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ORIGINAL ARTICLE

Transanal total mesorectal excision for rectal cancer with indocyanine green fluorescence angiography

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Abstract

Background The aim of this study was to evaluate the impact of fluorescence angiography (FA) on any change in proximal resection margin and/or anastomotic leak (AL) following transanal total mesorectal excision (TaTME) for rectal cancer (RC).

Methods This retrospective cohort study was conducted at two centers by three senior surgeons. Both institutions' prospectively maintained Institutional Review Board-approved databases were retrospectively queried for all consecutive patients between July 2015 and May 2017 who had laparoscopic hybrid trans-abdominal total mesorectal excision (TME) and TaTME for RC with colorectal or coloanal anastomosis < 10 cm from the anal verge. All patients had intraoperative FA to assess colonic perfusion of the planned proximal resection margin before bowel transection and after construction of the anastomosis. Primary outcomes measured any changes in proximal resection margins and AL rates.

Results Fifty-four patients (31 males; mean age 63 ± 12 years) were included; 30 (55%) of whom received neoadjuvant chemoradiation. The average anastomotic height was 3.6 cm from the anal verge and 8 (14.5%) patients required intersphincteric dissection. Forty-six patients (85%) had loop ileostomy. FA led to a change in the proximal resection margin in 10 patients (18.5%), one of whom had AL on postoperative day 3 requiring diagnostic laparoscopy and loop ileostomy. A second patient, without a change in the proximal resection margin, also had an AL. The overall AL rate was 3.7%.

Conclusions FA changed the planned proximal resection margin in 18.5% of patients, possibly accounting for the relatively low AL rate. FA is imperfect, and subjective but does have the potential to improve outcomes.

Keywords Transanal total mesorectal excision · Rectal cancer · Resection margin · Indocyanine green · Fluorescence angiography · Anastomotic leak

Introduction

Low anterior resection (LAR) with total mesorectal excision (TME) was first described by Heald et al. [1] and has since become the global standard surgical treatment for rectal cancer. During the last two decades, there has been ongoing debate as to the safest oncologic approach to TME. Initial randomized controlled trials (RCTs) comparing laparoscopic to open TME have shown equivalent short- and long-term oncologic outcomes [2–5]. However, two recent RCTs failed to show oncologic non-inferiority of the laparoscopic approach when compared to open TME [6, 7]. Regardless of the surgical approach, tumors in the middle and lower third of the rectum pose a significant challenge to the surgeon, especially in patients with a deep and narrow pelvis, male gender, obesity, following neoadjuvant chemoradiation, and those with a bulky tumor. The distal transection in the deep and narrow pelvis using the currently available laparoscopic or robotic staplers can be difficult and may require multiple linear stapler firings, which may be associated with increased rates of anastomotic leak (AL) [8–15]. Furthermore, limited exposure of the correct planes may lead to lower quality TME, resulting in worse oncologic outcomes. These challenges are reflected by high conversion rates of

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16% and 11.3% for laparoscopy reported in the COLOR II and ACOSOG Z6051 trials, respectively [2, 7].

Based on these concerns, the concept of transanal TME (TaTME) utilizing a "bottom up" approach has been proposed. TaTME has potentially significant benefits compared to the laparoscopic or open transabdominal TME in achieving a clear distal resection margin, as the entire dissection is performed under direct vision which commences distal to the tumor. Moreover, it enables better exposure of the mesorectal planes exactly at the point where the traditional approach struggles to. It also often allows a natural orifice for specimen extraction and so avoids an abdominal incision. Since first reported by Sylla et al. [16], a number of publications have shown promising results regarding TME quality and high rates of sphincter preservation while achieving a clear distal resection margin, and comparable postoperative morbidity [17–20]. Penna et al. reported an early leak rate of 7.8% in a series of 1594 patients who had TaTME [21].

AL is a major concern, particularly in high-risk anastomoses (< 10 cm from the anal verge and after neoadjuvant chemoradiation, as is the case in the majority of those having TaTME). Fluorescence angiography (FA) utilizing the fluorophore indocyanine green (ICG) allows for real-time intraoperative evaluation of bowel perfusion [22, 23]. Two recent consensus conferences concluded that FA is a promising technology to use in the attempt to minimize AL in colorectal surgery [24, 25]. The purpose of this study was to evaluate the impact of FA on the operative outcomes of TaTME for rectal cancer, specifically any change in proximal resection margin and AL.

Materials and methods

This retrospective cohort study was conducted at two high-volume centers by three high-volume expert colorectal surgeons (SDW, DRS, AML). After Institutional Review Board (IRB) approval, both institutions' prospectively maintained IRB-approved databases were retrospectively queried for all consecutive patients who had a hybrid transabdominal laparoscopic low anterior resection (LAR) and TaTME for rectal cancer between July 2015 and May 2017 with a colorectal or coloanal anastomosis < 10 cm from the anal verge. Since 2015 both surgeons routinely used FA during all left sided/rectal resections, therefore FA was used in all TaTME operations. Exclusion criteria were a planned laparotomy, a redo coloanal anastomosis, an urgent or emergent operation, and/or anastomosis > 10 cm from the anal verge, or a planned abdominoperineal resection. Patients who received neoadjuvant chemoradiation were scheduled for surgery 10–12 weeks after the completion of therapy. The decision to protect the anastomosis with a diverting loop ileostomy was at the discretion of the surgeon, as was the type of anastomosis (hand-sewn vs. stapled), anastomotic configuration (colonic J pouch, side to end or straight), and the decision to perform full mobilization of the splenic flexure. All patients had preoperative cathartic and oral antibiotic bowel preparation. High ligation of the inferior mesenteric artery (IMA) and inferior mesenteric vein (IMV) were routinely performed and were defined as proximal to the left colic artery and vein, respectively.

During the surgical procedure, the PINPOINT™ Endoscopic Fluorescence Imaging System (Novadaq, Toronto, ON, Canada) was used to assess colonic perfusion at two critical steps of the operation: (1) the planned point of proximal transection, just before bowel resection, and (2) after completion of the anastomosis, when the integrity of the serosal and mucosal aspect of the completed anastomosis was assessed via proctoscopy. The dose of the ICG should be kept below 2 mg/kg [23]. In the application of bowel perfusion, it 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 water resulting in a concentration of 2.5 mg per 1 ml.

At initial assessment, the surgeon marked the planned point of proximal colonic resection with an instrument under white or visible light before imaging with FA. This step was performed after high ligation of the IMA and ligation of the 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 proposed site was selected by the surgeon's clinical judgment, after which the anesthesiologist administered a bolus of 3.5 ml of intravenous indocyanine green (ICG), followed by a 10 ml flush of sterile normal saline (NS). After 20 s, perfusion of the colon was visualized and assessed via FA and the line of demarcation between ICG fluorescence and non-fluorescence was noted and compared with the initially planned transection 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 using 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 suspected based on a combination of clinical and laboratory findings including fever, tachycardia,

peritonitis, "murky" fluid in the drain, and leukocytosis. The imaging modality used was a computed tomography scan including rectal contrast.

The primary outcome measured was any change in the previously marked proximal resection point. Such a change was considered a "positive" FA evaluation. The secondary outcome was anastomotic leak occurring within 30 days of the initial operation. Anastomotic leak was defined according to the grading system published by the International Study Group of Rectal Cancer [26, 27] 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 perianastomotic fluid collection with pus or feculent aspirate. Pelvic fluid collections that were diagnosed on computed tomography (CT) imaging and drained revealing serous or serosanguinous fluid with sterile cultures were not considered as an anastomotic leak. Post-operative complications are described using the Clavien–Dindo classification system [28]. Late anastomotic complications (> 30 days after surgery), specifically stricture, sinus, and fistula were evaluated based on digital exam, endoscopy, and gastrografin enema in patients with a protecting ileostomy before stoma reversal.

Data are presented as the mean ± standard deviation. Statistical calculations for this descriptive analysis were completed using the statistical software SPSS version 20.0 (IBM, Armonk, NY, USA).

Table 1 Patient characteristics

	FA in TaTME ($N=54$)
Age, years (SD)	63 (12)
Male gender, *n* (%)	31 (53)
Body mass index, kg/m^2 (SD)	25.7 (5)
Neo-adjuvant chemo-radiation, *n* (%)	30 (55)
Comorbidities, *n* (%)	
Ischemic heart disease	16 (29)
Hypertension	25 (46)
Diabetes	5 (9)
Chronic renal failure	2 (4)
Current smoker	5 (9)
Former smoker	0 (0)
Tumor characteristics	
T Stage, *n* (%)	
Complete response	5 (9)
1	5 (9)
2	14 (26)
3	28 (52)
4	2 (4)
N stage, *n* (%)	
0	38 (70)
1	14 (26)
2	2 (4)
M stage, *n* (%)	
0	52 (96)
1	2 (4)

FA fluorescence angiography, *TaTME* transanal total mesorectal excision

Results

Between July 2015 and May 2017, 54 consecutive patients (31 males, mean age 63 ± 12 years) underwent elective laparoscopic hybrid LAR with TaTME for rectal cancer with a colorectal or coloanal anastomosis < 10 cm from the anal verge by 3 senior surgeons at 2 hospitals; FA was employed and was feasible in all patients. Patient demographics, the use of neoadjuvant chemoradiation, comorbidities, and tumor characteristics are reported in Table 1.

Operative data are presented in Table 2. The type of anastomosis (hand-sewn 44.5% vs. stapled 55.5%) was determined based on the distance from the anal verge. A straight anastomosis was created in 26 patients (48%), a side-to-end in 20 (37%) and a colonic J pouch in 8 (15%). Eight patients (14.5%) had intersphincteric dissection and 6 patients (11%) had a synchronous resection: liver ($n=2$), prostate and seminal vesicle ($n=2$), colon ($n=1$), and small bowel ($n=1$). Transanal extraction of the specimen was feasible in 30 patients (55.5%). There was no report of marginal artery shear during transanal extraction. In patients with a bulky tumor and/or a narrow pelvis, a transabdominal extraction was performed. Most of the patients underwent a protective loop ileostomy (85%). None of the eight patients who were not diverted received neoadjuvant chemoradiation and all eight anastomoses were between 5 and 10 cm from the anal verge.

FA changed the proximal resection margin in 10 patients (18.5%). One of these 10 patients, not diverted during his initial operation, had an AL on postoperative day 3 and was taken back to the operating room for laparoscopic abdominal wash-out and loop ileostomy. Five of the ten patients with a change in the proximal resection margin were > 70 years of age, and six of them had transanal extraction. Two of the five elderly patients had hypertension, one had ischemic heart disease and two had no co-morbidities. Two patients who were not diverted and who had a change in their proximal resection margin had an uneventful postoperative course. All anastomoses were assessed after construction with FA showing excellent

Table 2 Operative data

	FA in TaTME (*N* = 54)
Operative time, minutes (SD)	250 (124)
Distance from anal verge, cm (SD)	3.6 (2)
Anastomosis type, *n* (%)	
Hand-sewn	24 (44.5)
Stapled	30 (55.5)
Anastomotic configuration, *n* (%)	
Straight	26 (48)
Side-to-end	20 (37)
Colonic J pouch	8 (15)
Intersphincteric dissection, *n* (%)	8 (14.5)
Synchronous resection, *n* (%)	6 (11)
Extraction site, *n* (%)	
Transabdominal	24 (44.5)
Transanal	30 (55.5)
Loop ileostomy, *n* (%)	46 (85)
Splenic flexure mobilization, *n* (%)	42 (77)
Conversion, *n* (%)	0
Change in proximal resection margin, *n* (%)	10 (18.5)

FA fluorescence angiography, *TaTME* Transanal total mesorectal excision

Table 3 Postoperative outcomes

	FA in TaTME (*N* = 54)
Length of stay, days (SD)	6.9 (4)
Early (30 days) complications	
Minor complications	
Grade I	0
Grade II	
Ileus	7 (13)
Urinary retention	3 (5.5)
Fever	2 (3.7)
Deep vein thrombosis	2 (3.7)
Major complications	
Grade IIIa	
Anastomotic leak	1 (1.8)
Pelvic fluid collection	2 (3.7)
Urethral leak	1 (1.8)
Grade IIIb	
Anastomotic leak	1 (1.8)
Grade IV	0
Grade V	0
Late anastomotic complication	
Stricture	3 (5.5)
Sinus	0
Fistula	0

FA fluorescence angiography, *TaTME* Transanal total mesorectal excision

perfusion to both ends of the anastomoses and therefore no surgical revision of the anastomoses was required.

Two patients presented with an AL (3.7%). The first, mentioned above, was a 49-year-old female with a T2N0 tumor who underwent a straight, stapled anastomosis 5 cm from the anal verge without a diverting loop ileostomy. This patient had a change in the proximal resection margin and, despite FA confirming adequate blood supply to the anastomosis, an AL was diagnosed on postoperative day 3. The second patient was an 87-year-old male with a T2N0 tumor who had not been treated with neoadjuvant chemoradiation. He underwent an intersphincteric dissection with construction of a hand-sewn colonic J pouch anal anastomosis 2 cm from the anal verge and a diverting loop ileostomy. The AL was clinically and radiologically diagnosed on postoperative day 4 after which it was successfully non-operatively managed with intravenous antibiotics and bowel rest. The splenic flexure was not mobilized in either of these two patients who suffered a leak because the surgeon's impression in both cases was that of a completely tension-free anastomosis. Both patients who suffered a leak had transanal specimen extraction. Two other patients were diagnosed with a pelvic fluid collection. The collections were drained under computed tomography-guidance revealing serosanguinous fluid with no evidence of extra-luminal contrast extravasation. One patient developed a urethral leak after TaTME with trans-anal prostatectomy for a locally advanced T4 cancer. He was successfully managed with conservative treatment.

Late anastomotic failures such as sinus or fistulae were not detected; 3 patients (5.5%) were found to have strictures, which were easily dilated in two cases. One of these two patients was a 49-year-old female who had a leak after her index operation. Both patients were treated with office digital dilatation. The third patient had treatment with anal dilators in the operating room. All three patients had their stomas reversed. Strictures did not recur in any of these three patients. Other postoperative complications are listed in Table 3.

Discussion

We chose to study FA specifically in TaTME because most anastomoses during TaTME are very low and therefore considered high risk for developing leaks. Furthermore, the transanal "bottom up" dissection might result in patterns of ischemia to the lower rectum that are different from the ones observed during a transabdominal TME dissection. Lastly, TaTME is a relatively new approach to TME dissection and

as such any clinical data regarding its clinical outcomes are important for the colorectal surgery community.

Transanal TME is generally offered to patients with tumors in the middle and lower third of the rectum, resulting in a low anastomosis. Indeed, in our study, the average distance of the anastomosis was 3.6 cm from the anal verge. The creation of a tension-free low colorectal or coloanal anastomosis with adequate blood supply is best undertaken after performing high ligation of IMA and IMV and by fully mobilizing the splenic flexure. However, high vessel ligation may impair blood supply to the colonic portion of the anastomosis, potentially resulting in a higher risk for AL. Trencheva et al. [29] prospectively studied the risk factors for AL in 616 patients who underwent colorectal surgery and reported that patients who had high ligation of the IMA had a 3.8-fold higher chance of AL than did patients who had undergone low ligation. High ligation was defined as proximal to the left colic artery. A possible explanation might be that in 5% of patients, the marginal artery of Drummond may be absent and in up to 43% the connection at Griffith's point in the marginal artery of Drummond may be absent or diminutive, thus leaving the splenic flexure area at significant risk for ischemia [30]. FA is used to assess bowel perfusion and therefore to help ensure adequate perfusion following "high tie" ligation. We routinely perform high ligation of the IMA and IMV in patients with rectal cancer to increase lymph node yield and for create a tension-free anastomosis. This maneuver may have led to the relatively high rate of change in the proximal resection margin we encountered (18.5%). One can assume that had the margin not been changed due to FA, the AL rate would have been higher and more consistent with the currently reported incidence of 10–15% [24–27]. Twelve patients in our study did not have splenic flexure mobilization due to the surgeon's impression of a completely tension-free anastomosis. Despite this, 2 of these 12 patients had AL, further supporting routine splenic flexure mobilization to ensure a tension-free anastomosis. In addition, these two leaks highlight the multifactorial etiology of AL. Despite this precaution the largest to date series of TaTMEs included a 7.8% rate of early anastomotic leak [21]. Thus, even with TaTME, methods to decrease AL are important.

Several studies investigating FA, particularly in LAR, have reported a slightly lower rate of change in the proximal resection margin following FA [22, 31–35]. The PILLAR II multicenter study by Jafari et al. [22] is the largest published prospective case series ($n = 139$). The study included patients who had FA during left-sided colonic resection, with anastomoses 5–15 cm from the anal verge. Only 25.9% of patients had an anastomosis < 8 cm from the anal verge. FA changed the surgical plan in 11 patients (7.9%), none of who had AL. The reported AL rate was 1.4%. In a retrospective case–control study examining FA in robotic LAR resection, Kim et al. [31] included 123 and 313 patients in the study and control groups, respectively. The average height of anastomosis was 6.4 cm from the anal verge and the authors reported a 4.6% overall reduction in the AL rate (FA: 0.8% vs. control: 5.4%, $p = 0.03$) using ICG angiography. No change in the proximal resection margin was mentioned. Boni et al. [32] compared the operative outcomes of LARs performed by a single surgeon for rectal cancer with ($n = 42$) and without ($n = 38$) FA. 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. The authors reported a 4.7% change in proximal resection margin and a 5% overall reduction in the AL rate, although this was not statistically significant. The higher rate of change in the proximal resection margin in our study compared to the studies mentioned above can be explained by the lower anastomosis (average of 3.6 cm from the anal verge), and by high-vessel ligation of both the IMA and IMV. Furthermore, 5 of the 10 patients (50%) in whom the proximal resection margin was changed were > 70 years of age. Perhaps atherosclerotic disease in the elderly provides another possible explanation for the relatively high rate of change in the proximal resection margin we encountered. These findings should be further assessed in future studies and should alert surgeons to use FA in elderly patients. Lastly, six of the ten patients with changes in the proximal resection margin based on FA had transanal extraction whereby the marginal artery can potentially shear more proximally. We tried to mitigate against shear by dividing the entire mesentery from the high ligation to the bowel wall prior to specimen extraction transanal or transabdominal.

Similar results to ours have been obtained by Jafari et al. [33] who reported on 40 patients with rectal cancer who had robotic LAR (study group: 16 vs. control group: 24). The average height of the anastomosis was 3.5 cm in the study group and 5.5 cm in the control group. The authors reported a 19% change in proximal resection margin with no reported AL, and a 12% overall reduction in AL rate (study: 6% vs. control: 18%). Kawada et al. [34] investigated the use of the PDE-neo System™ (Hamamatsu Photonics K.K, Hamamatsu, Japan) in 68 patients undergoing laparoscopic left-sided colectomy for cancer. FA altered the proximal resection margin in 30.9% of patients: > 5 mm change in the proximal resection margin in 18 patients and a change of > 50 mm in the proximal resection margin in 3 patients. Three patients with a change in resection margin developed AL.

FA is imperfect in that one of the 10 patients who had a change in the proximal resection margin based on FA suffered a leak. The methodology of FA could be improved upon, with quantitative rather than qualitative fluorescence assessment.

The retrospective nature of our study has its obvious limitations regarding selection bias. Another potential limitation of the study is that one of the authors receives royalty payments from Karl Storz Endoscopy and from Intuitive Surgical, although not for ICG fluorescence imaging, and received consulting fees from Karl Storz Endoscopy, Medtronic, Intuitive Surgical, and Novadaq. In addition, the decision to perform a protecting loop ileostomy, the type of anastomosis performed, and splenic flexure mobilization were at the discretion of the surgeon. These variations add an important selection bias, especially when focusing on AL. Despite all three surgeons being experienced and high volume rectal cancer surgeons, there still exists potential for operator bias. Another limitation was the small sample size limiting the strength of our conclusions. Lastly, the surgeons did not state in every operative report the exact length of change in proximal transection margin, hence this could not be included in the data extracted. Despite its limitations, our study is, to the best of our knowledge, the first to report outcomes of FA exclusively during TaTME.

Conclusions

Our results show that FA may change the proximal resection margin in a considerable number of patients during TaTME, potentially reducing the incidence of AL in these high-risk patients.

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Compliance with ethical standards

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

Ethical approval This retrospective study was approved by the Institutional Review Board (IRB), or equivalent, of all centers participating in this study. In addition, the data was retrieved from IRB-approved databases from all centers. IRB approval from all centers has been clearly stated in the manuscript.

Informed consent All patients at all centers were consented prior to undergoing surgery.

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