Anastomosis Leak: Is There Still a Place for Indocyanine Green Fluorescence Imaging in Colon-Rectal Surgery? A Retrospective, Propensity Score-Matched Cohort Study

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Abstract
Anastomotic leakage (AL) represents one of the most relevant complications of colorectal cancer surgery. The aim of this study was to evaluate the utility of intraoperative indocyanine green (ICG) fluorescence imaging in the prevention of AL during laparoscopic colorectal surgery. *Methods.* We retrospectively analyzed 272 patients who underwent rectal and left colon surgery, consecutively enrolled between 2015 and 2019. Due to the heterogeneity of our groups, a propensity score matching (PSM) was performed with a 1:1 PSM cohort. *Results.* AL occurred in 36 (13.2%) patients. One hundred seventy-seven (65%) of them underwent an intraoperatory ICG test (ICG-group), whereas 95 patients (35%) did not receive the intraoperatory ICG test (no-ICG group). AL occurred in 10.8% of ICG group patients and in 17.8% of no-ICG group patients (P = 0.07). The ICG group registered significantly less type B and type C fistulas than the no-ICG group (57.9 vs 88.2%; P = .043). After PSM, the overall AL rate was less in the ICG group than the no-ICG group (9.3% vs 16%; P = 0.058), while type B and type C fistulas occurred in 5.48% in the ICG group vs 13.70% in the no-ICG group (P = 0.09). Univariate analysis demonstrated a protective effect of intraoperative ICG imaging against AL occurrence (odds ratio (OR: 0.66)). *Conclusions.* Hypoperfusion is a well-recognized cause of AL. The ICG assessment of colic vascularization is a simple, inexpensive, and side effects free method, which can sensibly reduce both overall AL and type B and type C fistulas when routinely used.

Keywords
Anastomosis leak, indocyanine green fluorescence, colon cancer, colon rectal surgery

Background

Colorectal cancer surgery can have many postoperative complications.[1] One of the major concerns is represented by anastomotic leakage (AL) which currently ranges between 3% and 20% in different case series[1-4] and can lead to increased morbidity and mortality (from 6% to 22%).[1-6]

Many authors demonstrated that AL is a multifactorial surgical complication associated with patient-related characteristics like male gender, diabetes, body mass index (BMI), preoperative hypoalbuminemia,[7] history of cardiac ischemia,[8] and sarcopenia.[9] It is possible to recognize some cancer-related risk factors such as low rectal localization of the lesion and the neoadjuvant radiochemotherapy. Furthermore, surgical procedure risk factors such as a blood loss superior to 250 mL, the number of fires utilized in the distal rectal resections,[10,11] the operative time,[11] and the good perfusion of the anastomotic stump play a substantial role in the pathogenesis of AL.[12-14] Not least, perfusion abnormalities are some of the most important risk factors associated to AL.

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Traditionally, the vascularization of the colonic stump is subjectively evaluated by the surgeon based on the color of the bowel wall, the bleeding of the colonic stump, and pulsation of the terminal artery. However, the surgical predictivity for an anastomotic complication seems to be poor.[15] Different methods[16] were tested to obtain an objective evaluation of the colonic vascularization. Among them, the intraoperative intestinal fluorescence technology, called near infrared (NIR) fluorescence technology with indocyanine green (ICG), allows an accurate evaluation of intestinal perfusion and could reduce the risk of AL.[14,17-19]

The aim of this study was to evaluate the current role and the utility of intraoperative ICG fluorescence imaging during laparoscopic colorectal surgery in the prevention of AL.

Methods

Study Population

We consecutively enrolled and retrospectively analyzed 272 patients undergoing rectal and left colon cancer surgery, from June 2015 to November 2019, in the Department of General Surgery of the University Hospital of Trieste.

From this database, we included 177 patients operated for left colon and rectal cancers that were submitted to a laparoscopic colorectal resection with an intraperitoneal colorectal or, in the case of a mid or low rectal cancer, an extra peritoneal colorectal anastomosis.

In our study, we excluded patients operated for benign disease in which we use a different vascular approach with a low ligation of the inferior mesenteric artery; patients that were operated in urgency with a laparotomic approach and all patients that were operated with laparotomic approach for other reasons. Moreover, patients in whom the operation was converted from laparoscopic to open surgery were also excluded due to the higher risk for anastomotic fistula in these specific groups.[10]

The control group was composed of 95 consecutive patients enrolled in our prospectively colorectal database from January 2012 to May 2015. These patients were operated with the same technique, although without using ICG florescence. The same exclusion criteria were also adopted in the control group.

All patients operated for a sigmoid lesion were treated with a fiber-free diet the week before surgery and with 2 water enemas the day before surgery. The patients with rectal lesion were submitted to the same dietary regimen, and a full colonic preparation with osmotic laxative was performed. Antibiotic prophylaxis with cefazolin 2 g and metronidazole 500 mg was administered 30 minutes before surgery and was continued for the next 24 hours. All patients received prophylactic dose of low molecular weight heparin starting from the evening before surgery and extended for 4 weeks after surgery.

In patients operated for rectal cancer in whom a temporary protective ileostomy was performed, a routine contrast enema was done one month after in order to check the anastomotic integrity before ileostomy closure. If a fistula was demonstrated, a second contrast enema was performed one month later to evaluate the complete healing before the ileostomy closure.

All patients were operated by a senior physician with a high level of expertise in laparoscopic colorectal surgery or by a supervised trainee surgeon.

Surgical Method

The surgical technique consists in a 4 or 5 trocars technique, depending on the surgical difficulty and tumor localization. A high ligation of the inferior mesenteric artery was adopted in all patients, and the lowering of the splenic flexure was systematically performed to avoid an anastomotic tension. An abdominal drain was placed only in the extraperitoneal rectal resections. In patients operated before 2015, we used to systematically place a non-aspirate abdominal drain also in case of intraperitoneal rectal resections.

All patients underwent a mechanical termino-terminal or latero-terminal Knight–Griffin anastomosis or a coloanal manual anastomosis in low rectal cancer. In selected patients, with middle or low rectal cancer, advanced lesions or narrow pelvis, a double equipe transanal total mesorectal excision, was performed.

The patients in the study group were submitted to the intraoperative test with ICG. The first injection of 0.2 mg/kg of ICG in 10 mL of physiologic solution was performed when the proximal resection point was selected and marked. The time from the intravenous injection to the detection of the vascularization of the selected colonic segment was recorded. If the vascularization was considerate "inadequate" (not equal distribution of the fluorescence or the absence of the angiographic effect) or "absent," the resection point was moved to a well-vascularized zone. The maximal time to obtain a good fluorescence image was considered 60 seconds.

A second evaluation with the same quantity of ICG was done when the anastomosis was performed, in order to evaluate the proximal and distal anastomotic stump. The interval of time between the injection and the achievement of a good fluorescence image was recorded. The maximal time to obtain a good fluorescence image was considered again 60 seconds. In low rectal cancer, this second evaluation was not possible because of the low localization that does not allow the evaluation of the anastomosis.

The ICG test was performed using a laparoscopic SPIES system for a laparoscopic procedure (Karl Storz, Germany) and a full HD camera system (Karl Storz Image 1-Professional Image Enhancement System-SPIES^{tm}, Karl Storz,Germany). A xenon light source was employed (D-Light P system, Karl Storz Endoscope®), providing both visible and NIR excitation light.

Clinical Definition of AL

Ahbari et al. define AL as any loss of the anastomosis confirmed by a radiographic examination with fluid/air bubbles surrounding the anastomosis, extravasation of endoluminal contrast enema, and/or abscess at the level of anastomosis.[20-22]

According to the impact on clinical management, the severity of AL is graded based on the classification of the "International Study Group of Rectal Cancer" as: Grade A (AL results in no change in patient management), Grade B (leakages manageable without reoperation), and Grade C (AL requires reoperation).[21]

The incidence and type of AL in the ICG study group compared to the control group were assessed according to the classification of the "International Study Group of Rectal Cancer."[21]

Statistical Analysis

Calculations were performed using IBM-SPSS (SPSS Inc., Chicago, Illinois), "R" (the R Foundation for Statistical Computing; version 3.5.0) and STATA 14.2 (StataCorp, College Station, Texas). The chi-square test was calculated for discrete variables using the Fisher exact test when necessary. The Shapiro–Wilk test was applied to continuous variables to verify their normal distribution.

Markers predictive of AL were searched by means of univariable logistic regression models, testing all clinical and instrumental variables measured at enrollment. Propensity score matching (PSM) was performed using the "MatchIt" package of the R software.

Results

Characterization of Patients

The baseline characteristics of the 272 enrolled patients (69.2 ± 10.8 years of age, 58.1% men) are shown in the first column of Table 1. Patients had a good nutritional status with an average BMI of 25.7 ± 4.3 and a basal albumin of 3.4 ± 1.5 g/dL.

Globally, 38.6% of patients were treated before surgery with neoadjuvant radiation and 36.4% with neoadjuvant chemotherapy; the mean ASA (the American Society of Anesthesiologists) score was 2, and the surgical procedure duration was 219 ± 71 minutes.

The baseline characteristics of the ICG group patients (177 patients) compared to the no-ICG group patients (95 patients) are reported in Table 1 (second and third column). AL incidence occurred less in the ICG group than in the non-ICG group although without reaching a statistically significant (10.8% vs 17.8%; $P = 0.07$).

On the other hand, a statistically significant difference was observed when type B and type C fistulas were compared between the 2 groups: globally, 57.9% in the ICG group and 88.2% in the no-ICG group ($P = .043$).

Due to the heterogeneity of our groups, PSM was performed (Table 2).

A 1:1 PSM cohort including 75 patients was created for each group and the baseline characteristics, comorbidities, tumor stage, and operative setting were therefore balanced.

After the homogenization of the 2 cohorts, the AL rate resulted less in the ICG group than the no-ICG group (9.3% vs 16%, respectively; $P = 0.058$).

Taking only in consideration the clinically evident fistulas (type B and type C-Table 3), the incidence of AL in the 2 groups was 5.48% in the ICG group vs 13.70% in the no-ICG group ($P = 0.09$), see Table 4 for univariate analysis for independent predictors of AL after PSM.

A univariate analysis was performed based on the variables significantly associated with AL previously described in the literature. The ASA score (odds ratio (OR) = 1.7; 95% CI 0.5–5.7; p = 0.395) and neoadjuvant radio-chemotherapy (OR = 1.6; 95% CI 0.46–5.72; p = 0.455) were associated with AL. Conversely, the use of the intraoperative ICG imaging demonstrated a protective effect against AL (OR 0.66; 95% CI 0.3–1.46; $P = .306$).

Discussion

NIR–ICG florescence imaging has been described for benign and malignant surgical procedures with different operative approaches including robotic surgery, transanal/rectal surgery, and minimally invasive surgery.[18,23-25]

Different studies have shown a clinical benefit from using ICG fluorescence in colorectal surgery against AL.[24,25] However, most of them were case series with small sample size.[20,26]

In this single-center study, we analyzed the prevalence of AL in the left colon, sigmoid, and rectal resection, providing important knowledge for the assessment of the early risk of AL in this surgery population.

The most important findings in our study are:

1. ICG could lead to a reduction of all type of AL, and ICG is helpful to reduce clinically significant type B and type C fistulas.

Prevalence, Characterization and Prognostic Assessment of AL

Insufficient vascularization is a well-recognized important risk factor for AL. Patients with AL are classically older,

Table 1. Baseline Characteristics of the Study Population.

	Patient (n = 272)	ICG (n = 177)	No-ICG (n = 95)	*P*-value
Age (years)	69.2 ± 10.8	69.9 ± 11.2	67.9 ± 10.0	*P* = .165
Male gender (%)	(146)53.6%	(109)61.4%	(37)38.6%	*P* = .085
BMI	25.7 ± 4.3	25.6 ± 4.3	27.3 ± 3.5	*P* = .458
Albumin	3.4 ± 1.5	4.15 ± 0.32	3.97 ± .35	*P* = .0002[a]
Diabetes %	(46)17.2%	(36)20.3%	(10)10.75%	*P* = .05[a]
CRF %	(17)6.3%	(10)5.58%	(7)7.3%	*P* = .14
HF %	(38)13.9%	(31)17.5%	(7)7.53%	*P* = .03[a]
ASA > 2	(247)90.8%	(163)92.4%	(84)88.18%	*P* = .007[a]
RT pre %	(105)38.6%	(68)38.7%	(37)39.3%	*P* = .408
CT pre %[a]	(99)36.4%	(61)34.3%	(38)39.7%	*P* = .289
TNM stage				
T > 2	(186)68%	(123)69.46%	(63)66.6%	*P* = .40
N > 1	(74)27%	(53)29.9%	(21)22.1%	*P* = .45
M = 0	(250)92%	(162)91.6%	(88)92.47%	*P* = .81
AJCC stage				
0	43(16%)	24 (13.74%)	19 (20.43%)	*P* = .67
I	99 (36%)	68 (38.17%)	31 (32.26%)	
II	45 (17%)	28 (16.03%)	17 (18.28%)	
III	65 (24%)	43 (24.43%)	22 (22.58%)	
IV	20 (7%)	14 (7.63%)	6 (6.45%)	
DL < 5 cm[a]	(58)21.3%	(38)21.5%	(20)21.2%	*P* = .538
DL > 5 cm extraperitoneal	(89)32.7%	(61)34.4%	(28)29%	*P* = .232
DL > 5 cm intraperitoneal	(128)47.1%	(81)45.7%	(47)49.5%	*P* = .330
Anastomosis (KG)	(235)86%	(150)84.73%	(85)89.25%	*P* = .33
Ileostomy	(109)40%	(78)44.27%	(31)32.26%	*P* = .07
Time of surgery	219 ± 71	219.1 ± 68.3	219.2 ± 76	*P* = .459
Blood loss < 500 mL	(241)88.7%	(150)84.6%	(91)96.2%	*P* = .131
AL (fistula)	36(13.2%)	19(10.8%)	17(17.8%)	*P* = .07
Type of fistula				
A	10(28%)	8(42.1%)	2(11.7%)	*P* = .043[a]
B	16(44%)	6(31.6%)	10(58.8%)	
C	10(28%)	5(26.3%)	5(29.4%)	

Values are mean SD, percentage, or median [interquartile range].
Abbreviations: CRF = chronic renal failure; HF = heart failure; RT = radiotherapy; CT = chemotherapy; ASA = American Society of Anesthesiologists score; DL = dentate line; KG = Knight–Griffen anastomosis; AL = Anastomotic leakage; ICG = indocyanine green fluorescence; TNM = Tumor-Nodes-Metastasis classification; AJCC = American Joint Committee on Cancer staging system.
[a]Statistically significant difference between ICG and no-ICG groups.

with many comorbidities and a high expected postoperative complications, reinforcing the importance of solid strategies to reduce AL.[20,25,27]

In our study, 11.3% (20 over 177 patients in the ICG group - data not shown) of patients underwent a change in the planned anastomotic level after intraoperative hypoperfusion of the resection segments was demonstrated by using the ICG method. The colic vascularization assessment based on various intraoperative findings such as the presence of arterial pulsation near the colic wall, the color of the bowel wall, and the bleeding of the colic stump was demonstrated by Krliczek et al. to be a poor predictor of anastomotic complications.[15]

The NIR–ICG fluorescence allows a more objective evaluation of vascular perfusion.[28,29] If hypoperfusion is suspected by visual assessment, NIR–ICG fluorescence can help to confirm the adequate perfusion and therefore indicate that the resection should not be extended further.[28]

The literature review clearly shows that perfusion assessment using the NIR–ICG fluorescence is technically feasible, reproducible, and adds minimal operative time (5 minutes on average).[29]

In the PILLAR II trial, the authors confirmed the safety and the high reproducibility of the procedure, and there were no reported complications or adverse reactions to ICG.[14]

Table 2. Baseline Characteristics of the Study Population After Propensity Score Matching.

	ICG (N = 75)	No ICG (N = 75)	*P*-value post-matching	*P*-value pre-matching
Age (years)	70.79 ± 10.95	68.12 ± 10.52	*P* = .187	*P* = .165
Male gender (%)	(41)54.79%	(49)65.75%	*P* = .078	*P* = .085
Diabetes %	(11)15.07%	(9)12.33%	*P* = .63	*P* = .05
CRF %	(3)4.11%	(1)1.3%	*P* = .25	*P* = .14
HF %	(7)9.59%	(6)8.22%	*P* = .587	*P* = .03[a]
ASA > 2	(68)90.51%	(66)87.67%	*P* = .09	*P* = .007[a]
RT pre %	(29)38.36%	(26)34.25%	*P* = .61	*P* = .408
CT-pre % [a]	(26)34.25%	(22)28.77%	*P* = .68	*P* = .289
Albumin	4.09 ± .32	3.97 ± .35	*P* = .769	*P* = .0002[a]
TNM stage				
T > 2	(49)65.7%	(45)60.28%	*P* = .56	*P* = .40
N >1	(19)26%	(24)31.5%	*P* = .67	*P* = .45
M > 0	(6)8.3%	(6)8.22%	*P* = .85	*P* = .81
AJCC stage				
0	11(15.07%)	19(24.66%)	*P* = .56	*P* = .67
I	26(34.25%)	25(32.88%)		
II	17(21.92%)	11(15.07%)		
III	14(19.18%)	15(20.55%)		
IV	7(9.59%)	5(6.85%)		
DL < 5 cm[a]	(21)27.4%	(19)24.7%	*P* = .71	*P* = .538
DL > 5 cm extraperitoneal	(26)34.25%	(24)31.51%	*P* = .73	*P* = .232
DL > 5 cm intraperitoneal	(29)38.36%	(33)43.84%	*P* = .50	*P* = .330
Anastomosis (KG)	(63)83.56%	(67)89.04%	*P* = .34	*P* = .33
Time of surgery	223 (90-355)	200 (63-427)	*P* = .43	*P* = .459
AL (fistula)	7(9.3%)	12(16%)	*P* = .058	*P* = .07

Values are mean SD, percentage, or median [interquartile range].
Abbreviations: CRF = chronic renal failure; HF = heart failure; RT = radiotherapy; CT = chemotherapy; ASA = American Society of Anesthesiologists score; DL = dentate line; KG = Knight–Griffen anastomosis; AL = Anastomotic leakage; ICG = indocyanine green fluorescence; TNM = Tumor-Nodes-Metastasis classification; AJCC = American Joint Committee on Cancer staging system.
[a]Statistically significant difference between ICG and no-ICG groups.

Table 3. Clinically and Symptomatic Fistula Rate After PSM.

	ICG (n = 75)	No-ICG (n = 75)	*P*-value
No fistula/type A	71 (94.52%)	65 (86.30%)	.09
Type B and type C	4 (5.48%)	10 (13.70%)	

Abbreviation: PSM = propensity score matching; ICG = indocyanine green fluorescence.

The PILLAR II study also demonstrated a zero-tax fistula in the patient in which the site of resection has been modified based on the ICG test.

Differently, in their review of the literature, van den Bos et al.[29] find that a positive ICG test could increase the risk of development of anastomotic dehiscence in the group of patients where the planned anastomotic level was changed.

A change in the planned anastomotic level, led by ICG fluorescence imaging, was shown in several studies[25,26,30-32] with a 3.7%-19% change in intraoperative surgical decision-making, following the perfusion assessment. Hypoperfusion should, therefore, guide the surgeon toward a change in the surgical strategy. This hypothesis is supported by the observation that ICG fluorescence imaging has lowered the AL rate by 4%-12% in the control studies of published cases.[26]

Table 4. Univariate Analysis for Independent Predictors of AL After PSM

Univariate variable			
Variable	OR	CI 95%	*P*
ICG	0.66	0.30-1.46	0.306
RT pre	1.62	0.46-5.72	0.455
ASA	1.7	0.5-5.7	0.395
Time of surgery	1	0.9-1	0.02

Abbreviations: AL = Anastomic leakage; PSM = propensity score matching; CI = confidence interval; OR = odds ratio; RT = radiotherapy; ASA = American Society of Anesthesiologists score.

We can put forward the hypothesis that the changing of the resection point reduces the incidence of symptomatic fistula. This may be also due, in some cases, to the decision of performing a diverting ileostomy in a patient in which the first ICG test demonstrates an insufficient vascularization.

Kin et al. reported a retrospective case-matched study where they show controversial results on the positive effect of ICG for the development of AL in colorectal resections.[30,31] They describe that 4.6% of patients had a change in the proximal resection margin,[31] but the reduction in the AL rate was no statistically significant in comparison with the control group.[25,31]

Not least, our study confirms a reduction in clinically significant type B and type C fistulas and with an increase in Grade A fistulas both in the pre-matching group and in the post-matching group.

As described by Boni et al., the evaluation of the risk of AL had a lot of limitations and one of that is that the quality of perfusion is subjectively assessed by a surgeon.[18,25]

The surgeon might be influenced by several factors such as the timing of injection and revelation of ICG, for example, in the distance between the tip of the endoscope and the bowel, light cable quality, NIR light intensity, and patient basal and hemodynamics characteristics.[23,25]

The increase in publications on the subject of NIR–ICG fluorescence imaging clearly indicates that an increase in interest and a continuous development of this type of imaging.

A multicenter phase II trial confirms that routine use of NIR–ICG in patients undergoing colorectal surgery is feasible and could be used to safely change intraoperative decisions.[33]

These findings were recently confirmed by Arezzo and colleagues.[34] In their study, they confirm that the incidence of AL may decrease when ICG fluorescence imaging is used to assess the perfusion of a colorectal anastomosis, and the overall morbidity and reintervention rate were positively influenced by the use of ICG.[34]

There are clearly open problems regarding the quantification of color intensity in vivo during the procedure as we consider a non-standardized quantification of the perfusion color in post-surgery useless.

Standardizing signal strength is very difficult.[15] Numerous experimental studies have attempted to identify a threshold of fluorescence who could indicate a good perfusion and a standardized practice to minimizing the intra- and inter-observational variability.[17,25]

Some studies, based on the measurement of the "time to peak" of the fluorescence have demonstrate that this technique requires standard conditions, a specific designated software and, last but not least, it is very difficult to achieve in clinical practice.[17,25]

Several studies tried to quantitatively evaluate colon perfusion patterns during surgery. Previously published studies included small cohorts of patients and non-standardized assessment methods.[25,35,36] Despite the promising results, large-scale studies are needed in order to benefit from this very important revolution in the future.

Conclusion

To conclude, in this study, we try to convince surgeons to consider this technique as a standard imaging procedure in the operating room of the future due to its multidisciplinary and versatile application possibilities.

The assessment of colic vascularization with ICG is a simple, inexpensive method, with no side effects for the patient, which does not result in a significant lengthening of the operating time but could help the surgeon in evaluating the anastomotic site by giving a real-time image of the vascularization.

In the face of an almost total absence of side effects and an increase in the irrelevant cost than the cost of the treatment of complicated patients with AL, this methodology allows a more objective evaluation, albeit with some limits of a highly determining factor.

The main limitations of our study are the retrospective nature, the size of the groups, the different period of time where patients were enrolled and compared and, in particular, the single-center study.

Future multicenter studies are needed to test these results on large and randomized populations, specifically investigating a setting typically poorly represented in the large clinical trials, in order to further improve the early stratification of the AL risk that remains a big challenging issue in the management in the surgical outcome in colorectal cancer.

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Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical Approval

The institutional ethical board approved the study and the informed consent was obtained under the institutional review board policies of hospital administration.

Statement of Informed Consent

Informed consent was obtained from all individual participants included in the study.

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References

1. Kingham TP, Pachter HL. Colonic anastomotic leak: Risk factors, diagnosis, and treatment. *J Am Coll Surg*. 2009; 208(2):269-278. doi:10.1016/j.jamcollsurg.2008.10.015
2. Branagan G, Finnis D, Wessex Colorectal Cancer Audit Working Group. Prognosis after anastomotic leakage in colorectal surgery. *Dis Colon Rectum*. 2005;48(5): 1021-1026. doi:10.1007/s10350-004-0869-4
3. Mirnezami A, Mirnezami R, Chandrakumaran K, Sasapu K, Sagar P, Finan P. Increased local recurrence and reduced survival from colorectal cancer following anastomotic leak. *Ann Surg*. 2011;253(5):890-899. doi:10.1097/SLA.0b013e3182128929
4. Kang CY, Halabi WJ, Chaudhry OO, et al. Risk factors for anastomotic leakage after anterior resection for rectal cancer. *JAMA Surgery*. 2013;148(1):65-71. doi:10.1001/2013.jamasurg.2
5. Hyman N, Manchester TL, Osler T, Burns B, Cataldo PA. Anastomotic leaks after intestinal anastomosis: It's later than you think. *Ann Surg*. 2007;245(2):254-258. doi:10.1097/01.sla.0000225083.27182.85
6. Rullier E, Laurent C, Garrelon JL, Michel P, Saric J, Parneix M. Risk factors for anastomotic leakage after resection of rectal cancer. *Br J Surg*. 1998;85(3):355-358. doi:10.1046/j.1365-2168.1998.00615.x
7. Truong A, Hanna MH, Moghadamyeghaneh Z, Stamos MJ. Implications of preoperative hypoalbuminemia in colorectal surgery. *World J Gastrointest Surg*. 2016;8(5):353-362. doi:10.4240/wjgs.v8.i5.353
8. Sciuto A, Merola G, Palma GDD, et al. Predictive factors for anastomotic leakage after laparoscopic colorectal surgery. *World J Gastroenterol*. 2018;24(21):2247-2260. doi:10.3748/wjg.v24.i21.2247
9. Nakanishi R, Oki E, Sasaki S, et al. Sarcopenia is an independent predictor of complications after colorectal cancer surgery. *Surg Today*. 2018;48(2):151-157. doi:10.1007/s00595-017-1564-0
10. Park JS, Huh JW, Park YA, et al. Risk factors of anastomotic leakage and long-term survival after colorectal surgery. *Medicine*. 2016;95(8):e2890. doi:10.1097/MD.0000000000002890
11. Braunschmid T, Hartig N, Baumann L, Dauser B, Herbst F. Influence of multiple stapler firings used for rectal division on colorectal anastomotic leak rate. *Surg Endosc*. 2017; 31(12):5318-5326. doi:10.1007/s00464-017-5611-0
12. Kologlu M, Yorganci K, Renda N, Sayek I. Effect of local and remote ischemia-reperfusion injury on healing of colonic anastomoses. *Surgery*. 2000;128(1):99-104. doi:10.1067/msy.2000.107414
13. Vignali A, Gianotti L, Braga M, Radaelli G, Malvezzi L, Carlo VD. Altered microperfusion at the rectal stump is predictive for rectal anastomotic leak. *Dis Colon Rectum*. 2000;43(1):76-82.
14. Jafari MD, Wexner SD, Martz JE, et al. Perfusion assessment in laparoscopic left-sided/anterior resection (PILLAR II): A multi-institutional study. *J Am Coll Surg*. 2015;220(1):82-92. doi:10.1016/j.jamcollsurg.2014.09.015
15. Karliczek A, Harlaar NJ, Zeebregts CJ, Wiggers T, Baas PC, van Dam GM. Surgeons lack predictive accuracy for anastomotic leakage in gastrointestinal surgery. *Int J Colorectal Dis*. 2009;24(5):569-576. doi:10.1007/s00384-009-0658-6
16. Cooperman M, Martin EW Jr, Carey LC. Determination of intestinal viability by Doppler ultrasonography in venous infarction. *Ann Surg*. 1980;191(1):57-58. doi:10.1097/00000658-198001000-00011
17. Kawada K, Hasegawa S, Hida K, et al. Risk factors for anastomotic leakage after laparoscopic low anterior resection with DST anastomosis. *Surg Endosc*. 2014;28(10): 2988-2995. doi:10.1007/s00464-014-3564-0
18. Boni L, Fingerhut A, Marzorati A, Rausei S, Dionigi G, Cassinotti E. Indocyanine green fluorescence angiography during laparoscopic low anterior resection: Results of a case-matched study. *Surg Endosc*. 2017;31(4):1836-1840. doi:10.1007/s00464-016-5181-6
19. De Nardi P, Elmore U, Maggi G, et al. Intraoperative angiography with indocyanine green to assess anastomosis perfusion in patients undergoing laparoscopic colorectal resection: Results of a multicenter randomized controlled trial. *Surg Endosc*. 2020;34(1):53-60. doi:10.1007/s00464-019-06730-0
20. Mizrahi I, Wexner SD. Clinical role of fluorescence imaging in colorectal surgery-A review. *Expet Rev Med Dev*. 2017; 14(1):75-82. doi:10.1080/17434440.2017.1265444
21. Rahbari NN, Weitz J, Hohenberger W, et al. Definition and grading of anastomotic leakage following anterior resection of the rectum: A proposal by the international study group of rectal cancer. *Surgery*. 2010;147(3):339-351. doi:10.1016/j.surg.2009.10.012
22. Park JS, Choi G-S, Kim SH, et al. Multicenter analysis of risk factors for anastomotic leakage after laparoscopic rectal cancer excision. *Ann Surg*. 2013;257(4):665-671. doi:10.1097/SLA.0b013e31827b8ed9

23. Protyniak B, Dinallo AM, Boyan WP Jr, Dressner RM, Arvanitis ML. Intraoperative indocyanine green fluorescence angiography-An objective evaluation of anastomotic perfusion in colorectal surgery. *Am Surg*. 2015;81(6): 580-584.
24. Marshall MV, Rasmussen JC, Tan I-C, et al. Near-infrared fluorescence imaging in humans with indocyanine green: A review and update. *Open Surg Oncol J*. 2010;2(2):12-25. doi:10.2174/1876504101002010012
25. Boni L, David G, Dionigi G, Rausei S, Cassinotti E, Fingerhut A. Indocyanine green-enhanced fluorescence to assess bowel perfusion during laparoscopic colorectal resection. *Surg Endosc*. 2016;30(7):2736-2742. doi:10.1007/s00464-015-4540-z
26. Hellan M, Spinoglio G, Pigazzi A, Lagares-Garcia JA. The influence of fluorescence imaging on the location of bowel transection during robotic left-sided colorectal surgery. *Surg Endosc*. 2014;28(5):1695-1702. doi:10.1007/s00464-013-3377-6
27. Blanco-Colino R, Espin-Basany E. Intraoperative use of ICG fluorescence imaging to reduce the risk of anastomotic leakage in colorectal surgery: A systematic review and meta-analysis. *Tech Coloproctol*. 2018;22(1):15-23. doi:10.1007/s10151-017-1731-8
28. Kudszus S, Roesel C, Schachtrupp A, Höer JJ. Intraoperative laser fluorescence angiography in colorectal surgery: A noninvasive analysis to reduce the rate of anastomotic leakage. *Langenbeck's Arch Surg*. 2010;395(8): 1025-1030. doi:10.1007/s00423-010-0699-x
29. van den Bos J, Al-Taher M, Schols RM, van Kuijk S, Bouvy ND, Stassen LPS. Near-infrared fluorescence imaging for real-time intraoperative guidance in anastomotic colorectal surgery: A systematic review of literature. *J Laparoendosc Adv Surg Tech*. 2018;28(2):157-167. doi:10.1089/lap.2017.0231
30. Kim JC, Lee JL, Yoon YS, Alotaibi AM, Kim J. Utility of indocyanine-green fluorescent imaging during robot-assisted sphincter-saving surgery on rectal cancer patients. *Int J Med Robot Comput Assist Surg*. 2016;12(4): 710-717. doi:10.1002/rcs.1710
31. Kin C, Vo H, Welton L, Welton M. Equivocal effect of intraoperative fluorescence angiography on colorectal anastomotic leaks. *Dis Colon Rectum*. 2015;58(6):582-587. doi:10.1097/DCR.0000000000000320
32. Watanabe J, Ota M, Suwa Y, et al. Evaluation of the intestinal blood flow near the rectosigmoid junction using the indocyanine green fluorescence method in a colorectal cancer surgery. *Int J Colorectal Dis*. 2015;30(3):329-335. doi:10.1007/s00384-015-2129-6
33. Ris F, Liot E, Buchs NC, et al. Multicentre phase II trial of near-infrared imaging in elective colorectal surgery. *Br J Surg*. 2018;105(10):1359-1367. doi:10.1002/bjs.10844
34. Alberto A, Bonino MA, Ris F, et al. Intraoperative use of fluorescence with indocyanine green reduces anastomotic leak rates in rectal cancer surgery: An individual participant data analysis. *Surg Endosc*. 2020;34:4281-4290. doi:10.1007/s00464-020-07735-w
35. Boni GM, Kwon MS, Kim Y, Kim J, Kim SH, Lee JW. Quantitative analysis of colon perfusion pattern using indocyanine green (ICG) angiography in laparoscopic colorectal surgery. *Surg Endosc*. 2019;33(5):1640-1649. doi:10.1007/s00464-018-6439-y
36. Iwamoto H, Matsuda K, Hayami S, et al. Quantitative indocyanine green fluorescence imaging used to predict anastomotic leakage focused on rectal stump during laparoscopic anterior resection. *J Laparoendosc Adv Surg Tech*. 2020;30(5):542-546. doi:10.1089/lap.2019.0788