional review board (IRB)-approved database was retrospectively queried for all patients who underwent an elective laparoscopic LAR for a rectal neoplasm with a colorectal or coloanal anastomosis < 5 cm from the anal verge between 2013 and 2016 by a single surgeon (SDW).

Informed consent For this type of study, informed consent is not required.

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