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The impact of fluorescence angiography on anastomotic leak rate following transanal total mesorectal excision for rectal cancer: a comparative study

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Abstract

Background Anastomotic leak (AL) is the most feared complication in colorectal surgery. Indocyanine green (ICG) fluorescence angiography allows for real-time intraoperative evaluation of bowel perfusion. This study aimed to assess the impact of ICG on perioperative outcomes in patients treated with transanal total mesorectal excision (TaTME) for rectal cancer.

Methods Comparative study based on a retrospective analysis of prospectively collected data, to validate the use of ICG assessment (ICGA) during TaTME (November/2011–June/2018). The primary outcome was the clinical AL rate. The secondary outcomes included modification of proximal colonic transection, anastomotic redo, additional surgical maneuvers and surgical morbidity.

Results Two hundred and eighty-four patients were included, 204 (71.8%) in non-ICG group and 80 (28.2%) in ICG group. No significant differences were found in patient and tumor features. Mean anastomotic height was 4.85 cm vs. 5.04 cm ($p=0.500$), diverting stoma was constructed in 205 patients (72.1% vs. 72.5%; $p=0.941$). Fluorescence angiography modified the surgical plan in 23 patients (28.7%). AL was diagnosed in 23 patients (11.3%) in the non-ICG group and in two patients (2.5%) in the ICG group ($p=0.020$). Postoperative intraabdominal collection was diagnosed in 19 patients (7.4% vs. 5.1%; $p=0.490$), and reintervention was needed in 24 patients (10.8% vs. 7.6%; $p=0.420$). Median length of hospital stay was 6.0 (IQR 5.0–9) vs. 4.0 (IQR 3.0–8.5) ($p=0.005$). ICGA was found as independent protective factor for AL in the multivariate analysis of the whole cohort ($n=284$) (OR 0.142; 95% CI 0.032–0.633; $p=0.010$).

Conclusion ICG fluorescence angiography modified the proximal colonic transection in more than one-quarter of patients, leading to a significant decrease of AL rate.

Keywords ICG · Colorectal surgery · TaTME · Rectal cancer · Anastomotic leak · New technologies

Anastomotic leak (AL) is the most feared complication in colorectal surgery, occurring in 7–11% of patients following restorative low anterior resection [1–8]. This complication significantly increases morbidity and mortality, leads to reoperations and radiological interventions, and has a direct impact on healthcare costs. Moreover, the risk of a permanent stoma is also increased. Besides, several studies have reported worse oncologic outcome in terms of increased local recurrence, although this remains a controversial issue [9, 10]. The most critical causes of AL are anastomotic tension, mechanical failure, and compromised perfusion. Cardiovascular disease, diabetes, smoking habit, perioperative blood transfusion and previous treatment with chemoradiotherapy are some of the causes that contribute to impaired microperfusion [5, 6, 11].

The use of indocyanine green (ICG) allows for intraoperative evaluation of bowel perfusion and is considered as a promising tool to reduce the AL rate [12, 13]. ICG is administered intravenously, and perfusion can be evaluated via fluorescence angiography. Based on the line of demarcation, a site of bowel transection is decided. Several research groups have reported that this technique may change the proximal resection margin in up to 8% of patients with rectal anastomosis, with an average AL rate of 1.4–4% [6, 14].

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The enhanced recovery provided by minimal access techniques has been a solid reason for the implementation of laparoscopy in rectal cancer surgery. However, the laparoscopic approach to the total mesorectal excision (TME) is still challenging to perform, especially in difficult cases with narrow pelvises and low tumors. Robotic TME seems to overcome this issue, although there is a global debate about its cost-effectiveness. The development of the transanal total mesorectal excision (TaTME) represents the last step forward, whose feasibility and quality has been well evaluated by different studies and international registries [15–21]. This study aimed to assess the impact of ICG on perioperative outcomes in patients treated with TaTME for rectal cancer. We hypothesized that the use of ICG fluorescence angiography would reduce the AL rate.

Methods

This was a single-center comparative study based on a retrospective analysis of prospectively collected data. The study population comprised patients with rectal cancer treated with TaTME between November 2011 and June 2018. Cohorts were based on the date when ICG assessment (ICGA) was incorporated to our routine practice: from November 2011 to February 2016 for the non-ICGA group, and from March 2016 to June 2018 for the ICGA group. The primary outcome was the early clinical AL rate (during the first 30 days after index surgery). The secondary outcomes included the modification of the proximal colonic transection rate, the need for an anastomotic redo, additional surgical maneuvers, and surgical morbidity.

Inclusion criteria were adult patients diagnosed with primary rectal cancer, undergoing elective curative TaTME with planned colorectal/coloanal anastomosis. Patients treated with abdominoperineal resection or Hartmann, pregnant or breastfeeding women, and those with non-adenocarcinoma tumors were excluded. Patients with known allergy to ICG or iodine and patients treated with iodine dyes or drugs known to interact with ICG (anticonvulsants, drugs containing bisulfite, methadone, nitrofurantoin) were not eligible. Before surgery, patients signed informed consent to participate in the study before surgery. The Institutional Review Board of the Hospital Clinic of Barcelona approved the feasibility of the trial.

Gathered data included demographic variables (age, sex, Body Mass Index (BMI), American Society of Anesthesiologists classification (ASA), tobacco or alcohol consumption, complete medical history, nutritional status), preoperative blood test, tumor characteristics (distance from the anal verge, TNM stage, neoadjuvant chemoradiotherapy), safety profile of ICG (allergic reactions, complications), surgical characteristics (level of ligation of inferior mesenteric artery (IMA), splenic flexure mobilization, level and type of anastomosis, extraction site, surgical time, stoma), 30-day morbidity, reinterventions and hospital stay. Specifically, for the ICG group, we recorded the modification of the proximal colonic transection line, which was defined as a variation in the original transection line due to deficient perfusion observed with fluorescence ICG angiography. The need for additional surgical maneuvers was also recorded, such as splenic flexure mobilization or influence in the decision of performing a protective stoma were also recorded.

Our group has described the TaTME technique in previous studies, and we refer to those manuscripts for an extensive explanation [22]. Rectal cancer was defined as a tumor with a distal margin within 15 cm of the rectum through endoscopic and/or radiological evaluation. IMA ligation proximal to the left colic vessels was labeled "high," and ligation of rectalis superior with preservation of arteria colica sinistra as "low." The decision to protect the anastomosis with a diverting stoma was at the discretion of the surgeon. Clinical AL was defined as a confirmed defect of the intestinal wall at the level of the anastomosis, which leads to intra and extraluminal communication, as proven by the following: anastomotic defect noted on digital rectal examination, or radiologic evidence of extravasation of rectal contrast that has an impact on patient management [23].

ICG assessment

The PINPOINT® Endoscopic Fluorescence Imaging System from Novadaq Technologies Inc. used at our center allows the surgeon to evaluate perfusion with visible high-definition endoscopic fluorescence (VIS) and near-infrared spectroscopy (NIR) images in real time. The PINPOINT® system includes an optimized laparoscope and camera head for VIS and NIR illumination and visualization, generating simultaneous standard high-definition white light images and real-time VIS and NIR high-definition fluorescence images. Real-time NIR fluorescence video images can be viewed in two ways: PINPOINT® image, in which the NIR fluorescence is superimposed on pseudocolor (green) on a white light image; and the SPY image, in which a black and white NIR fluorescence image is displayed. PINPOINT® is designed to connect to a high-definition monitor, and all components can be mounted in a laparoscopic tower.

The PINPOINT® was used to assess the intestinal perfusion in two critical steps of the operation: just before the proximal colonic transection, and after performing the anastomosis, evaluating the mucosa by transanal visualization. For the initial evaluation, the planned transection colonic line was marked by the surgeon, usually with electrocautery, under white light before injecting ICG. This was made after bowel mobilization, transection of the rectum, section of the inferior mesenteric vessels, mobilization of

the splenic flexure (if considered necessary) and the section of the mesocolon, once the specimen was externalized transabdominally or transanally and before the creation of the anastomosis. Following the manufacturer's instructions, a bolus of ICG of 2.5 mg/ml was administered intravenously by the anesthesiology team. The fluorescence intensity in the proximal colon was subjectively evaluated as "fluorescent" or "non-fluorescent." Colonic perfusion was assessed using the PINPOINT® system, and the line between perfused and non-perfused tissue was marked and compared with the planned initial transection point.

The anastomosis was then constructed after which an endoluminal evaluation of the anastomotic perfusion was performed with a second ICG bolus of 2.5 mg/ml. Through the transanal device placed again in the anus, the PINPOINT® endoscope was introduced. A third dose of ICG was allowed (for example, after an additional surgical maneuver such as mobilization of the splenic flexure) if the surgeon considered it necessary.

Statistical analysis

Parametric data were reported as means with standard deviation (SD), and non-parametric data were reported as medians with corresponding interquartile range (IQR). The qualitative variables were expressed as relative and absolute frequencies. To identify differences between the study groups, Student *t* test or Mann–Whitney U test were used in the continuous variables. Chi-squared test and Fisher's exact test were used in the qualitative variables. A *p* value lower or equal to 0.05 was considered to represent statistical significance for all comparisons. Univariate logistic regression was applied, after categorizing continuous variables into clinically relevant groups. Those variables with *p* value lower or equal to 0.100 were included in the multivariate logistic regression analysis. All statistical analyses were performed in the Statistical Package for Social Sciences (SPSS) of IBM Statistics, version 24 (IBM Corp., Armonk, NY, USA).

Results

During the study period, a total of 284 patients met the inclusion criteria and were analyzed (204 in the non-ICGA group and 80 in the ICGA group). No significant differences were observed in baseline characteristics, so no statistical measures to avoid allocation bias were required. Patient and tumor features are detailed in Table 1.

Operative details are noted in Table 2. All patients were operated by TaTME assisted by laparoscopy. The specimen exteriorization was performed transanally in 116 (56.9%) patients in the non-ICGA group vs. 19 (24.1%) in the ICGA group ($p < 0.001$).

Successful fluorescence images were obtained in all ICG cases, without any adverse reactions. The fluorescence angiography evaluation altered the surgical plan in 23 patients (28.7%). In 22 patients the proximal colonic transection was modified, with a mean of 2.84 cm, all before the performance of any anastomosis. In one patient the transanal assessment showed insufficient anastomotic perfusion. This led to splenic flexure mobilization and tissue perfusion improved without further measures. AL occurred in 23 cases (11.3%) in the non-ICGA group vs. two (2.5%) cases in the ICGA group ($p = 0.020$). The rest of the complications are detailed in Table 3.

Four patients (5.1%) in the ICGA group presented abdominal/pelvic abscess formation. The first patient visited the outpatient clinic 15 days after index surgery explaining pelvic pain. An abdominal CT was performed showing a perianastomotic collection, without leakage of rectal contrast or pneumoperitoneum. In the second patient, the postoperative course was complicated by abdominal bleeding which required blood transfusion. Subsequently, on postoperative day 3, the patient developed fever, and a CT scan showed small presacral collection classified as hematoma, with no contrast extravasation. The patient was treated with antibiotics and could be discharged on postoperative day 8. The other two patients were those who presented an AL.

The median hospital stay was 6.0 (IQR 5.0–9.0) days in the non-ICG group vs. 4.0 (IQR 3.0–8.5) days in the ICGA group ($p = 0.005$). The mortality rate was 1% ($n = 2$), only in the non-ICGA group, being the cause of these two deaths an acute myocardial infarction in the immediate postoperative period, and a spontaneous esophageal perforation 3 months after the surgery.

From the whole sample size of patients ($n = 284$), univariate analysis identified three variables to be associated with the risk of developing AL (Table 4): transabdominal specimen extraction (OR 2.551; 95% CI 1.031–6.317, $p = 0.043$), diverting stoma (OR 0.265; 95% CI 0.114–0.612, $p = 0.002$), and ICGA (OR 0.204; 95 CI 0.047–0.888, $p = 0.034$). The defunctioning stoma has been shown not to prevent leakages, but to reduce the consequences of an anastomotic dehiscence [24]. Therefore, it was not included in the multivariate analysis, which showed that both ICGA and transabdominal specimen extraction remained statistically significant (Table 4).

Discussion

In this study, a cohort of patients operated by TaTME with ICGA was evaluated and compared with the largest unicentric cohort of patients treated with TaTME without ICGA. AL occurred in two cases (2.5%) in the ICGA group, while in the control group occurred in 23 cases (11.3%), ($p = 0.020$). The incidence of AL might have been reduced

Table 1 Patient and tumor characteristics

	No ICG ($n=204$)	ICG ($n=80$)	p value
Mean age, years (SD)	66.6 (12.3)	68.0 (11.4)	0.591
Gender			0.392
Male	123 (60.3%)	51 (63.7%)	
Female	81 (39.7%)	29 (36.2%)	
Mean BMI, kg/m^2 (SD)	25.4 (SD 3.9)	26.1 (SD 4.1)	0.213
<20 kg/m^2	13 (6.4%)	4 (5.1%)	
20–24.9 kg/m^2	76 (37.3%)	28 (35.4%)	
25–30 kg/m^2	87 (42.6%)	35 (44.3%)	
>30 kg/m^2	28 (13.7%)	12 (15.2%)	
ASA score			0.792
I	8 (3.9%)	2 (2.5%)	
II	169 (82.8%)	65 (81.2%)	
III	26 (12.7%)	12 (15.0%)	
IV	1 (0.5%)	1 (1.2%)	
Smoking	63 (30.9%)	20 (25.0%)	0.327
Diabetes mellitus	28 (13.7%)	17 (21.2%)	0.118
Hypertension	96 (47.1%)	42 (52.5%)	0.409
Dyslipidemia	52 (25.5%)	24 (30%)	0.440
Renal disease	12 (5.9%)	4 (5%)	0.772
Chronic obstructive pulmonary disease	18 (8.8%)	6 (7.5%)	0.718
Hepatic disease	5 (2.5%)	1 (1.2%)	0.527
Vascular disease	19 (7.6%)	6 (24%)	0.627
Ischemic heart disease	37 (18.1%)	16 (20%)	0.717
Previous abdominal surgery	74 (36.3%)	23 (28.7%)	0.229
Mean height from AV, cm (SD)	8.18 (3.4)	8.79 (3.3)	0.500
Clinical T-stage			0.115
T1	8 (3.9%)	9 (11.2%)	
T2	43 (21.1%)	17 (21.2%)	
T3	135 (66.2%)	46 (57.5%)	
T4	18 (8.8%)	8 (10%)	
Clinical N-stage			0.238
N0	112 (54.9%)	48 (60%)	
N1	75 (36.8%)	22 (27.5%)	
N2	15 (7.4%)	10 (12.5%)	
Clinical M-stage			0.278
M0	186 (91.2%)	76 (95.0%)	
M1	18 (8.8%)	4 (5.0%)	
Neoadjuvant treatment	113 (55.7%)	37 (46.2%)	0.153
Chemoradiotherapy	102 (50.2%)	36 (45%)	0.427
Only chemotherapy	6 (3%)	1 (1.2%)	0.157
Only radiotherapy	5 (2.5%)	0 (0.0%)	0.405

ASA American Society of Anaesthesiologists, *BMI* Body Mass Index, *SD* standard deviation, *AV* anal verge, *MRI* magnetic resonance imaging, *SD* standard deviation

by a significant variation in the decision of where to transect the proximal colon.

The risk factors for colorectal AL have been well documented, and include preoperative variables (often not modifiable), intraoperative and postoperative. One of the essential intraoperative factors is that the edges to be anastomosed are well irrigated. ICGA is an easy-to-use, accessible and reproducible technology that allows real-time evaluation of the tissue perfusion, which visually helps the surgeon in deciding the proximal colonic transection line. This study not only demonstrated that ICGA is associated with a lower AL rate, but the absence of adverse effects validated its safety.

Table 2 Operative characteristics

	No ICG ($n=204$)	ICG ($n=80$)	p value
Type of surgery			0.646
High anterior resection	53 (26.0%)	18 (22.5%)	
Low anterior resection	113 (55.4%)	52 (65%)	
Ultra-low anterior resection	38 (18.6%)	10 (12.5%)	
Splenic flexure mobilization	70 (34.3%)	27 (33.75%)	0.983
Anastomotic technique			0.080
Stapled	160 (78.4%)	70 (87.5%)	
Manual	44 (21.6%)	10 (12.5%)	
Anastomotic configuration			0.239
End-to-end	114 (55.9%)	39 (48.8%)	
Side-to-end	84 (41.2%)	41 (51.2%)	
Mini-J	6 (3%)	0 (0%)	
Intersphincteric resection			0.087
Total	20 (9.8%)	2 (2.5%)	
Partial	17 (8.3%)	5 (6.2%)	
Mean anastomosis height from AV, cm (SD)	4.85 (2.50)	5.04 (2.01)	0.500
Specimen extraction site			< 0.001
Transanal	116 (56.9%)	19 (24.1%)	
Transabdominal	88 (43.1%)	60 (75.9%)	
Diverting ileostomy	147 (72.1%)	58 (72.5%)	0.941
Drain	199 (97.5%)	80 (100%)	0.158
Mean operative time, min (SD)	146.71 (53.15)	144.35 (44.18)	0.712
Abdominal conversion	1 (0.5%)	0 (0%)	0.530

AV anal verge, *SD* standard deviation

Table 3 Postoperative outcomes

	No ICG ($n=204$)	ICG ($n=80$)	p value
Anastomotic leakage	23 (11.3%)	2 (2.5%)	0.020
Abdominal/pelvic abscess	15 (7.4%)	4 (5.1%)	0.490
Surgical reinterventions	22 (10.8%)	6 (7.6%)	0.420
Ileus	19 (9.3%)	12 (15.2%)	0.156
Bleeding	8 (3.9%)	3 (3.8%)	0.134
Acute urinary retention	8 (3.9%)	1 (1.3%)	0.253
Surgical wound infection	1 (0.5%)	2 (2.5%)	0.133
Median length of hospital stay, days (IQR)	6.0 (5.0–9)	4.0 (3.0–8.5)	0.005
Postoperative morbidity at 30 days	80 (39.2%)	27 (34.2%)	0.433
Clavien–Dindo classification at 30 days			0.825
I	29 (14.2%)	13 (16.5%)	
II	20 (9.8%)	8 (10.1%)	
III	25 (12.3%)	6 (7.6%)	
IV	5 (2.5%)	1 (1.3%)	
V	1 (0.5%)	0 (0%)	
Hospital readmissions	27 (13.4%)	11 (14.1%)	0.872
Surgical reinterventions	22 (10.8%)	6 (7.6%)	0.420

Moreover, fluorescence images were successfully obtained in all cases. The impressive outcomes of ICGA have made that many surgeons use this technology for all colorectal anastomoses.

Table 4 Univariable and multivariable analysis for anastomotic leak in all patients ($n=284$)

	Event rate (%)	Univariate Analysis			Multivariate Analysis		
		Odds ratio	CI	*p*	Odds ratio	CI	*p*
Gender							
Male	19/173 (11.0%)	2.139	0.826–5.535	0.117	–	–	–
Female	6/110 (5.5%)	Ref					
Smoking							
Yes	9/83 (10.8%)	1.399	0.592–3.305	0.445	–	–	–
No	16/200 (8.0%)	Ref					
Diabetes mellitus							
Yes	6/45 (13.3%)	1.773	0.666–4.720	0.251	–	–	–
No	19/238 (8.0%)	Ref					
Vascular disease							
Yes	4/25 (16.0%)	2.150	0.675–6.848	0.195	–	–	–
No	21/258 (8.1%)	Ref					
ASA III–IV							
Yes	3/40 (7.5%)	0.814	0.232–2.859	0.749	–	–	–
No	22/243 (9.1%)	Ref					
BMI > 30 kg/m^2							
Yes	3/41 (7.3%)	0.786	0.224–2.755	0.707	–	–	–
No	22/241 (9.1%)	Ref					
Low rectal tumor							
Yes	4/62 (6.5%)	0.654	0.216–1.980	0.452	–	–	–
No	21/220 (9.5%)	Ref					
Neoadjuvant treatment							
Yes	11/150 (7.3%)	0.667	0.292–1.525	0.337	–	–	–
No	14/132 (10.6%)	Ref					
Abdominal conversion							
Yes	0/1 (0.0%)	0.000	–	1.000	–	–	–
No	25/282 (8.9%)	Ref					
Transabdominal extraction							
Yes	18/147 (12.2%)	2.551	1.031–6.317	**0.043**	3.596	1.424–9.083	**0.007**
No	7/135 (5.2%)	Ref					
Diverting ileostomy							
Yes	11/204 (5.4%)	0.256	0.114–0.612	**0.002**	NP	NP	NP
No	14/79 (18.7%)	Ref					
ICGA							
Yes	2/80 (2.5%)	0.204	0.047–0.888	**0.034**	0.142	0.032–0.633	**0.010**
No	23/204 (11.3%)	Ref					

Bold values are statistically significant

CI confidence interval, *NP* not performed, *ASA* American Society of Anaesthesiologists, *BMI* Body Mass Index

In the ICGA group, one of the two patients suffering an AL was a 49-year-old male, diagnosed with a rectal tumor located 9 cm from the anal verge, preoperatively staged as cT2N0M0. His BMI was 28 kg/m^2, and he was a smoker and had dyslipidemia. A low IMA ligation was performed, and an end-to-end stapled anastomosis was constructed without diverting ileostomy nor splenic flexure mobilization. The use of ICGA had led to a change in the surgical plan, modifying the colon transection line by 3 cm. The other patient was a 70-year-old male, diagnosed with a rectal tumor located 4 cm from the anal verge, preoperatively staged as cT3N2bM0 and receiving chemoradiotherapy. His BMI was 26 kg/m^2. An end-to-end manual anastomosis with a diverting stoma had been performed. The use of ICGA did not change the surgical plan.

Several groups have correlated ICG fluorescence angiography with a lower risk of leakage. Results from the PILAR II study reported an AL of 1.4% ($n=139$), with no leakages

in 11 patients (7.9%) who had a change in the surgical plan after ICGA [6]. We have confirmed this fact in a cohort of patients representative of the general community, obtaining an AL rate of 2.5%, while the rate obtained in the control group (11.3%) was similar to the one reported in the literature [25, 26]. Moreover, the observed reduction in the incidence of leakage in the ICGA group was consistent with the identification of ICGA as a protective factor in the multivariate analysis. This is of at least promising and supports the investment in this new technology.

The use of ICGA made us modify the proximal margin of resection in 27.5% patients. Kudszus et al. [10] reported a change in 14% of cases by laser fluorescence angiography. These findings were confirmed by Jafari et al. [27] using the Firefly system (Intuitive Surgical Inc), who reported a 19% change in the proximal resection margin compared to a 4.5% with visible light during low anterior robotic resections (study group: 16 vs. control group: 24), leading to decrease of AL by more than a half overall (60–65%). This suggests that conventional methods of evaluating bowel perfusion are not entirely reliable [10, 25, 28]. To date, methods such as hemorrhage, palpable pulse in the mesocolon and intestinal coloration have been used. However, these methods are based on the clinical judgment of the surgeon, which has been associated with an underestimation of the AL risk [28, 29]. Moreover, in colonic resections, the surgeon's judgment might be impaired by the deficient haptic and direct visual feedback of laparoscopic surgery. Besides, in our study, 14 of the 22 patients (63.63%) in whom the proximal resection margin was changed were older than 65, with an increased risk of atherosclerotic disease that might explain the relatively high rate of modification of the proximal colonic transection rate.

In a retrospective study, the role of ICGA was examined in patients undergoing anterior robotic resections [30]. The groups included 123 and 313 patients, and the average height of the anastomosis was 6.4 cm. An overall reduction of 4.6% in the AL rate (ICGA 0.8% vs. control: 5.4%, $p=0.03$) was reported. In another retrospective study [31], Kin et al. included 173 patients and reported that 8 patients (5%) had a change in the proximal margin resection after using ICGA, one of which presented AL. The authors did not show differences in the AL rate between patients who were evaluated by ICGA (7.5%) and those who did not (6.4%).

Kawada et al. investigated the use of the PDE-neo ™ system (Hamamatsu Photonics K.K, Hamamatsu, Japan) in 68 patients undergoing laparoscopic left hemicolectomy for cancer [32]. The use of ICGA changed the proximal resection margin in 30.9% of the patients, with a change of more than 5 mm in the proximal resection margin in 18 patients, and a change of more han 50 mm in 3 patients. In this study, 3 patients with a change in the resection margin developed AL. Mizrahi et al. recently reported a study that included 60 patients: 30 patients in the ICGA group and 30 patients in the control group undergoing laparoscopic low anterior resection for rectal neoplasia with anastomoses < 5 cm from the anal verge [33]. All patients were diverted with a loop ileostomy. ICGA led to a change in surgical plan in four patients (13.3%), none of whom suffered an AL.

In general, TaTME is offered to patients with mid and low rectal tumors, resulting in lower anastomoses compared to other approaches [34]. The preparation of a distal anastomosis without tension is more feasible after splenic flexure mobilization and high ligation of the inferior mesenteric vessels. The role of IMA ligation in the risk of leakage remains controversial. Trencheva et al. found that a high ligation of the IMA entailed 3.8 times greater probability of AL [35], which might be explained by anatomical variations in the marginal artery of Drummond and in the vascular connection in the Griffith's point [36]. However, in the ICGA group of our study, the change of proximal margin of resection in patients with high and low IMA ligation was of 25.7% and 35.7% respectively, suggesting that high ligation does not result in tissue hypoperfusion. This is consistent with the randomized trial of Fuiji et al. [37] and the HIGHLOW study [38].

The splenic flexure was mobilized in 34.3% of the patients, 70 cases in which ICGA was not used and 27 cases in patients in the ICGA group (34.3% vs. 34.2%, $p=0.983$). From those, no AL was detected in patients in whom ICGA was performed. In one patient, splenic flexure mobilization was carried out after anastomosis performance due to poor perfusion in the ICGA. Therefore, ICG might also serve as an indicator of requiring additional maneuvers that relieve tension.

The increased transanal specimen exteriorization observed in the non-ICGA group can be explained by a decrease in the use of the transanal route after having observed some cases of mesorectal damaging over time. This, together with the theoretical risk of a proximal shearing of the marginal artery during transanal extraction, has made us to reserve this specimen extraction route for selected cases with wide pelvis and small tumors. Finally, a shorter length of hospital stay was observed in the ICGA group [4.0 (IQR 3.0–8.5) vs. 6.0 (IQR 5.0–9.0) days, $p=0.005$]. This may be a consequence of the lower AL rate, as well as by the recent implementation of the Enhanced Recovery After Surgery (ERAS) protocol in our hospital .

Despite a similar defunctioning stoma rate, the decision to perform it was not protocolized but was at the discretion of the surgeon. Residual confounding might still be present, since unknown sublical leakages might have gone unnoticed. Another limitation of this study is the use of historic controls, which can increase the presence of biases due to the impossibility of blinding. However, between current patients and historical controls there have been no changes when

it comes to extracting information and in the methodology to diagnose anastomotic leakages, minimizing the detection bias. Another limitation is its observational nature and the lack of sample size calculation. However, all consecutive patients were included, limiting the possibility of inclusion bias and providing a representative TaTME cohort with clinical applicability. The fact that the same surgical team has operated all patients and all the specimens evaluated by the same pathology team increased the internal validity, and external validity should be further addressed in randomized clinical trials. Also, our unit has been performing TaTME for more than 7 years, and the results obtained may not be applicable in centers at the beginning of their learning curve. That is why multicenter registries and controlled randomized studies are needed to facilitate a safe implementation in the routine clinical practice. Finally, the pathophysiology of AL is multifactorial, and factors with probable influence on its development such as gut microbiota, nutritional status, or the use of transanal drainage might also be taken into account for their confounding potential [39].

In conclusion, this comparative study showed that ICG fluorescence angiography is feasible, safe, and associated with a lower rate of AL in patients with rectal cancer treated by TaTME. ICGA modified the proximal colonic transection in more than one-quarter of patients. Moreover, it was found to be an independent protective factor for AL in the whole cohort of patients. Further research and the development of quantitative rather than qualitative fluorescence evaluation will clarify if the outcomes can continue to improve.

Compliance with ethical standards

Disclosures Dr. Antonio M. Lacy is a consultant for Medtronic, Conmed Corporation, Olympus Medical, Touchstone International Medical Science Co. Ltd., Applied Medical, and Johnson & Johnson. Drs. Otero-Piñeiro AM, de Lacy FB, Van Laarhoven JJ, Martín-Perez B, Valverde S, Bravo R has no conflicts of interest or financial ties to disclose.

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