Fluorescence angiography in gastrointestinal surgery

The journey towards quantifying tissue perfusion

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Fluorescence angiography in gastrointestinal surgery

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CHAPTER 1

General introduction and thesis outline

GENERAL INTRODUCTION

The cornerstone in the treatment of most gastrointestinal cancers still remains surgical resection followed by restoration of continuity by creating an anastomosis. A feared complication is anastomotic leakage and this rate depends on the location in the digestive tract, but literature from high volume centres report rates of 10-25% after esophagectomy with gastric conduit reconstruction, and 10-20% in colorectal anastomoses (1-3).

The etiology of anastomotic leakage is complex and multifactorial as it is caused by multiple modifiable and non-modifiable risk factors, related to various patient-, tumor- and intraoperative technical characteristics. Among known risk factors are male gender, smoking status, obesity, an unfavorable microbiome, previous neoadjuvant radiotherapy, tension on, and inadequate perfusion of the anastomotic site (4, 5). Of all these factors, poor perfusion is regarded as one of the most critical aspects and is an intraoperative potentially modifiable factor, if recognized. Surgeons traditionally assessed visceral perfusion by visual inspection of tissue color, peristalsis, bleeding from cut edges, and palpation of feeding vessels. All these assessments are subjective and therefore considered not very reliable.

In addition, minimal invasive surgery, either laparoscopic or robotically-assisted, is increasingly used in the last two decades. Despite its advantages, this application also brought new challenges as it particularly makes the tactile diagnostics tools to assess perfusion even more difficult. Therefore, there is a clear unmet need for imaging modalities that facilitate the detection of true tissue perfusion in real time during the surgical procedure (6, 7). Understandably, this challenge sparked the interest in novel intraoperative visualization techniques, such as near-infrared (NIR) fluorescence imaging. Fluorescence imaging caught the attention of surgeons across all specialties to provide intraoperative enhanced reality. NIR light (650–900 nm) is favorable for intraoperative imaging compared to visible light because of its better depth penetration in tissue (up to 10 mm). Moreover, the fluorescent agents will not interfere with the standard surgical field visualization, as the human eye is unable to detect light within these NIR wavelengths.

Indocyanine Green- Fluorescence angiography (ICG-FA) is conducted by the acquisition of light corresponding to the emission spectrum of an injected fluorophore. By absorbing light from a specific wavelength, the electrons of the fluorophore are shifted to an excited state (excitation). When electrons return to their ground state, they emit energy as photons called fluorescence (emission) at a lower wavelength than the excitation. An image with high contrast is produced when the emitted light (fluorescence) is filtered from the excitation light (9, 10). ICG is currently the most widely used fluorophore to measure perfusion, as The United States Federal Drug Administration approved ICG as early as 1956 (11). ICG, which is administered intravenously adheres to plasma proteins, particularly lipoproteins, resulting in a macromolecule structure leading to little extravascular leakage. The plasma half-life of ICG is around 3-4 minutes in healthy patients (12). The combination of a fluorescent agent and imaging system can be used for multiple intraoperative applications including detection of tissue perfusion, vital structures, tumor tissue, and/or (sentinel) lymph nodes, depending on the characteristics of the agent.

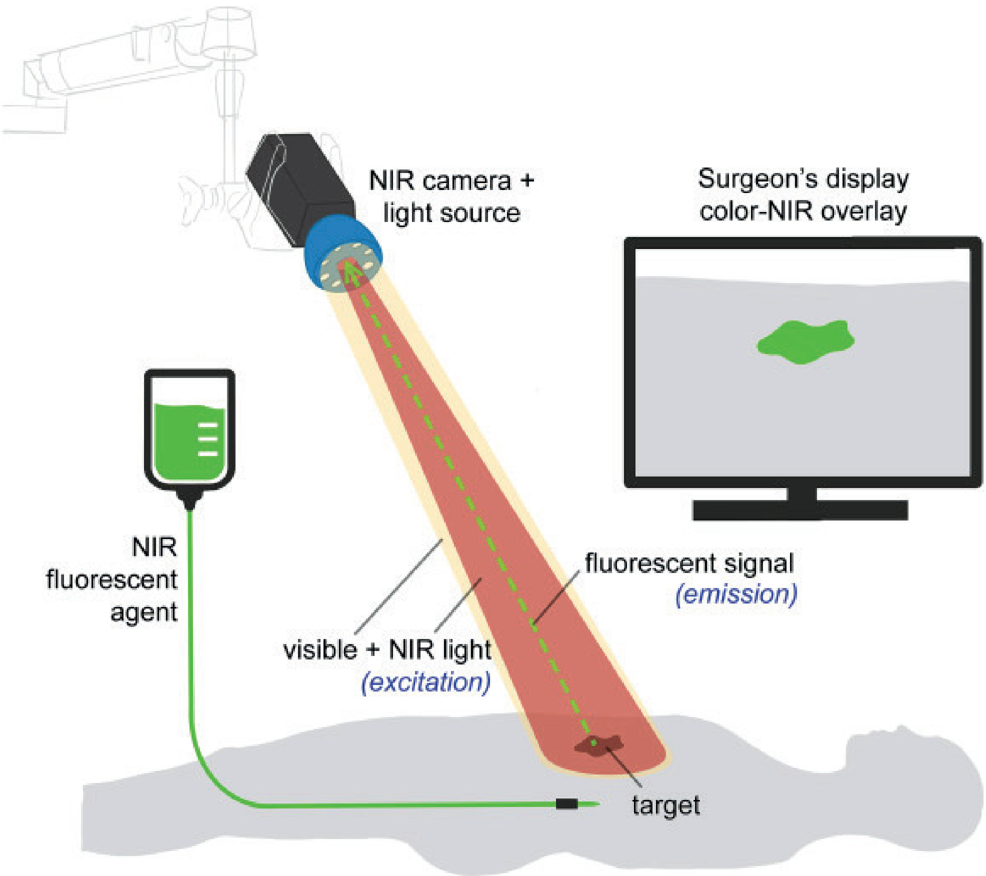

Figure 1. Schematic display of fluorescence imaging set up (8)

Since the early 2000s, ICG in combination with fluorescence imaging has been utilized in gastrointestinal surgery to assess tissue perfusion, especially in elective colorectal surgery

(6, 13). It has gained popularity as a tool in securing good perfusion of the anastomosis as a vital piece of the puzzle towards reducing anastomotic leakage(14-16). This thesis mainly focuses on the use and value of ICG-FA for this purpose.

Although randomized controlled studies are still being conducted, the available literature suggests that ICG-FA affects user's decision-making in about 5-20% of situations (13, 15). Yet, reductions in anastomotic leakage rates with ICG-FA are inconsistently shown in recent meta-analyses (17-19). However, most of these meta-analyses on ICG- FA are based on observational studies and performed with a qualitative visual assessment of the angiogram. This subjective qualitative assessment was interpreted as binary: either well perfused or non-perfused (6). When ICG- FA is interpreted subjectively, there is room for observer bias and a lack of reproducibility (20). This expresses the need for a quantitative approach to objectify the assessment. Quantitative ICG-FA is feasible and might overcome these limitations of ICG-FA interpretations (21).

The objective of this thesis is to explore the modus operandi of qualitative ICG-FA measurements at this moment and to achieve objective and reproducible ICG-FA assessments by defining a threshold for adequate perfusion in gastrointestinal surgery.

The first hypothesis is that this subjective method of angiogram interpretation is sensitive to inter-observer variation among surgeons. Thereby, there is no uniformity in the literature of applying ICG-FA, and mostly it is not performed in a standardised manner. Hereby, it is difficult to compare studies and pool these data. Our second hypothesis is that the introduction of standardization will reduce inter-user variation. Thirdly, it is hypothesized that quantification is possible and deriving a threshold to determine sufficient perfusion is feasible. In this way objectivity and reproducibility of measurements is increased. Finally, there might be a bigger role for NIR imaging to identify other structures intraoperative, for instance to visualize the urological tract during complex abdominal surgeries.

THE AIM AND OUTLINE OF THE THESIS

In this thesis, several components of fluorescence angiography in gastrointestinal surgery are addressed and steps are taken in the journey towards quantifying tissue perfusion. The main objective of this thesis is to achieve objective and reproducible ICG-FA assessments to define adequate in gastrointestinal surgery. A large body of literature has shown change of management rates with the use of ICG-FA in elective surgery, while data on the use of this technique in the acute setting is lacking. Therefore, in **chapter 2**, the impact of ICG- FA in surgical decision making in the acute setting is evaluated regarding bowel resection for intestinal ischaemia. Surgical decision making is addressed with a particular focus on the change of management and impact on outcomes in these patients.

In **chapter 3** qualitative ICG-FA use for colonic interpositions after esophagectomy is addressed in order to choose the preferred vascular pedicle of the colonic segment. Secondly, anastomotic leakage rates are compared between an historic group without ICG-FA.

The impact of qualitative assessments of ICG-FA is measured in **chapter 4**, by looking at the inter-user variability of interpretation of gastric conduit perfusion in esophageal cancer surgery is and this is compared between expert and non-expert users.

During ileal pouch- anal anastomosis (IPAA) additional lengthening measures, such as vascular ligation might be necessary to gain ileal length to make the anastomosis reach. This might affect perfusion of the pouch, in **chapter 5**, the potential value of ICG- FA is described during IPAA surgery, especially after vascular ligation.

Chapter 6 examines the derivation of quantitative parameters by investigating time until fluorescent enhancement, comparing patients with and without vascular ligation in IPAA surgery.

In **chapter 7***,* the road towards objective interpretation continues and pouch perfusion is assessed by fluorescent parameters of fluorescence time curves. Quantitative values are compared between patients with vascular ligation or intact vascular pedicles. Both inflow as outflow is examined.

In **chapter 8**, fluorescent time curves are evaluated to quantitatively assess perfusion in the gastric conduit reconstruction during esophagectomy. The derived fluorescent parameters are compared between patients with and without anastomotic leakage to determine a threshold for adequate perfusion and predict anastomotic leakage.

In **chapter 9**, illumination differences which is called the periphery-center effect of the camera are investigated among five different NIR imaging devices by a fluorescent phantom. This physical phenomenon is explored and compensated for in order to improve fluorescent angiogram interpretation and in choosing representable region of interests while quantifying the fluorescence signal.

In **chapter 10**, the incidence of iatrogenic injuries of the urinary tract is reported occurring during redo operations for chronic pelvic sepsis and the potential role for NIR imaging is considered.

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CHAPTER 2

The use of fluorescence angiography to assess bowel viability in the acute setting : an international, multi-centre case series

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Surgical Endoscopy, 2022

ABSTRACT

Introduction: Assessing bowel viability can be challenging during acute surgical procedures, especially when it comes to mesenteric ischaemia. Intraoperative fluorescence angiography (FA) may be a valuable tool for the surgeon to determine whether bowel resection is necessary, and to define the most appropriate resection margins. The aim of this study is to report on the use of FA in the acute setting and to judge its impact on intraoperative decision making.

Materials and methods: This is a multi-centre, retrospective case series of patients that underwent FA-guided emergency abdominal surgery between February 2016 and February 2021 in three colorectal units where intraoperative FA was performed to assess bowel viability. Primary endpoint was change of management after the FA assessment.

Results: A total of 93 patients (50 males, 66.6 ± 19.2 years, ASA score ≥III in 85%) were operated on in the acute setting. Surgical approach was laparotomy in 66 (71%) patients and laparoscopy in 27 (29%) of which seven (25%) were converted. The most common aetiologies were mesenteric ischaemia (n=42, 45%) and adhesional/herniae-related strangulation (n=41, 44%). In 50 patients a bowel resection was performed. Overall rates of anastomosis after resection, reoperation and 30-day mortality were 48% (24/50, one leak), 12% and 18% respectively. FA changed management in 27 (29%) patients. In four patients, resection was avoided and in 21 (23% overall) extra bowel length was preserved (median 50 cm of bowel saved, IQR 28-98) although three patients developed further ischaemia. In six (5%) patients an extended resection (median of 20cm, IQR 10-50 extra bowel) was prompted.

Conclusion: The intraoperative use of FA impacts surgical decisions regarding bowel resection for intestinal ischaemia, potentially leading to bowel preservation in approximately one out of four patients. Prospective studies are needed to optimize the best use of this technology for this indication and to determine standards for the interpretation of FA images and the potential subsequent need for second look surgeries.

INTRODUCTION

Intestinal ischaemia develops as a consequence of severe hypo-perfusion caused by a variety of reasons which, if left untreated, leads to transmural necrosis of the bowel wall followed by perforation, peritonitis, sepsis and organ failure. This cascade results in high mortality rates exceeding 60%[1-3]. Patients survival depends on prompt recognition and treatment, either adhesiolysis or revascularisation before ischemia progresses to intestinal gangrene or resection of ischaemic segments of bowel. The incidence of treatable intestinal ischemia appears to be rising, partly due to an increased awareness among clinicians but also an increasing incidence due to an aging population surviving with severe cardiovascular or systemic disease[4].

At operation, determination of adequacy of bowel perfusion is essential and, where frank ischaemia is present, judgment of resection margins is vital. Extensive resections should be carefully considered, as removal of large segments of small bowel can result in short bowel syndrome (SBS) with intestinal failure. This is associated with poor quality of life and significant morbidity that increases with age [5]. If, however, the surgical approach is too conservative, and ischaemic bowel is left in situ, further clinical deterioration may result needing re-operation and increasing the risk of death. In the acute setting, judging the most appropriate resection extent may be difficult as a wide range of variables including hemodynamic instability and vasopressor support may co-exist. Also surgeon experience may be important [6]. Although many tools for intraoperative intestinal perfusion assessment have been considered over the years [7, 8], none have become standard due to their complexity and difficulty in reproducibility as well as their cost. A straight forward and useful intraoperative test would be very helpful.

Intraoperative, real time fluorescence angiography (FA) is a promising technique that has shown value for evaluation of adequate perfusion in gastrointestinal anastomoses in the elective setting[9, 10]. Unfortunately, little is known about the application of FA in the acute setting[11]. Therefore, we aimed to report the impact of the use of FA in the acute setting on intraoperative decisions and clinical outcomes in three academic centres.

MATERIALS AND METHODS

We performed a retrospective analysis of a non-consecutive case series of all patients undergoing emergency surgery for bowel ischaemia in which FA was performed between January 2016 and February 2021 in three tertiary referral centres. This study has been approved by the medical ethical committee of the Amsterdam University Medical Centres (AUMC) – location Amsterdam Medical Centre and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Inclusion criteria were patients over 18 years old that underwent FA using indocyanine green (ICG) to assess intestinal perfusion during an emergency procedure for suspicion of bowel ischaemia. Patients were excluded when FA was performed after intestinal resection or with the sole purpose to assess perfusion of an anastomosis. Patient data with baseline characteristics, operative details and post-operative outcomes were retrospectively collected from the prospective maintained electronic patient systems of the different hospitals.

FA procedure and endpoints

All patients underwent acute surgical exploration, either via laparoscopy or laparotomy. In the case of mesenteric ischaemia, revascularization was performed prior to fluorescence assessment. In all, intestinal perfusion appeared compromised (by macroscopical colourisation of the bowel) and firstly the surgeon assessed the compromised segment of bowel by visual examination and determined a possible surgical plan; i.e. if bowel resection was necessary and if so the resection margins, subsequently FA assessment was performed by intravenous injection of a single bolus of indocyanine green (Verdye, Diagnostic Green, Aschheim-Dornach, Germany). The definitive surgical plan based on the FA was then determined and carried out. Change of management due to FA (CoM-FA) was defined as any deviation from the initial strategy determined by visual examination according to the result of the FA assessment. FA was performed with Stryker (Stryker, Kalamazoo, MI, U.S.A.) imaging systems: PINPOINT laparoscopic imaging system, SPY Portable Handheld Imager (SPY-PHI). The primary outcome was CoM-FA. Secondary outcomes included length of additional bowel resected or length of preserved bowel (in cm) after FA, number of reoperations, and mortality within 30 days. Reoperations were divided in planned (second look) and unplanned reoperations.

Statistics

All analyses were executed in IBM SPSS version 26 (IBM Corp. in Armonk, NY). The Shapiro-Wilk normality test was used to assess normal distribution. Data are expressed as mean and standard deviation (SD) for normally distributed continuous variables, median and interquartile range for non-normally distributed variables and proportions for binary variables.

This case series has been reported in line with the PROCESS Guideline[12].

RESULTS

Patient characteristics

In total, 93 patients were included in the study with a mean age of 66.6 years at time of surgery (SD 19.2) and an American Society of Anaesthesiologists (ASA) score of more than two in 85%. Of all patients, 50 (54%) were male. The patient characteristics are outlined in Table 1. The interventions were performed by 38 different surgeons with various level of surgical experience and more than half of the surgeries (n=52/93) were performed by senior surgical trainees.

Table 1. Patient characteristics

	Total	CoM- FA	No CoM-FA
Total number of patients	93	27	66
Male	50 (54%)	15 (56%)	35 (53%)
Female	43 (46%)	12 (44%)	31 (47%)
Age in years, mean ± SD	66.6 ± 19.2	64.3± 20.3	67.6± 18.8
ASA score			
I	0	0	0
II	5	2 (7%)	12 (18%)
III	53 (57%)	13 (48%)	40 (61%)
IV	26 (28%)	12 (44%)	14 (21%)
Mean BMI, (Kg/m2) ± SD	25.2 ± 5.0	25.1± 4.4	25.2 ± 5.2
Cardiovascular history	32 (34%)	10 (37%)	22 (33%)
Diabetes	22 (24%)	10 (37%)	12 (18%)

Abbreviations: CoM-FA: change of management due to fluorescence angiography, ASA: American Society of Anaesthesiology, BMI: Body Mass Index

Operation characteristics

In the majority of cases (n=66/93, 71%), a laparotomy was performed. The remainder had their surgery commenced with laparoscopy with seven then needing conversion to laparotomy. Of laparotomies, 52% (n= 34/66) were performed by consultants and 48% (n=32/66) by senior trainees and of laparoscopy 35% (n=7/20) and 65% (n=13/20) respectively. All laparoscopic procedures (n=7) which required conversion, were carried out by senior trainees. The most common underlying aetiology of the ischaemia was mesenteric ischaemia in 45% (n=42/93) of patients. In 44% (n=41/93) the ischaemia was caused by strangulation due to adhesions or internal herniation and in 4% (n=4/93) by a volvulus, the last 6% (n=6/93) concerned other causes: such as occlusive tumor and perforation. In 50 out of 93 patients, bowel resection was carried out (12 colonic, 24 small bowel and 14 both colonic and small bowel). Among them, 48% (n=24/50) had an anastomosis constructed.

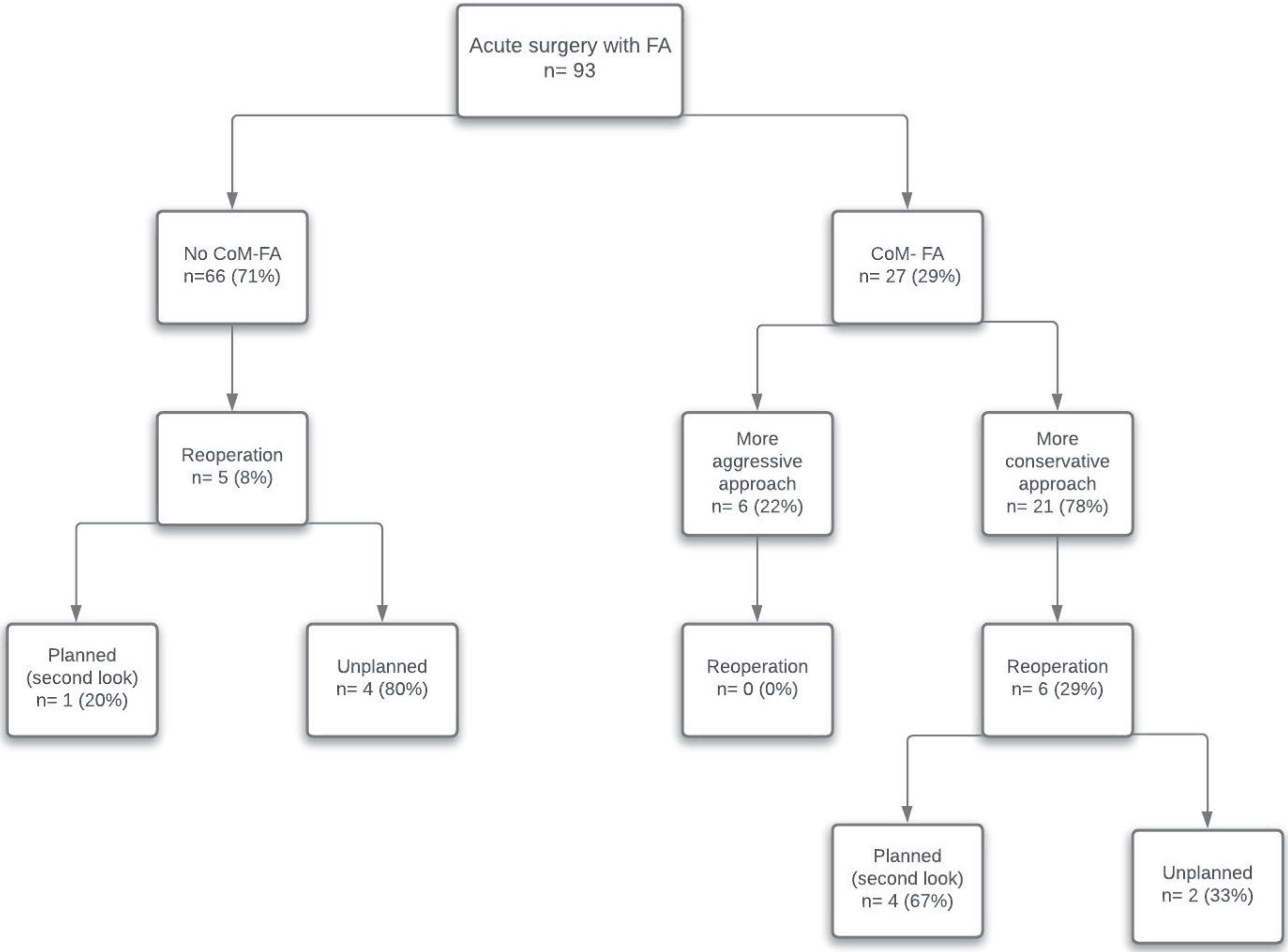

Figure 1. Represents a flowchart of all patients with and without a change of management due to FA(CoM-FA/no CoM-FA) and the reoperation rates of the groups

Change of management due to FA (CoM-FA)

FA resulted in a CoM in 29% of patients (n=27/93). CoM-FA led to either a more conservative or a more aggressive approach. The patient characteristics between the two groups are portrayed in Table 1. Change to a more conservative approach occurred in 21 patients (Figure 1 and Table 2), in four of these patients (n=4/21, 19%) resection was avoided (Figure 2) and in the remaining 17 (81%) FA led to resection of a shorter segment of bowel. In this group, CoM-FA supporting a more conservative approach, a median of 50 cm of bowel (IQR 28-98) was preserved (for more detailed overview, supplementary table 1).

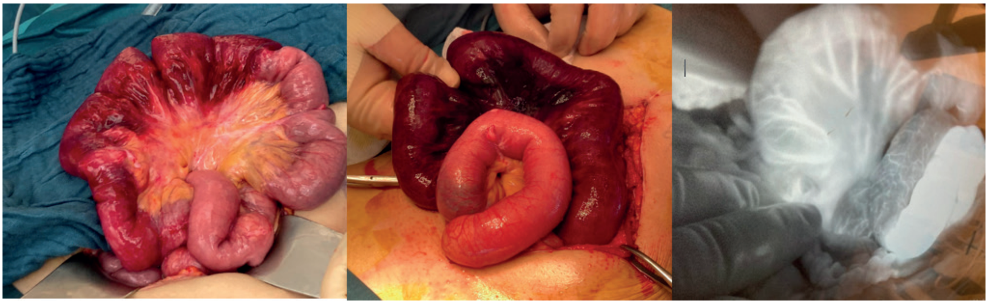

Figure 2. Represents a case in which the perfusion was compromised in visual examination. FA assessment showed clear fluorescence enhancement, no resection was carried out. The patient had an uncomplicated postoperative course.

In the CoM- FA group, FA assessment resulted in a more aggressive approach in six patients (n=6/27), leading to a median of 20 cm (IQR 10-50) of additional resected bowel. The different aetiologies among the CoM-FA groups are summarized in Table 2. The seniority of the surgeons was not decisive in the frequency of altering the surgical plan after FA; 52% of the cases in CoM-FA were by a senior surgeons versus 48% by a senior surgical trainee.

Reoperations

The overall 30 day reoperation rate was 12% (n=11) with four patients having progressive ischaemia (Table 3). In the group without a CoM-FA (n=66/93), there was a reoperation rate of 8% (n=5/66); comprising four unplanned reoperations and one planned second look. One patient in this group had further bowel ischaemia identified (one of the four unplanned reoperations). In the CoM- FA group 22% (n=6/27) of the patients had a reoperation, all concerning patients with a more conservative approach after FA. Four planned (second look) surgeries (two of whom had further bowel ischaemia needing resection) and two unplanned operations (of whom one had further ischaemia). In patients who did not undergo a resection, 5% (n=2/43) needed a reoperation because of progressive ischaemia. Reoperation rates were 20% (n=8/41) for consultants and 6% (n=3/52) for senior surgical trainees. Regarding the surgical approach, 15% (n=10/66) of laparotomies and 4% (n=1/20) of laparoscopies required reoperation. An anastomotic leak occurred in one out of 24 patients (4%) with an anastomosis with the diagnosis being made during a planned second look surgery.

Table 2. Outcomes

Outcome	No change of management	Change of management		Total
		More conservative approach	More aggressive approach	
	66 (63%)	21 (23%)	6 (6%)	93 (100%)
Aetiology ischaemia				
Mesenteric ischaemia	25 (38%)	12 (57%)	5 (83%)	42(45%)
Strangulation	32 (48%)	8 (38%)	1 (17%)	41(44%)
Volvulus	3 (5%)	1 (5%)	0	4 (4%)
Other	6 (9%)	0	0	6 (6%)
Bowel additionally preserved/resected in cm, median (IQR)	n.a.	50 (28-98)	20 (6-50)	n.a.
Reoperation rate	5 (8%)	6 (29%)	0	11 (12%)
Planned reoperations	1 (2%)	4 (19%)	0	5 (5%)
Unplanned reoperations	4 (7%)	2 (10%)	0	6 (6%)
Mortality	10 (15%)	5 (24%)	2 (33%)	17 (18%)

Mortality

In total, 17 patients died in this cohort, with an overall 30 day mortality rate of 18% (table 2). Mortality rates were 15% (n=10/66) in the no CoM-FA group, 24% (n=5/21) in the group with a more conservative approach and 33% (n=2/6) with a more aggressive approach. In 76% (n=13/17) of patients who died, the underlying aetiology was mesenteric ischaemia and in 24% (n=4/17) strangulation. Among the patients who died, 12 died due to sepsis and multi organ failure. Other causes of death were pneumonia (n=2), cardiac arrest (n=1) and liver failure (n=1), acute haemorrhage after a thrombectomy of the superior mesenteric artery (n=1). The mortality rate was higher in the laparotomy group: 23% (n=15/66), compared to the laparoscopic or conversion group (5%, n=1/20), 14% (n=1/7) respectively. Among surgeries performed by consultants mortality rates were 27% (n=11/41) compared to 12% (n=6/52) performed by senior surgical trainees.

Table 3. Reoperations specified per patient group

Patient group	Unplanned reoperation:	Planned reoperation (second look):
No CoM-FA (n=5/66)	1. Intra-abdominal bleeding query, no bleeding found 2. Intra-abdominal bleeding query, additional resection of ischaemic cecal pole 3. Intra-abdominal lavage because of infected hematoma 4. Intra-abdominal lavage because of infected hematoma	1. Restoration of bowel continuity
CoM-FA		
More conservative approach (n=6/27)	1. Evisceration and intra-peritoneal mesh placement 2. Progressive ischaemia: 30 cm additional bowel resected	1. Negative second look 2. Restoration of bowel continuity 3. Progressive ischaemia: additional resection of 50 cm small bowel 4. Progressive ischaemia: additional resection of 230 cm small bowel
More aggressive approach (n=0/6)	n.a.	n.a.

DISCUSSION

This international, multi-centre cohort study describes the use and outcomes of FA in the acute setting. Although FA has been widely implemented in the clinical setting for elective surgery, the potential added value in the acute setting has been barely studied. Among 93 operations for acute bowel ischaemia, a change of management was observed in 29%, resulting in bowel preservation in one out of five patients without a substantial increase in unplanned reoperations. The overall reoperation rate was 12%, and 30 days mortality was 18%, both of which are low compared to other published series[1-4, 13]. In half of the patients that underwent bowel resection a primary anastomosis was made. In these patients an acceptable leak rate of 4% was found.

This study also emphasizes that a median of 50 centimetre (IQR 28-98) of bowel could be spared among patients with a CoM-FA with a more conservative approach. Preserving 50 cm of small bowel or colon could make the difference in patients with extensive resections in preventing subsequent short bowel syndrome (which tends to occur when less of 100cm of functioning bowel remains)[14].

The number of CoM-FA reported in this study corresponds with two prior studies investigating the use of FA in the acute setting; in both studies FA provided additional information in

32-34.6 % of the cases [15, 16].While definitive randomized control trials are currently ongoing[17], existing literature indicates that ICG use in vascularization assessment impacts the user's decision making in the elective setting in approximately 5–15% of cases[18, 19]. It seems therefore that FA assessments alter the surgical strategy more often in the acute than in the elective setting.

In our study, there was an overall reoperation rate of 12%. This was 29% in patients in whom the CoM- FA encouraged preservation of bowel versus 8% in those in whom there was no CoM-FA. It's concerning that three patients in this group had further ischemia identified and the mortality of this group was also higher than those in whom either no change or a more aggressive approach was followed. Some of the increased reoperation rate may be due to surgeons planning a second look with a lower threshold or to perform a delayed anastomosis after a more conservative approach is conceivable. Unplanned operation rates were similar between those without CoM-FA (7%) as with those in whom CoM-FA preserved bowel (10%) and in both groups one patient was found to have progressive ischemia. Three of the four cases requiring additional resection however took place in the conservative group, indicating that FA interpretation could be misleading and might require a proper learning curve to be proficient. As acute surgery is often performed out of office hours, the surgeon on call might have less experience using FA and interpret the FA differently than a more experienced user would, it has recently been demonstrated that there is a significant inter observer variability of the interpretation of fluorescence imaging between expert and non-expert users in the elective setting[20]. Besides, in the acute setting the surgeon has to contend with hemodynamic unstable patients with vasopressor requirement, which might result in difficult to interpret fluorescence images. When preserving bowel due to FA there does seem to be a higher risk of progressive ischaemia and performing a planned reoperation (second look) at a lower threshold should be considered when preserving bowel.

The overall 30-day mortality was 18% (n=17/93) in this series. If one looks at the mortality rates within the CoM-FA groups (table 2), there is a higher mortality rate (24% in conservative group and 33% in the more aggressive approach group), compared to the no CoM-FA group (15%). This is noteworthy; however this does not necessarily mean that this is related to the change of management itself. The CoM-FA groups have a different aetiology than the no change group, i.e. a higher proportion of mesenteric ischaemia, which is associated with a higher morbidity and mortality [3, 4]. Besides, in the CoM- FA group there was a higher proportion of patients with an ASA score of IV; 44% versus 21% (table 1).

While FA seems associated with positive outcomes in the overall group, the concerns identified in this study accentuate the need for further careful research including perhaps databanking of the videos to allow understanding of the perfusion appearances and user interpretations. For instance, after reviewing FA images of patients who had progressive ischaemia during reoperation, two videos gave the impression of diffusion rather than adequate perfusion in the more conservative group and in our opinion should have been resected initially. This would also allow for training of surgeons without each having to acquire individual expert experience on the job. Furthermore quantification methods, with quantitative values that define a threshold for adequate perfusion, may help standardise interpretations. In addition, protocolised approaches are needed to be developed. From our own experience endorsed by this study, we suggest that perfusion assessment should be determined within the first minute as, even though the bowel may fluoresce later this may be falsely positive occurring due to diffusion of ICG into the tissue rather than true perfusion[21].

This study was limited by its retrospective nature. However, CoM-FA was reported in the operation reports prospectively. Yet, due to the retrospective nature of this study we could not distinguish between the different kinds of aetiology of non-adhesional and non-volvulus bowel ischaemia (i.e. whether low flow, thrombotic disease, non-occlusive mesenteric ischaemia). In addition, quantitative values such as time to fluorescence were not captured. Besides, patients were not consecutively included, which may resulted in a selection bias. There is also a lack of contemporaneous control data to give context to the clinical outcomes here reported. Prospective studies which both include quantitative fluorescence values as well as differentiate between the different manifestations of intestinal ischaemia are needed.

In conclusion, this study, the largest multi-centre case series yet, presents the use of FA in the acute setting of patients operated on because of ischaemia. Results from this study support that FA can provide useful, additional information besides visual evaluation alone on a reproducible manner. However, prospective studies are needed to optimize the best use of this technology for this indication and to determine standards for the interpretation of FA images and the potential subsequent need for second look surgeries.

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SUPPLEMENTARY MATERIAL

Supplementary table 1. Overview of the changes in bowel length preserved and additionally resected for CoM-FA groups

CoM-FA: more conservative approach			**CoM-FA: more aggressive approach**		
Patient	Specifications bowel	Amount(cm)	Patient	Specifications bowel	Amount(cm)
1.	no resection: small bowel preserved	30	1.	colon and small bowel	50
2.	small bowel	25	2.	colon and small bowel	10
3.	small bowel	60	3.	colon and small bowel	2
4.	small bowel	5	4.	small bowel	50
5.	small bowel	50	5.	small bowel	20
6.	small bowel	70	6.	small bowel	20
7.	small bowel	10			
8.	colon and small bowel	170			
9.	colon and small bowel	5			
10.	colon and small bowel	50			
11	colon and small bowel	170			
12.	small bowel	50			
13.	small bowel	95			
14.	small bowel	50			
15.	small bowel	100			
16.	small bowel	40			
17.	small bowel	200			
18.	colon and small bowel	100			
19.	no resection: small bowel preserved	70			
20.	no resection: small bowel preserved	20			
21.	no resection: small bowel preserved	50			

CHAPTER 3

The role of fluorescence angiography in colonic interposition after esophagectomy

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ABSTRACT

Background: Colonic interposition is an alternative for gastric conduit reconstruction after esophagectomy. Anastomotic leakage(AL) occurs in 15-25% of patients and may be attributed to reduced blood supply after vascular ligation. Indocyanine green fluorescence angiography(ICG-FA) can visualize tissue perfusion. We aimed to give an overview of the first experiences of ICG-FA and AL rate in colonic interposition.

Methods: This study included all consecutive patients who underwent a colonic interposition between January 2015-December 2021 at a tertiary referral centre. Surgery was performed for the following indications: inability to use the stomach because of previous surgery or extensive tumor involvement, cancer recurrence in the gastric conduit, or because of complications after initial esophagectomy. Since 2018 ICG-FA was performed prior to anastomotic reconstruction by administration of ICG injection(0.1 mg/kg/bolus), using the Spy-phi(Stryker, Kalamazoo, MI, U.S.A.).

Results: 28 patients (nine female, mean age 62.8), underwent colonic interposition of whom 15(54%) underwent ICG-FA guided surgery. Within the ICG-FA group three (20%) AL occurred, whereas in the non-ICG-FA group three AL and one graft necrosis(31%) occurred (p=0.67). There was a change of management due to the FA assessment in three patients in the FA group(20%) which led to the choice of a different bowel segment for the anastomosis. Mean operative times in the ICG-FA and non-ICG-FA groups were 372±99 and 399±113 minutes, respectively(p=0.85).

Conclusions: ICG-FA is a safe, easy and feasible technique to assess perfusion of colonic interpositions. ICG-FA is of added value leading to a change in management in a considerable percentage of patients. Its role in prevention of AL remains to be elucidated.

INTRODUCTION

Surgical resection of the esophagus combined with a lymph node dissection is the cornerstone of esophageal cancer treatment (1-3). Restoration of continuity is generally achieved by the formation of a gastric conduit (4). The stomach is preferred because of its blood supply: due to the existence of abundant vascular anastomoses between the right and left gastric and gastroepiploic arteries, even after transection of the left gastric and left gastro-epiploic vessels, blood supply to the fundus remains substantial. Furthermore, the stomach has the ability to reach the neck to allow for a tension-free anastomosis and a gastric conduit is a less extensive operation with less anatomical changes compared to a colonic interposition(5).

However, in certain circumstances (i.e. extensive tumor involvement of the stomach, loss, after gastrectomy) ;the stomach cannot be used as a conduit, in these cases a colonic interposition is the alternative of choice (6, 7).

Despite improvements in surgical technique, perioperative care and technology, the morbidity rate in colonic interpositions remains high at 60% (8, 9). Graft necrosis, anastomotic leakage (AL) and anastomotic strictures are reported in 10-30% of patients (9). The high morbidity rate is attributed to the complexity of the operation, longer operating times and the additional anastomoses

Adequate perfusion of the conduit and anastomosis is an important condition for establishing a viable anastomosis (10). Indocyanine green fluorescence angiography (ICG-FA) is a technique that is able to assess perfusion real-time and is proven a safe tool to show perfusion margins. Its added value in esophageal and colorectal anastomosis assessment in the elective setting is widely investigated and recognized (11, 12).

However, data regarding its feasibility and application during colonic interpositions is limited to case reports (13-15). In addition, to our knowledge no one has reported the utility or first experiences of ICG-FA for colonic interpositions in a case series. The aim of this study is to describe the use of ICG-FA in this patient group and postoperative anastomotic outcomes.

METHODS

This is a cohort study of all consecutive patients who underwent colonic interposition at Amsterdam UMC from January 2015 until December 2021. Clinical data of consenting patients were prospectively collected in an electronic patient system.

Colonic interposition was performed as a primary or secondary reconstruction for a number of indications: 1) inability to use the stomach as a result of a previous gastric resection or 2) extensive tumor involvement of both stomach and esophagus, 3) oncologic recurrence in the gastric conduit requiring resection or 4) complications after initial esophagectomy with reconstruction failure and resection of the gastric conduit (i.e. ischaemia/necrosis). In patients with a secondary reconstruction after several months, the colonic interposition was placed anteriorly in the mediastinum (retrosternally).

From the beginning of 2018, ICG-FA was implemented as standard procedure; patients after this time underwent ICG-FA guided surgery.

Surgical procedure and formation of colonic interposition

In preparation to the surgery, patients were given a mechanical bowel preparation 24-48 hours before the operation. In all patients, the right hemicolon was used, including the terminal ileum for an isoperistaltic interposition. After midline laparotomy, the omentum was dissected (if still present) and the right hemicolon was mobilized. The definitive choice of the colonic segment relied on the intraoperative evaluation of the efficiency of the right colic artery or right branch of the middle colic artery, after sequential clamping of the ileocolic artery and the arcade at dissection level of the ileum during a 30 minute clamping test with bulldog clamps. The vascular pedicles of the right colic artery and the ileocolic artery were dissected up to their origin to preserve all proximal vascular anastomoses between the main pedicles. The viability was assessed anticipating on the general aspect of the bowel and the absence of venous congestion. Other cues such as peristalsis, bleeding at the resection line and palpation of the vascular pedicle were taken into account. In the ICG-FA group, additional assessment of viability was done by using ICG-FA. When the right hemicolon was judged as viable for the use of interposition, the ileocolic artery was ligated. The colonic interposition was then pulled up to the neck through the posterior mediastinum in primary surgery or retrosternally in secondary surgery; when both these routes were not available, for example after prior sternotomy, a subcutaneous tunnel was used. In order to obtain sufficient reach, the colon was fully mobilized, no additional maneuvers (for instance manubrium resection) were standardly carried out. The cervical anastomosis was manually constructed between the esophagus and preferably the terminal ileum and otherwise the colon, in an end-to-end manner using a two layered technique (in esophago-colonic anastomosis only part of the cross stapling was opened to ensure similar diameter). Further continuity was performed by a colo-jejunal anastomosis, with a Roux-Y limb, and an ileo- colonic anastomosis. Finally, the mesenteric defects were closed and a feeding jejunostomy was created. Patients were postoperatively fed by parenteral nutrition until bowel movement, then tube feeding via the jejunostomy and oral diet were gradually introduced. A nasogastric tube was placed in the colonic interposition intraoperatively to decompress the colonic interposition in the early postoperative period.

ICG-FA and endpoints

ICG-FA was performed with Stryker (Stryker, Kalamazoo, MI, U.S.A.) imaging system: SPY Portable Handheld Imager (SPY-PHI). To create vascular contrast, a single bolus of indocyanine green (Verdye, Diagnostic Green, Aschleim) was administered intravenously. The ICG-FA video was evaluated in real time on a high-resolution monitor. Perfusion at the initially planned anastomotic site was judged adequate after 'white light' assessment in all patients. Decision making upon FA was based on the subjective interpretation (without the use of quantification of the fluorescent signal) of the images by the surgeon. All assessments were interpreted by the same surgeon (MvBH).

The primary endpoint was feasibility of ICG-FA in colonic interpositions. Other endpoints were the the occurrence of postoperative anastomotic complications in the ICG-FA group versus the non ICG-FA group, reoperations and mortality within 90 days and change of management due to the FA. Postoperative anastomotic complications included cervical AL, graft necrosis and anastomotic stricture. Only cervical anastomotic leakages are impacted by FA assessments. Cervical AL and graft necrosis were defined according to the Esophagectomy Complications Consensus Group classification and reinterventions were classified according to the Clavien–Dindo (CD) score (16) (17). Clinically relevant benign strictures were defined as a score for dysphagia $\geq$2 and treatment by $\geq$1 dilatation. Change of management was defined as any deviation from the initial strategy, according to the result of the FA test.

Statistics

Categorical data are presented as number of cases and percentages, whilst continuous data are shown as either mean ± standard deviation or as median and interquartile range (IQR), depending on data distribution. Length of stay in days between patients with or without ICG-FA was compared using the Mann–Whitney U test. Categorical variables were compared using a χ^2 test. A P-value $\leq$0.05 was considered statistically significant. Data were analysed using the Statistical Package for Social Sciences (SPSS) of IBM Statistics (IBM Corp., Armonk, NY, USA), version 26.0.

RESULTS

Patient characteristics

In total, 28 patients were included in this study with a mean age of 62.8 +9.9 years at time of the colonic interposition surgery. Nine patients (32%) were female. Patient characteristics are outlined in Table 1. Most patients (78%) underwent a secondary colonic interposition. The indications of the colonic interpositions are summarized in Table 2A and 2B.

Table 1. Patient characteristics

	ICG- FA (n=15)	no ICG-FA (n=13)	Total (n=28)
Sex, female	5 (33)	4 (31)	9 (32)
Age in years, mean +SD	64.5+10.8	60.9+ 8.8	62.8+9.9
BMI(kg/m2) mean +SD	25.6+3.5	23.5+ 5.2	24.6+4.4
ASA classification			
>2	7 (48)	2 (15)	9 (32)
Smoker			
Active	3 (20)	1 (8)	4 (14)
Stopped (<10jr)	7 (47)	8 (62)	15 (54)
No*	5 (33)	4 (31)	9 (32)
Pulmonary history	2 (13)	0	2 (7)
Cardiovascular history	4 (27)	2 (15)	6 (21)
Diabetes Mellitus	3 (20)	0	3 (11)

Data shown in n (%) unless otherwise stated, * or stopped > 10 years ago. Vascular comorbidity: brain infarction, myocardial infarction, or peripheral vascular disease. Pulmonary comorbidity: asthma or COPD Abbreviations: ASA: American Society of Anaesthesiology, BMI: Body Mass Index, SD: standard deviation

Operation characteristics

More than half of the patients underwent intraoperative ICG-FA (54%). In all but one patient (96%), the ascending colon (right coloplasty) was used as interposition segment; in the remaining patient, the transverse colon with the left branch of the middle colic artery as vascular pedicle was used as colonic segment. The right colonic segment was mainly pedicled on the right branch of the middle colic artery. However in one patient there was not sufficient reach to obtain an anastomosis and subsequently the right branch of the middle colic artery was ligated to obtain a tension free anastomosis.

The interposition was positioned retrosternally in the anterior mediastinum in 17 patients (61%), in the posterior mediastinum in 10 patients (36%) and subcutaneously in 1 (4%) patient. Mean operative time was 385+100 minutes; in the ICG-FA group and the non ICG-FA group this was 372± 99 and 399± 113 minutes, respectively (p=0.85). Median intraoperative blood loss was 400 mL (IQR 300-500) in the ICG-FA group and 435 mL (IQR 263 –875) in the non ICG-FA group.

Table 2a Patient characteristics of Non FA guided colonic interposition

Non FA guided- primary coloplasty						
Patient	**Histology**	**Tumor location**	**Reason for coloplasty**	**Neoadjuvant treatment †**	**ypT**	**ypN**
1	AC	Distal esophagus	Tumor invasion into cardia	Yes, CRT	3	1
2	AC	Cardia	Tumor invasion into esophagus	Yes, CT	2	0
3	AC	Distal esophagus	Previous bariatric surgery	Yes, CRT	3	0
4	AC	Cardia	Tumor invasion into esophagus	Yes, CT	3	1
Non FA guided- secondary coloplasty						
Patient	**Histology**	**Initial procedure**	**Reason for coloplasty**	**Neoadjuvant treatment †**	**(y) pT**	**(y) pN**
5	AC	MI Ivor Lewis	Restoration of continuity	No	-	-
6	Carcinosarcoma	Acute THE without reconstruction due to perforation pT4aN3 tumor	Restoration of continuity	No	-	-
7	AC	Open Ivor Lewis for esophageal benign stenosis	Primary tumor in gastric conduit	Yes, CRT	2	0
8	AC	Open Ivor Lewis	Recurrence in gastric conduit	Yes, CRT	3	0
9	AC	MI McKeown	Restoration of continuity	No	-	-
10	AC	Total gastrectomy	Recurrence esophagojejunostomy	No	3	2
11	AC	Open Ivor Lewis for achalasia	Primary tumor in gastric conduit	Yes, CRT	2	0
12	SCC	MI McKeown	Restoration of continuity	No	-	-
13	AC	MI Ivor Lewis	Restoration of continuity	No	-	-

ICG-FA

ICG-FA was performed successfully in all patients with the intention on using fluorescence imaging (Figure 1 and 2), without any adverse events following ICG administration. Perfusion of the colonic interposition at the initially planned anastomotic site was judged adequate after 'white light' assessment in all patients.

Table 2B. Patient characteristics of ICG FA guided colonic interposition

FA guided primary coloplasty						
Patient	**Histology**	**Location**	**Reason for coloplasty**	**Neoadjuvant treatment †**	**(y) pT**	**(y) pN**
14	AC	Cardia	Tumor invasion into esophagus	No	4a	3b
15	AC	Distal esophagus	Previous gastric surgery	Yes, CRT	0	0
FA guided secondary coloplasty						
Patient	**Histology**	**Initial procedure**	**Reason for coloplasty**	**Neoadjuvant treatment †**	**(y) pT**	**(y) pN**
16	AC	Open Ivor Lewis	Restoration of continuity	No	-	-
17	AC	Open Ivor Lewis because of erosion of esophagus by etchant	Primary tumor in gastric conduit	Yes, CRT	0	0
FA guided secondary coloplasty						
Patient	**Histology**	**Initial procedure**	**Reason for coloplasty**	**Neoadjuvant treatment †**	**(y) pT**	**(y) pN**
18	AC	MI Ivor Lewis	Restoration of continuity	No	-	-
19	AC	MI McKeown	Restoration of continuity	No	-	-
20	AC	MI McKeown	Restoration of continuity	No	-	-
21	AC	MI McKeown	Restoration of continuity	No	-	-
22	AC	MI McKeown	Restoration of continuity	No	-	-
23	-	Open proximal gastrectomy for incarcerated hernia diaphragmatica	Restoration of continuity	No	-	-
24	SCC	Open Ivor Lewis	Restoration of continuity	No	-	-
25	SCC	MI McKeown	Restoration of continuity	No	-	-
26	AC	Total gastrectomy	Recurrence of tumor esophagus	Yes, CT	3	0
27	AC	MI McKeown	Restoration of continuity	No		
28	Diffuse gastric AC	MI Ivor Lewis	Diffuse gastric tumor in gastric conduit	No	3	2

†This includes neoadjuvant treatment before the colonic interposition procedure
Abbreviations: AC: adenocarcinoma, SCC: squamous cell carcinoma, MI: minimal invasive, GEJ: gastroesophageal junction, CT: chemotherapy, CRT: chemoradiotherapy, THE: transhiatal esophagectomy

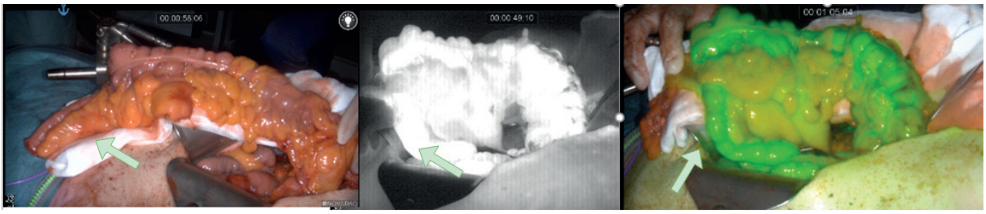

Figure 1. This figure represents a patient with clear fluorescence enhancement on the planned anastomotic site of the colonic segment after clamping, before ligation. Right hemicolon and terminal ileum used for isoperistaltic colonic interposition. Green arrow marks the proximal anastomotic site.

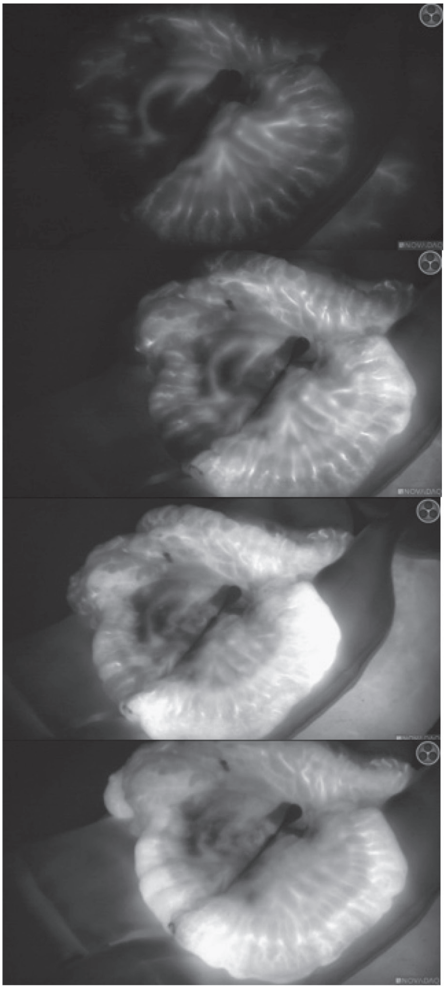

Figure 2. This figure represents a patient with clear fluorescence enhancement of the right hemicolon (terminal ileum not visible) after clamping, before ligation. The images show fluorescent enhancement after 20, 25, 30 and 50 seconds after ICG administration.

Based on the FA, a change of management was opted in three patients (20%). This change of management (Figure 3) consisted of additionally resecting 5-10 cm length of the ileum in two patients and in one patient using the ascending colon for the anastomosis instead of the terminal ileum. One of the patients in whom 5-10 cm ileum was additionally ligated, developed an AL. During endoscopy a small anastomotic dehiscence was observed, insufficient to place a endosponge. The cervical wound was opened, rinsed and antibiotic were intravenously administered.

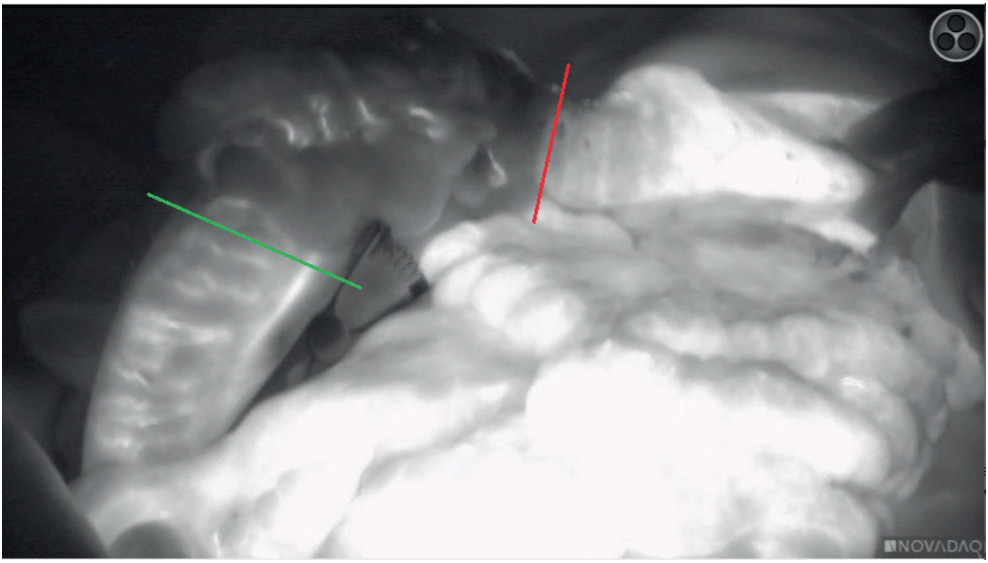

Figure 3. This figure represents a patient with a change of management due to the ICG-FA during a right hemicolon and terminal ileum for isoperistaltic colonic interposition. The red line represents the planned proximal anastomotic site of the ileum and the green line the actual anastomotic site after the ICG- FA assessment

Endpoints

Postoperative outcomes are summarized for both groups in Table 3. Anastomotic leakage was observed in seven out of 28 patients (25%), which in one patient was secondary to graft necrosis. In the ICG-FA group, three patients (20%) had an anastomotic leakage, whereas in the non ICG-FA group an anastomotic leakage occurred in four patients (31%) (p=0.67).

One of the patients in the ICG-FA-group with an anastomotic leakage, had undergone a change of management due to FA intraoperatively. The Clavien Dindo score (CD) was ≥4 in 7% in the ICG-FA group (n=1) and 8% in the non ICG- FA group (n=1).

Reoperation for AL was required in one patient in the ICG-FA group as well as one in the non-ICG-FA group. The patient in the non-ICG-FA group, a necrotic colonic interposition was resected and subsequently an esophagostoma was created. The patient in the ICG- FA group had surgery and a new end-side cervical anastomosis was constructed.

An anastomotic stricture was observed in two patients (15%) in the non ICG-FA group and in one patient (7%) of the ICG-FA group. Mortality within 90 days was observed in one patient of the ICG-FA group. This was not related to postoperative anastomotic complications: the patient died at postoperative day eight because of a cardiac arrest after hematemesis from the nasopharynx.

Table 3. Outcomes

	ICG- FA (n=15)	***CoM (n=3)**	**Non-ICG-FA (n=13)**	**p-value****	**Total (n=28)**
Anastomotic leakage	3 (20)	*1 (33)*	4 (31)	0.67	7 (25)
Graft necrosis	*0*	*0*	*1 (8)*		*1 (4)*
Anastomotic stricture	1 (7)	*0*	2 (15)	0.59	3 (11)
Management of AL					
CD <2	2 (13)	*1 (33)*	2 (15)		4 (14)
CD 3a	0	*0*	0		0
CD 3b	0	*0*	0		0
CD 4a	1 (7)	*2 (7)*	1 (8)		2 (7)
CD 4b	0	*0*	0	0.61	0
Other complication					
CD 2	1 (7)	*0*	2 (15)		3 (11)
CD 3a	0	*0*	0		0
CD 3b	2 (13)	*1 (33)*	0		2 (7)
CD 4a	3 (20)	*1 (33)*	4 (31)		7 (25)
CD 5	1 (7)	*0*	0	0.63	1 (4)
Total LOS, days (median (IQR))	14 (10-27)	*(18-21-25)*	17 (11-22)	0.70	16 (11-25)
LOS IC, days (median (IQR))	0 (0-3)	*(0-1-4)*	1 (1-7)	0.12	1 (0-4)
Readmission due to AL	0	*0*	2 (15)	0.55	2 (7)
90 days- mortality	1 (7)	*0*	0	0.48	1 (4)

Data shown in n (%) unless otherwise stated, * CoM patients are part of the ICG-FA group** p- value calculated between ICG-FA and non ICG- FA group.
Abbreviations: AL; anastomotic leakage, LOS; length of stay, ICU: intensive care unit, CD: Clavien Dindo

DISCUSSION

In this study, ICG-FA guided colonic interposition was described and the role of ICG-FA was evaluated with regard to postoperative anastomotic outcomes. ICG-FA proved to be a safe and feasible technique to assess perfusion of the colonic segment and potentially assures the surgeon in the choice of the colonic segment for the interposition. This study showed that 20% of patients had a change in management due to ICG. Anastomotic leakage remains a frequently encountered complication, also with the use of ICG-FA. In this cohort, there was no significant difference in AL between patients operated with and without the use of ICG-FA.

Despite the extensive body of research regarding the role of ICG-FA in perfusion in colorectal and in esophageal cancer surgery investigating perfusion, there is a paucity of studies available regarding the use of ICG-FA during colonic interpositions. So far, it has only been described in case reports: Wiesel *et al* were the first to report the technical description for assessing the perfusion of the colonic interponate with ICG-FA (13). Recently, a video vignette by Galema and a case study by Gupta described the feasibility of ICG-FA in colonic interposition (14, 15). This study is the first cohort study to assess the role of ICG-FA to assess perfusion in colonic segments. The ICG-FA assessment confirmed adequate perfusion of the colonic conduit and its chosen vascular pedicle, and induced a change of management in 20% of patients, in whom a different site for the anastomosis was chosen after ICG-FA.

ICG-FA has gained widespread attention for anastomotic perfusion assessment due to its relative ease of use, low cost, and good safety profile relative to other intraoperative modalities. AL secondary to perfusion restriction might be prevented by careful assessment of perfusion under guidance of ICG-FA. Recent meta-analyses in colorectal and upper gastrointestinal surgery with gastric conduit reconstruction demonstrate that standard use of ICG-FA results in a decrease in AL and graft necrosis (18, 19). In the current study, occurrence of postoperative anastomotic complications did not differ between patients with or without ICG-FA in colonic interposition. This is certainly due to the small number of patients, but the subjective interpretation of the fluorescence angiogram may also play a role. In ICG-FA in general, there is a need for quantification methods, with quantitative values that define a threshold for adequate perfusion; this may help to standardise interpretations.

The 20% rate in change of management is higher than what has been described during gastric conduit reconstruction (20). This might be due to the fact that in a gastric conduit there is generally little room for additional resection of the gastric conduit, as tension on the anastomosis might increase too much to make a reliable anastomosis. During colonic interposition there are more possibilities for additional resections without putting the colonic interponate length at risk. Of the three change of management patients, one patient developed an AL. The occurrence of AL after change of management due to ICG-FA is known and described in gastric conduit reconstruction as well. This might be caused by impaired vascularization by other factors jeopardizing the perfusion of the colonic conduit and subsequently, an AL may have been inevitable(21).

This study has some limitations. Although it is the largest series of ICG-FA up to date, the number of included patients is still small. Collection of patient and operative data was performed retrospectively. There was also a low number of events regarding anastomotic complications. Correction for the multifactorial etiology of anastomotic leakage was not possible owing to a low absolute number of events. Despite these limitations, this is the first cohort study describing a consecutive series of patients, with the best available evidence up till now regarding the safety and feasibility and treatment consequences of ICG-FA, and the AL rate in ICG-FA guided colonic interposition. The ICG-FA interpretation in this study was based on the surgeon's own judgement, and is therefore subjective. Recently is has been demonstrated that there is a considerable inter-user variation in interpretation of FA during esophagostomy with gastric conduit reconstruction(22). However, this has not been assessed during reconstructions with the colonic conduit. In this study, FA was assessed by the same surgeon. However, this might have been different by someone else. There are no thresholds to guide whether the perfusion as assessed by FA is sufficient or not. Further work on ICG-FA in colonic interpositions should focus on gaining more experience with the technique and its applications, and quantification of the perfusion, thereby establishing a threshold for adequate perfusion of the colonic conduit.

In conclusion, ICG-FA is a safe, easy and feasible technique to assess perfusion of colonic interpositions. ICG- FA is of added value, leading to a change in management in a considerable percentage of patients. Its role in prevention of AL remains to be elucidated.

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CHAPTER 4

Evaluation of inter-user variability in indocyanine green fluorescence angiography to assess gastric conduit perfusion in esophageal cancer surgery

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ABSTRACT

Introduction: Indocyanine Green Fluorescence Angiography (ICGFA) has been deployed to tackle malperfusion-related anastomotic complications. This study assesses variations in operator interpretation of pre-anastomotic ICGFA inflow in the gastric conduit.

Methods: Utilising an innovative online interactive multimedia platform (Mindstamp), esophageal surgeons completed a baseline opinion-practice questionnaire and proceeded to interpret, and then digitally assign, a distal transection point on 8 ICGFA videos of esophageal resections (6 Ivor Lewis, 2 McKeown). Annotations regarding gastric conduit transection by ICGFA were compared between expert users versus non-expert participants using ImageJ to delineate longitudinal distances with Shapiro Wilk and t-tests to ascertain significance. Expert versus non-expert correlation was assessed via Intra-class Correlation Coefficients(ICC).

Results: Thirty participants (thirteen consultants, six ICGFA experts) completed the study in all aspects. Of these, a high majority (29) stated ICGFA should be used routinely with most (21, including 5/6 experts) stating that 11-50 cases were needed for competency in interpretation. Among users, there were wide variations in dosing (0.05-3mg/kg) and practice impact. Agreement regarding ICGFA video interpretation concerning transection level among experts was "moderate" (ICC=0.717) overall but "good" (ICC=0.871) among seven videos with leave-one-out exclusion of the video with highest disagreement. Agreement among non-experts was moderate (ICC=0.641) overall and in every subgroup including among consultants (ICC=0.626). Experts choose levels that preserved more gastric conduit length versus non-experts in all but one video(p=0.02).

Conclusion: Considerable variability exists with ICGFA interpretation and indeed impact. Even adept users may be challenged in specific cases. Standardized training and/or computerized quantitative fluorescence may help better usage.

INTRODUCTION

Anastomotic complications represent significant causes of morbidity among patients with esophageal cancer undergoing esophagectomy. Anastomotic leakage (AL) has a reported incidence of 11.4-21.2%, anastomotic stenosis 18%-42% and graft necrosis 0.5-10.4% (1-8). AL and graft necrosis may lead to mediastinitis, requiring a prolonged postoperative course with multiple reinterventions and a high mortality risk. Anastomotic stricture impeding passage of nutrition necessitates serial endoscopic interventions to maintain esophageal patency over time and significantly impacts patient quality of life in the long term.

Although multifactorial in nature, conduit malperfusion is thought to play a major role in the development of these complications. As a result, fluorescence-guided surgery using indocyanine green (ICG), and near-infrared (NIR) laparoscopy is being increasingly deployed as a means to demonstrate and evaluate perfusion of the gastric conduit around the time of anastomosis formation. Following venous administration, ICG, a protein bound fluorophore that emits a fluorescent signal in the near-infrared range, is distributed throughout the systemic vasculature. Detection of ICG using NIR imaging systems therefore results in the visualization of tissue perfusion in real time. Several animal studies have demonstrated a significant linear correlation between fluorescence parameters and levels of local lactate or radioactive microspheres under normal and compromised perfusion conditions(9-12). The usefulness of indocyanine green fluorescence angiography (ICGFA) in reducing AL however is not clear with reductions in AL rates being inconsistently demonstrated(13-15). Previous work has demonstrated that there is variability in the interpretation of fluorescence images amongst colorectal surgeons and that, whilst variability is reduced with experience, the learning curve is considerable and likely represents a challenge to the optimum deployment of ICGFA broadly, at least in its current form(16, 17). However, this has not been investigated during esophagectomies with gastric conduit construction.

In this study, we explored clinician opinions pertaining to the use of ICG in practice as well as analyzing the variation in ICGFA interpretation between very experienced and inexperienced users in esophageal surgery by challenging participants with dynamic ICG perfusion videos from patient surgeries for their evaluation.

METHODS

Surgeons of varying esophageal surgery experience (from trainee to consultant) were invited to take part in this study including specific invitation of some with high levels of

ICGFA experience to act as a reference “expert” group. Suitable individuals were identified, and their participation invited via institutional online academic and clinical networks. Participating individuals were provided with an online link to complete the opinion-practice questionnaire followed by a short instructional tutorial on using the interactive software (Mindstamp: The interactive Video Platform www.mindstamp.io). The questionnaire documented participant clinical standing (stage of training or consultancy), prior experience in the area of ICGFA and their opinion on its learning curve as well as, among ICGFA users, information on their experience of ICGFA in practice (including the brand of NIR system used, ICG dosing, volume of cases performed and opinion of ICGFA).

Thereafter, and following a short user-tutorial, a sequence of eight anonymized, edited videos of esophageal resections typical of general practice showing the ICGFA acquisition phase at the time of gastric conduit transection were shown in sequence. Automatic pausing of each video at a pre-defined, fixed frame (just after early outflow phase of ICG) allowed participants viewing the videos to annotate directly on screen to show where they would place their stapler. Participants were requested to “draw a line at the most cranial aspect of the gastric tube that you deem adequately perfused” (i.e., saving as much length as possible). This facilitated direct comparison of the transection points across all participants. In order to most realistically simulate clinical practice, only a single viewing of each video was permitted.

The videos, six Ivor Lewis and two McKeown procedures (performed in a standard fashion as previously described)(18, 19), were taken from real-life cases at a high-volume institution with specialist ICGFA expertise. ICGFA was performed in each case after the gastric conduit was brought up into the thorax (Ivor Lewis procedure) or exteriorly through the accessory abdominal incision and placed onto the thorax before delivery to the cervical region (McKeown) and before creation of the anastomosis. Standardized per weight dosing (0.05 mg/kg/bolus) of ICG was used. ICGFA imaging was performed using the Pinpoint Fluorescence Imaging System (Stryker Corp, Kalamazoo, MI, USA) in all cases. This system simultaneously displays NIR, white-light and overlay views in three smaller stacked boxes to the left of the screen with a larger version of the black/white NIR mode as the principal display (see Figure 1). Video length ranged from 90 to 120 seconds and consisted of the inflow and early outflow phases of the fluorescence angiogram. Written consent was obtained from all study patients, as per standard institutional protocol and institutional review board approval, to allow the use of anonymized clinical videos for training and research purposes.

Questionnaire responses were aggregated and examined for significance between the groups. To facilitate comparative analysis of ICGFA interpretation, stapler locations were compared using Image J (National Institutes of Health, USA) by drawing a straight line from a fixed location proximally (with x, y co-ordinates ensuring accurate comparisons across participants) parallel to the conduit until it intersected the annotated stapler location (see Figure 1). This fixed location was determined following collection of all data and located caudally (with respect to the gastric conduit) to all chosen participant stapler locations. Measuring from this chosen location to all participant stapler locations therefore resulted in a positive value enabling easy comparison for all stapler locations in each video. With this method of distance measurement (in arbitrary units) the larger the value the more towards the cranial aspect of the gastric conduit the stapler location. Using these numerical units, inter-rater reliability of transection location was compared across groups. Statistical analysis was performed using SPSS Statistics version26 (IBM, Armonk, NY, US). Group data were compared using the 2-sided Fischer Exact, Shapiro Wilk and t-tests as appropriate ($p<0.05$ = statistical significance). For ICGFA interpretation, Intraclass Correlation Coefficient (ICC), two-way mixed model, absolute agreement, single measures was used with Leave One Out (LOO) cross validation performed to assess for the presence of disproportionate disagreement for any one video.

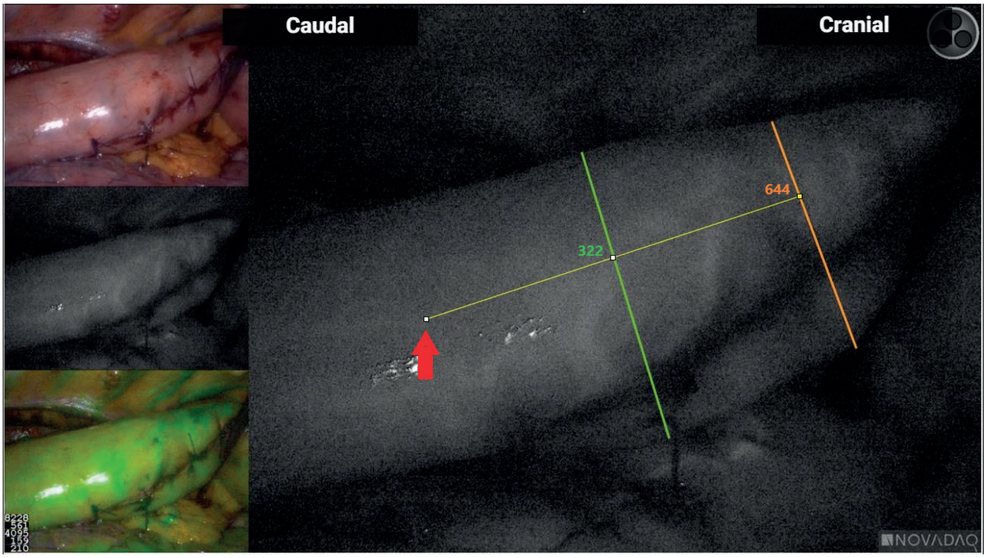

Figure 1. Screen shot image from representative video of the proximal conduit in a patient undergoing esophagectomy demonstrating the ICGFA display with also the analytic methodology used in this study. This screen display from the Stryker Pinpoint Endoscopic System shows the white light view in the top left, the NIR view in the middle left and a composite view in the bottom left with the user’s choice of these being viewed in the main component. In this image of a video shown via the Mindstamp platform, two separate study participants have marked their stapler placement based on the dynamic ICG signal inflow (green and orange lines). ImageJ is thereafter used to identify distance in arbitrary units from a predetermined fixed location (red arrow with x, y co-ordinates ensuring accurate comparison between participants) on the proximal conduit.

RESULTS

Thirty participants completed all aspects of the study. Six were recognized ICGFA experts with 24 being non-experts. The non-expert group consisted of seven consultants with specialist upper gastrointestinal surgery interest, seven surgeons in the late stages of their training (>5 years of specialty training), four in their middle training years (early specialist training/3-5 years surgical experience) and six trainees in their early stages of training (core trainee/1-3 years of surgical experience). Of those in the non-expert cohort, 38% (9/24) declared themselves as upper gastrointestinal surgeons, 50% (12/24) as general surgeons, 8% (2/24) as gastrointestinal surgeons and 4% (1/24) as a general surgeon with specialist interest in gastrointestinal surgical oncology. Twenty nine percent (7/24) of the non-expert group had no prior experience at all with ICGFA. Questionnaire data at baseline (see Table 1) demonstrated that the majority 97% (29/30) believed ICG should be used routinely to assess the gastric conduit with 70% (21/30, including 5/6 experts) stating that 11-50 cases were needed to reach ICG competency. Nearly two thirds of ICGFA users (61%, 14/23) felt ICGFA changed their clinical decision 5-15% of the time with two non-experts reporting it impacted over 15% of cases.

Table 1: Participant demographics and opinion survey/questionnaire on ICG use

	Clinical experience/Stage of Training (Total n=30)					
	Early training	Middle	Late	Consultant	Non-experts	Experts (All consultants)
	6	4	7	13	24	6
	How many cases does it take to become a competent ICG user for perfusion assessment?					**p value Fischer Exact Test (2 sided)**
	1-3	4-10	11-50	50+		
All	0	6	22	2		
Inexpert	0	5	17	2		1.000
Expert	0	1	5	0		
	How often does ICG change your clinical decision?					
	Never	<5%	5-15%	>15%	I don't use ICG	
All	1	6	14	2	7	
Inexpert	1	4	10	2	7	0.677
Expert	0	2	4	0	0	
	Should ICGFA of the gastric conduit should be used routinely or in exceptional cases?					
	Exceptional	Routine				
All	1	29				
Inexpert	1	23				1.000
Expert	0	6				
	How many cases of ICGFA have you been involved in?					
	none	1-10	11-50	>50		
All	7	8	6	9		
Inexpert	7	8	6	3		<0.001*
Expert	0	0	0	6		

ICG dosages varied widely among users with “fixed” (n=6) (2.5mg-7.5mg) and “per weight” (n=17) (0.05mg/kg-3mg/kg) regimens both being reported. Stryker was the most commonly used NIR system manufacturer (n=18) followed by Olympus (n=5), Storz (n=3) and Intuitive Firefly (n=1) (some individuals reported using more than one system).

Regarding ICGFA interpretation on the eight video case series, stapler locations are diagrammatically represented on operative stills in Figure 2 and graphically in Figure 3. Regarding video interpretation, there was a disproportionate level of disagreement in one single video (video 3) among experts meaning ICC in this group overall was moderate overall but “good” agreement in 7 of 8 videos (ICC 0.871, LOO analysis) excluding this one (see Table 2).

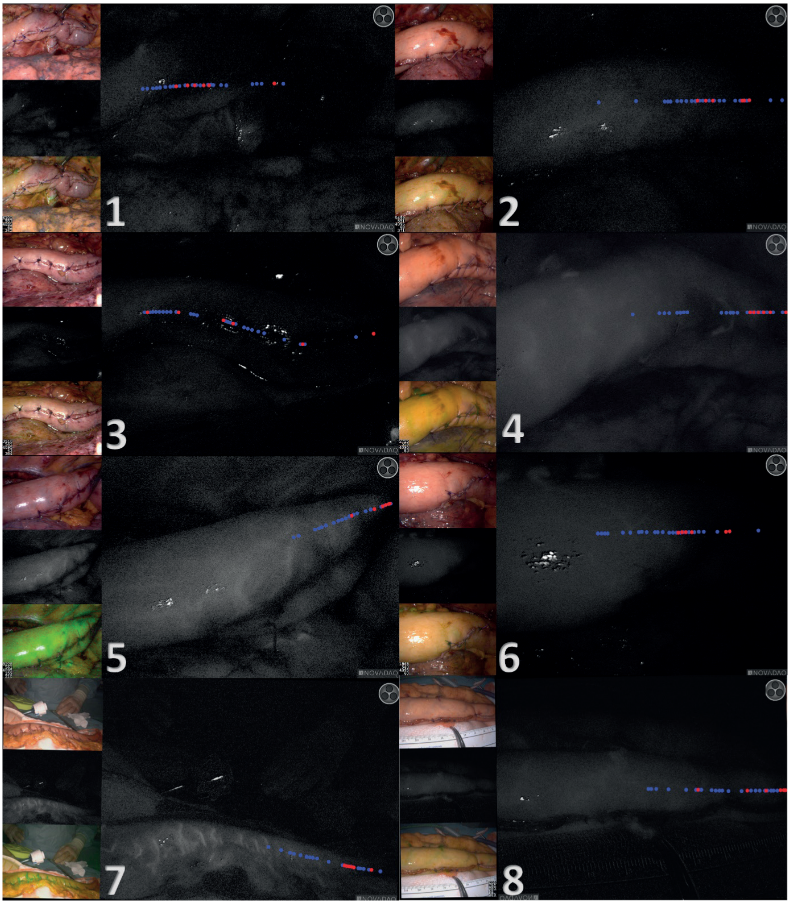

Figure 2. Composite image showing the final still image from all eight videos viewed and annotated by participants. Each dot (red = expert, blue = non-expert) represents a single participant’s chosen stapler location. Images demonstrate the gastric conduit with the proximal aspect to the left of the image and distal to the right side.

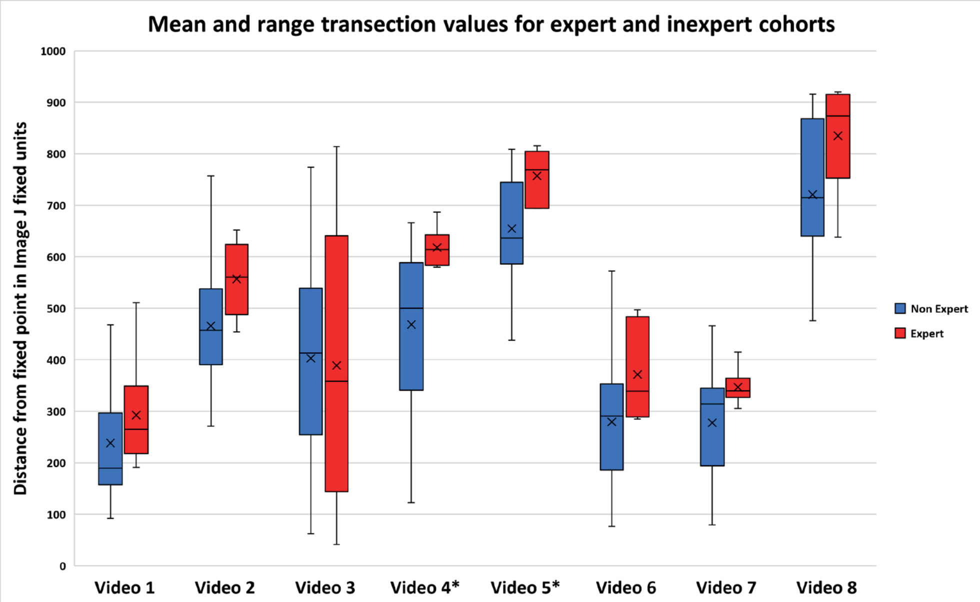

Figure 3. Box plot representation of measured distances (in arbitrary fixed Image J units) from the fixed point to participant chosen stapler locations by video. * Denotes statistical significance difference between groups.

Agreement was moderate for all non-expert video permutations (ICC 0.641), including separate subgroup analysis among consultant non-experts (ICC 0.626). Experts tended to choose more cranial positions for their staplers with respect to the gastric conduit (p=0.02) (i.e., were less conservative than non-experts). Comparison between individuals that reported using ICG in their practice and those that did not demonstrated that ICG users chose, on average, more distal locations than non-users, with respect to the gastric conduit (see supplementary figure 3).

Table 2: Inter-rater reliability for ratings by observers of the videos showing proximal gastric conduit transection by their level of expertise in ICGFA (Intraclass Correlation Coefficient values for interpretation of reliability/agreement: <0.5 = poor reliability, 0.5-0.75 = moderate, 0.75-0.9 = good, >0.9 = excellent)

Gastric Conduit Transection Videos	**Intra Class Correlation Coefficient**	**95% CI**
Expert Users (n=6)	0.717 (moderate) – all videos included 0.871 (good)–vid 3 excluded on leave one out analysis	0.460 – 0.920 0.676 – 0.973
Other users (n=24)	0.641 (moderate) 0.626 (moderate) for consultants in this group (n=7)	0.421 – 0.884 0.346 – 0.885

DISCUSSION

Determining appropriate perfusion remains a major challenge in visceral surgery and especially in esophageal surgery. Somewhat uniquely in esophageal surgery, consideration must not only be given to adequate anastomosis perfusion, but also to the gastric conduit length where over-trimming can lead to increased anastomotic tension, or an inability to anastomose altogether. Whilst techniques such as colonic and small intestine interpositions can be used in such situations, they add significant complexity and morbidity. Thus, preservation of maximum tissue length, both of gastric conduit and esophagus, with sufficient healing perfusion capability would be of considerable benefit to patient and operator(20, 21). For these reasons, there has been great recent interest in using ICGFA, however study outcomes differ as to its usefulness.

This study discovers and details variability in interpretation of ICG enhanced fluorescence angiograms during the assessment of gastric conduit perfusion among surgeons which may underlie some of those study outcome differences. While there is reduction in variance seen with mastery of the technique, fallibility of operator interpretation even occurred among expert uses in one case. These findings overall are consistent with a similar study in colorectal surgery(16), with the singular video interpretation disagreement (in the setting of high levels of agreement for all other videos) likely reflecting the greater complexity of ICGFA interpretation in esophageal surgery. Possible explanations for the interpretive discordance seen include a reduced fluorescence enhancement throughout the entire conduit length as well as the obvious presence of an oblique suture line which may have derailed participant fluorescence interpretation.

Such findings are concerning for upper GI surgeons, as malperfusion at the anastomotic site during esophagectomy with gastric conduit reconstruction is especially problematic as the gastric conduit length usually leaves little room for additional resections. Importantly, in case of vascular deficiency, the balance with anastomotic tension is even more important. This study showed that experts tended to choose a more cranial location on the gastric conduit. This may be explained by their heightened awareness (compared to less experienced junior surgeons in this study) of the need for gastric conduit length however this also requires confidence in the ICG signal interpretation, which we feel is highlighted in this finding amongst experts. Nevertheless, ICGFA might identify patients with an increased risk in developing an AL and in case there are no intraoperative possibilities, additional pre-emptive measures could be taken postoperatively (for instance, endoscopy at day 3, prophylactic endosponge and/or antibiotics) in cases where suboptimal perfusion is seen. Variability in interpretation of a test meant to offset subjectivity in surgeon judgement is concerning especially as experts felt considerable case numbers are needed to perfect interpretation (although of course this study also suggests through extrapolation a video methodology to offset such variability through watching pre-recorded videos and comparing interpretations with experts).

The variability observed could also be explained in part by known pitfalls in the human, subjective interpretation of ICG including the challenges posed by the complex temporospatial nature of the fluorescence angiogram(22). Additionally physical phenomena such as "ICG creep" (passive diffusion of ICG through tissue different to active perfusion) may also play a role(18). Such complexities may be mitigated by use of computerized methodologies and even artificial intelligence to better display and detail the fluorescence curves(23, 24). Attempts to quantify and simplify interpretation through the use of metrics such as "time to fluorescent enhancement of the gastric conduits" have been described and can be more easily utilized in the clinical setting(25). It is likely so that subsequent iterations of this technology will benefit from the use of more complex quantification methods, such as fluorescence time curves and computer vision (extracting meaningful data from digital inputs to guide operations in real time), although acquisition and application of such technologies has some challenges (including a need to factor in distance-intensity and screen centre versus periphery considerations) (26, 27). In the interim, collated videos permitting participant interaction followed by expert annotation and discussion may allow naïve users valuable insights into the use of ICGFA without the need for real-life clinical experience which may be both difficult to obtain and costly for the patient and health service provision in the case of any misinterpretation.

It should be noted that this study is limited given its relatively small number of participants and videos that, although chosen for their high-fidelity nature, were interpreted by users in an artificial online setting that may not replicate participant decision-making in a real clinical setting. Furthermore, in this study, videos were portrayed for 90-120 seconds each. Durations of 90 seconds have previously been reported by some groups as the maximum time threshold by which the gastric conduit should demonstrate fluorescence enhancement in order to be considered adequately perfused(28). However, in some videos only the onset of outflow was visible and this may have limited comprehensive interpretation given that outflow problems (i.e. venous congestion) have been known to contribute to the development of AL (29). However, its exact impact is unknown and the clinical evaluation of this, observing subtle changes over prolonged periods of time, is challenging without computer assistance. While a lot of work has been done so far towards quantification, defining outflow parameters remains difficult.

As the interim results of the IntAct trial approach (utilizing ICG to prevent anastomotic leakage in rectal cancer surgery), there are currently no ongoing equivalent trials in esophageal cancer and a recent systematic review and meta-analysis of existing ICG studies in AL prevention in minimally invasive Ivor-Lewis esophagectomy has shown no significant benefit in its use(13, 30). Demonstration of any significant differences with the use of ICG in its current clinical form is likely to be challenging, however. The user variation seen in this study, combined with the infrequency in which ICG changes clinical decision (5-15% reported in this study) and the difficulty of adequate powering as seen in the colorectal equivalent studies make such studies challenging to execute successfully(17).

In conclusion, clear variability exists in ICGFA interpretations and also practice impact. This study demonstrates too that even adept users may still be challenged in specific cases during esophagectomy with gastric conduit reconstruction implying training and/or quantitative fluorescence values and computerized interpretation are needed to help better usage in the future.

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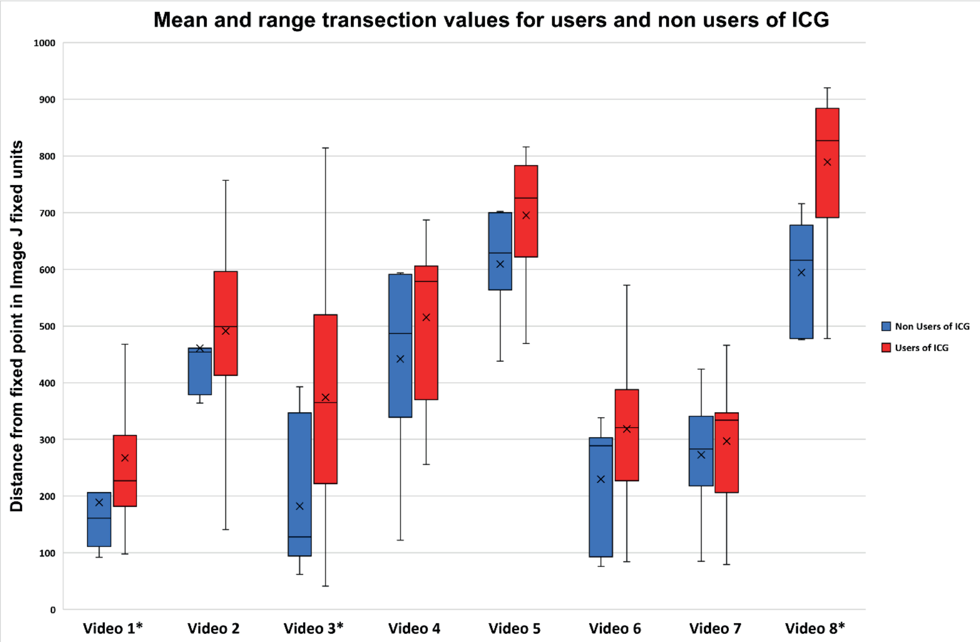
SUPPLEMENTARY MATERIAL



Supplementary Figure 1: Box plot representation of measured distances (in arbitrary fixed Image J units) from the fixed point to participant chosen stapler locations by video. Groups divided into ICG users vs non ICG users for comparison. * Denotes statistical significance difference between groups.

CHAPTER 5

Fluorescence angiography after vascular ligation to make the ileo-anal pouch reach, a technical note

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W.A. Bemelman,R. Hompes

Techniques in Coloproctology, 2021

ABSTRACT

The two most essential technical aspects for any gastrointestinal anastomosis are adequate perfusion and sufficient reach. For ileal pouch-anal anastomosis (IPAA), a trade-off exists between these two factors, as lengthening manoeuvers to avoid tension may require vascular ligation.

In this technical note, we describe two cases in which we used indocyanine green (ICG) fluorescence angiography (FA) to assess perfusion of the pouch after vascular ligation to acquire sufficient reach. In both cases, FA allowed to distinguish better between an arterial inflow problem and venous congestion than white light assessment. Both pouches remained viable and no anastomotic leakage occurred..

ICG FA showed to be of great value after vascular ligation to obtain reach during IPAA.

INTRODUCTION

Restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA) is the surgical treatment of choice in patients with familial adenomatous polyposis (FAP), ulcerative colitis (UC) and well selected patients with Crohn's colitis [1]. One of the Achilles heels of pouch surgery is anastomotic leakage with a reported incidence up to 15% [2-3].

Key in anastomotic healing is a traction free anastomosis that is well-vascularized [4]. To acquire length in IPAA, routine lengthening measures are taken that include mobilization of mesenteric root up to the duodenum and bilateral transverse peritoneal incisions approximately every 3 centimeters. In case adequate length cannot be obtained by these routine manoeuvers, tailored lengthening measures, involving vascular ligation, might be required. The ileocolic trunk (if still present) or interconnecting terminal ileal branches can be sacrificed to gain additional ileal length for the pouch to reach [5]. However, by ligating part of the arterial supply and venous drainage of the ileum, pouch perfusion can be impaired.

Intraoperative fluorescence angiography (FA) using indocyanine green (ICG) is nowadays widely applied to assess colonic vascular perfusion and could contribute to the prevention of anastomotic leakage secondary to perfusion restriction [6-7]. So far, little is known about the role of FA in IPAA. Spinelli et al. [8] have shown that the postoperative anastomotic leakage rate after IPAA in their FA group was similar to a non-FA group, even though ligation of the ileocolic artery was performed more often within the FA group than non-FA group (47% versus 16%).

In this technical note, we demonstrate the potential value of FA in decision making after ligation of vessels in order to obtain adequate length for a tension free anastomosis in two cases.

TECHNICAL NOTE

As a standard technique, the completion proctectomy and IPAA were performed by a combined abdominal and transanal minimally invasive approach. After adhesiolysis, the root of the small bowel mesentery was mobilized to the level of the duodenum followed by multiple transverse peritoneal incisions. After completion of these steps, the terminal ileum was exteriorised through a Pfannenstiel incision or the stoma site. The yardstick for sufficient length was when the apex of the J-pouch reached 1-2 cm below the pubic bone. If these routine lengthening measures were insufficient, the ileocolic trunk and/or interconnecting terminal ileal branches were ligated. After sufficient length was achieved, the J-pouch was constructed by a side-to-side ileal anastomosis using a linear stapler. The anvil was placed at the apex of the J-pouch, after which the redundant blind loop was resected using a linear stapler and reinforced by sutures.

After visual inspection of the pouch in white light, ICG (VERDYE, Diagnostic Green dissolved in 10 ml sterile water) 0.1 mg/kg/bolus was injected intravenously for FA. Imaging was performed by a laparoscopic 1688 AIM camera (Stryker, Kalamazoo, MI, U.S.A.). After assessment by FA and necessary changes based on FA findings, a double purse string single stapled ileo-anal anastomosis was fashioned followed by routine suture reinforcement of the anastomosis. A deverting ileostomy was only created in case of technical problems (e.g. staple misfire, positive reverse leak test, insufficient reach) or impression of suboptimal perfusion on FA. The ileo-anal anastomosis was assessed endoscopically within two weeks after surgery if a diverting ileostomy had been fashioned.

The first case regarded a 23-year old female patient diagnosed with UC. Due to biological therapy refractory disease, she underwent a subtotal colectomy and ileostomy procedure. During this procedure, the ileocolic artery was already ligated. After a four month convalescence period, she was referred to our unit for the second stage of a modified two stage IPAA procedure. Intraoperatively, there was insufficient length after applying the routine lengthening measures. To gain additional length, interconnecting terminal ileal branches were ligated. After pouch construction, there was the impression of perfusion impairment of the apex of the pouch (Figure 1) that was not observed by white light assessment.

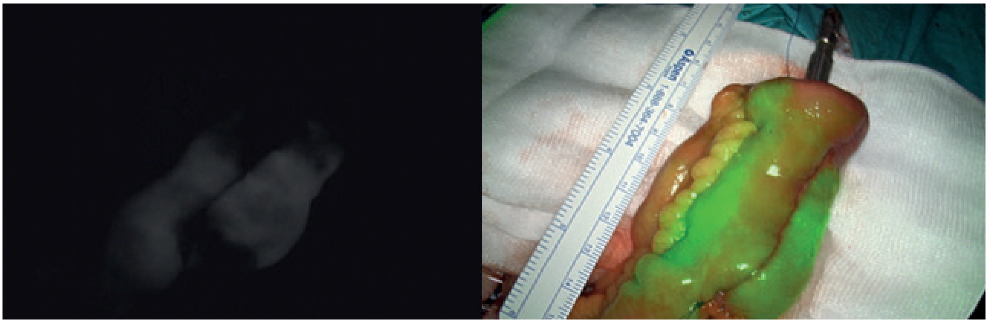

Figure 1 Intraoperative fluorescent and overlay image of pouch showing poor fluorescent enhancement of the apex of the pouch

This area was reinforced by separate sutures PDS® 4.0 (Ethicon, Germany) (Figure 2). These findings also led to a further change in routine management, namely the creation of a diverting ileostomy.

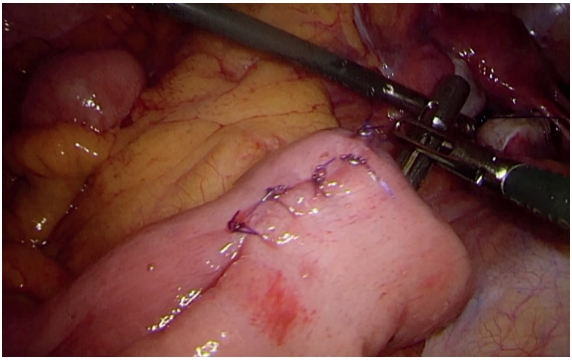

Figure 2. Suture re-inforcement of the apex of the pouch was performed after the fluorescent images

Postoperative endoscopy of the pouch two weeks after the procedure showed a well-vascularized apex of the pouch, pouch body (Figure 3) and intact anastomosis. The patient was planned for stoma reversal in six weeks time.

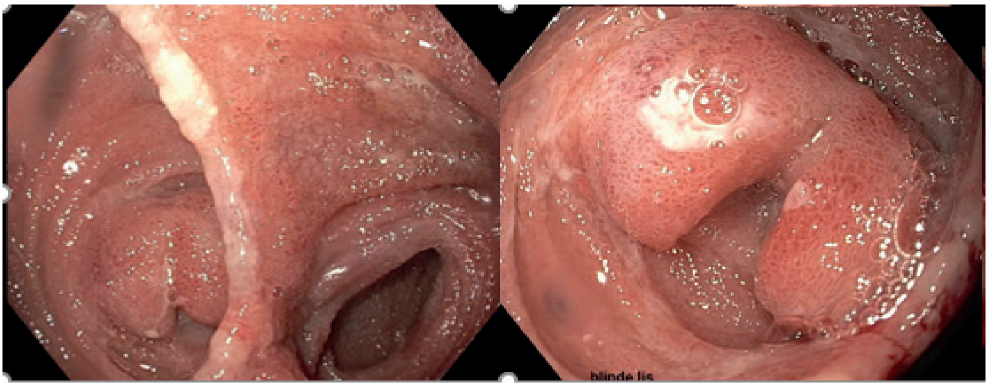

Figure 3. Endoscopy images of the pouch two weeks postoperative showing a vital apex of the pouch and pouch body

The second case involved a 53 year old man with a history of biological refractory UC, now in clinical and endoscopic remission under upadacitinib. Because of a sigmoid carcinoma, his immunosuppressants had to be stopped and surgery was indicated. This patient underwent a restorative proctocolectomy and pouch procedure as a planned single staged procedure. Also, in this case, after performing routine lengthening measures, the reach remained insufficient and additional lengthening measures were indicated. The interconnecting terminal ileal branches were ligated. While constructing the pouch, the body of the pouch discolored gradually (Figure 4).

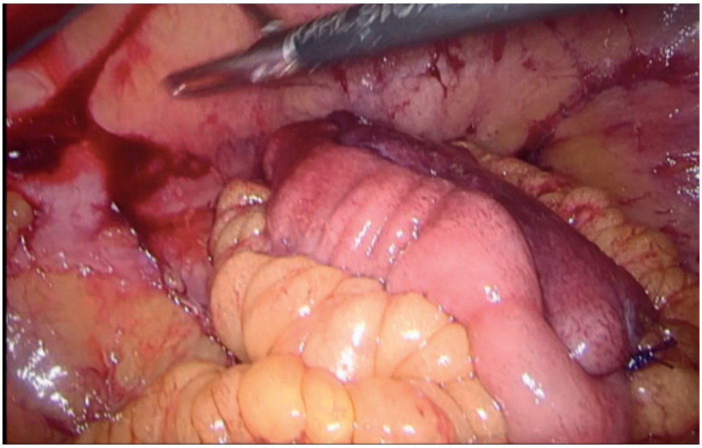

Figure 4. Intraoperative discoloring of the afferent loop of the pouch

Subsequent FA showed uniform fluorescent enhancement of the pouch in 33 seconds (Figure 5), despite clear discoloration in white light suggesting venous congestion. Given the FA findings, the pouch was not redone and a double purse string single stapled anastomosis was pursued. However, the operative plan was changed from a one-stage to a two-stage procedure.

Figure 5. Intraoperative fluorescent and overlay images of pouch-perfusion

Because of the potential dubious vascularization due to the venous congestion, a pouchoscopy was performed three days postoperative. Extensive mucosal ischemia and sloughing was observed, but the underlying muscular wall seemed well perfused. During repetitive endoscopic follow up, re-epithelialization of the mucosa was noticed (Figure 6). No anastomotic leakage occurred and the patient was planned for stoma reversal.

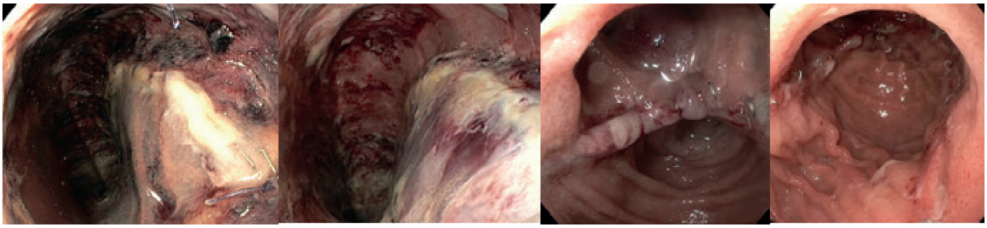

Figure 6. Endoscopy images of the pouch five days, eight days, three weeks and six weeks postoperative (portrayed from left to right) showing mucosal ischemia and re-epithelization over time

DISCUSSION

During IPAA surgery, it might be necessary to perform lengthening maneuvers that require vessel ligation in order to make the pouch reach [9-10]. Particularly in these cases, FA might be of value to rule out significant perfusion problems, and even distinguish arterial inflow from venous congestive problems. However, literature describing FA during IPAA is scarce, and change of management after FA has thus far not been recorded [8].

The described case reports show that FA was of added value in the intra-operative decision making. In the first case, vascularization of a small area of the pouch body seemed compromised after ligation of both the ileocolic artery and interconnecting terminal ileal branches. FA assessment led to change of management through suture reinforcement of the hypo-perfused area and ileostomy formation. In the second case, even though pouch vascularization in white light seemed severely compromised, fluorescent enhancement occurred in the entire pouch, although in a delayed fashion. Discoloration of the pouch was therefore more likely due to venous congestion. Because of this finding, the surgeons pursued anastomotic construction, and an uneventful postoperative course followed.

Although no literature concurs on this subject, FA assessment seems of value if devascularizing measures are required for additional reach. A limitation of this study is the subjective evaluation of the fluorescence images by the surgeon. Quantitative values are warranted to define a threshold for adequate perfusion and venous congestion. Moreover, literature on postoperative outcomes after devascularization to acquire reach without FA assessment is absent. Future comparative studies with larger cohorts are awaited to emphasize the potential added value of FA in pouch surgery, particularly in those cases whereby vessel ligation is indicated to obtain reach.

CONCLUSION

ICG FA showed to be of value after ligation of vessels to obtain reach during IPAA.

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CHAPTER 6

Fluorescence perfusion assessment of vascular ligation during ileal pouch-anal anastomosis

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Techniques in Coloproctology, 2022

ABSTRACT

Background: Intraoperative fluorescence angiography (FA) is of potential added value during ileal pouch-anal anastomosis (IPAA), especially after vascular ligation as part of lengthening measures. In this study, time to fluorescent enhancement during FA was evaluated in patients with or without vascular ligation during IPAA.

Methods: This is a retrospective cohort study of all consecutive patients that underwent FA-guided IPAA between August 2018 and December 2019 in our tertiary referral centre. Vascular ligation was defined as disruption of the ileocolic arcade or ligation of interconnecting terminal ileal branches. FA was performed before and after ileoanal anastomotic reconstruction. During FA, time to fluorescent enhancement was recorded at different sites of the pouch.

Results: Thirty-eight patients(55.3% male, median age 45 years [IQR 24-51]) were included, of whom the majority (89.5%) underwent a modified-2-stage restorative proctocolectomy. Vascular ligation was performed in 15 patients (39.5%), and concerned central ligation of the ileocolic arcade in three cases, interconnecting branches in 10, and a combination in two. For the entire cohort, time between indocyanine green (ICG) injection and first fluorescent signal in the pouch was 20 seconds (IQR 15-31) before and 25 sec (20-36) after anal anastomotic reconstruction. Time from ICG injection to the first fluorescent signal at the inlet, anvil and blind loop of the pouch were non-significantly prolonged in patients that received vascular ligation.

Conclusions: Results from this study indicate that time to fluorescence enhancement during FA might be prolonged due to arterial rerouting through the arcade or venous outflow obstruction in case of vascular ligation.

INTRODUCTION

Ileal pouch-anal anastomosis (IPAA) is a surgical procedure to restore continuity after proctocolectomy for inflammatory bowel disease or inherited colorectal cancer disorders. After IPAA, anastomotic leakage is a severe complication occurring in up to 15% of patients [1-3]. Patients with anastomotic leakage are at risk of developing pouch dysfunction or failure due to chronic pelvic sepsis, which can only be solved by complex salvage surgery or pouch excision.

Essential in the prevention of anastomotic leaks is a tension-free and well-vascularized ileoanal anastomosis. However, balancing between tension and perfusion is challenging as these two factors may oppose one another. Additional length of the terminal ileal mesentery can be achieved by mobilization of the mesenteric root to the level of the duodenum and transverse peritoneal incisions. When sufficient length cannot be achieved by these basic lengthening manoeuvres, vascular ligations might be required. The ileocolic arcade or interconnecting terminal ileal branches can be sacrificed to gain extra length [4] (figure 1). Hereby the pouch can be exposed to vascularization problems, by disruption of in- or outflow [5].

Intraoperative fluorescence angiography (FA) using indocyanine green (ICG) is an emerging technique that is widely applied to assess bowel perfusion [6]. During IPAA, FA is proposed to be of added value, especially after vascular ligation [7-9]. However, its current interpretation is subjective, and does not routinely discriminate between an inflow or outflow problem. Time dependent change of FA appears more objective and is a promising method for quantification predicting both in- or outflow problems [10].

The primary objective of the present study was to assess the time dependent FA characteristics of ileoanal pouches with intact vascularization as opposed to pouches where vascular lengthening measures are required.

METHODS

This was a retrospective cohort study of all consecutive patients that underwent FA-guided IPAA in a tertiary referral centre, from introduction of FA in August 2018 until December 2019. Two groups were compared: patients with and without vascular ligation. Patients were excluded if they had undergone re-do IPAA, when FA was not performed, or when FA was performed using another imaging platform than specified below. Since introduction of FA, FA data were routinely recorded in the electronic medical record. Patient data were retrospectively collected from the electronic medical records.

The Institutional Review Board of the Amsterdam University Medical Centres (UMC), location Academic Medical Centre (AMC), approved the study protocol and confirmed that the Medical Research lnvolving Human Subjects Act (WMO) did not apply. In compliance to the General Data Protection Regulation, need for written informed consent was waived due to the retrospective nature of the study. All patients were sent information concerning the study including an opt-out letter. If patients did not reply within 4 weeks, approval for use of data was assumed.

Fluorescence-guided IPAA

Different strategies for restorative proctocolectomy with IPAA were applied [11]. Completion proctectomy and IPAA were performed as previously described [12]. At our centre, the ileocolic pedicle management method at time of subtotal colectomy is to preserve the ileocolic arcade. The ileocolic artery can be ligated at different levels to make the pouch reach the pelvic floor if lengthening manoeuvres are required, as indicated in Figure 1. Either a stapled or hand-sewn IPAA was created. A hand-sewn IPAA was preceded by mucosectomy of the rectal stump.

Perfusion of the J-pouch was assessed before (serosal assessment) and after (mucosal assessment) ileoanal anastomotic reconstruction. Serosal assessment was performed after J-pouch construction, however in a minority of cases this was done before pouch creation after final decision on vessel ligation. Visual inspection was followed by ICG injection (0.1 mg/kg/bolus) for FA. Imaging was performed by laparoscopic PINPOINT or hand-held Spy-phi (Stryker, Kalamazoo, MI, U.S.A.).

In case of anastomotic leaks, reoperation was performed for ileostomy creation, if not performed primarily. This was followed by immediate surgical transanal closure of the defect if small, Endo-SPONGE® (B. Braun Surgical S.A., Barcelona, Spain) vacuum assisted closure (EVAC) of the defect [13], or restorative redo surgery at a later stage.

Outcomes

The primary outcome was time to fluorescent enhancement, a quantitative FA characteristic, in patients with or without vascular ligation. Details on vascular ligation were retrieved from the surgical report and was scored when the ileocolic arcade or interconnecting terminal ileal branches (referred to as: interconnecting branches) were ligated. Assessment of time to fluorescent enhancement is displayed in Figure 2. Time-points were manually assessed using a digital clock and recorded. If sites changed due to change in management, time-points were adjusted accordingly. Time values were the difference between time-points in seconds, with time-point of ICG injection, inlet/first signal, or the anvil/pouch-anal anastomosis as t=0.

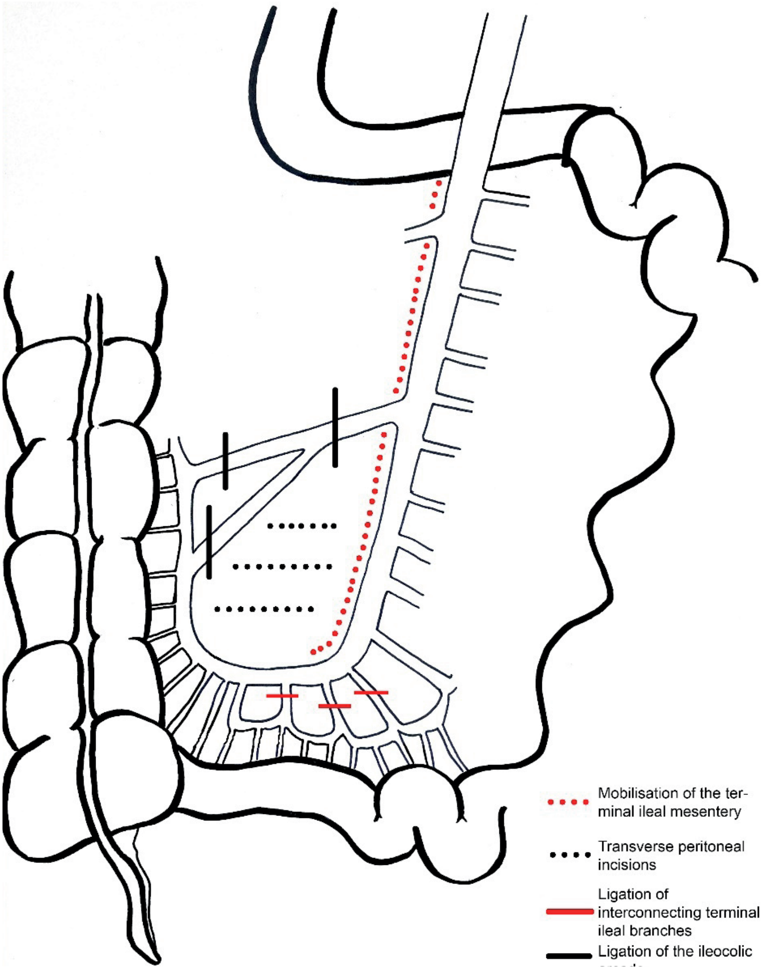

Figure 1: Lengthening manoeuvres of the ileal pouch

Secondary outcomes included other FA characteristics, including change in management and additional surgical time, hemodynamic parameters during FA, anastomotic leakage within 90 days, postoperative stay and mortality rate within 90 days. The interpretation of the FA was at surgeon's discretion. Change in management was defined as every measure taken based on the results of FA only. Change of management was mainly based on small versus large areas of poor or no fluorescent signal versus delayed fluorescent enhancement and to a lesser extent the time to fluorescence. Change in management included suture reinforcement of hypoperfused regions, additional resections, selecting a more proximal loop for pouch creation or ileostomy creation. Additional surgical time was recorded from beginning to end of the fluorescent mode in minutes. Hemodynamic parameters included mean arterial pressure , heart rate and noradrenaline usage and dosage. Anastomotic leakage was recorded when an anastomotic defect was objectified by CT-scan, during endoscopy or reoperation, and was graded according to impact on clinical management. [1]. For anastomotic leakage, details were collected including location, signs of ischaemia and retraction, type of management and time to stoma closure.

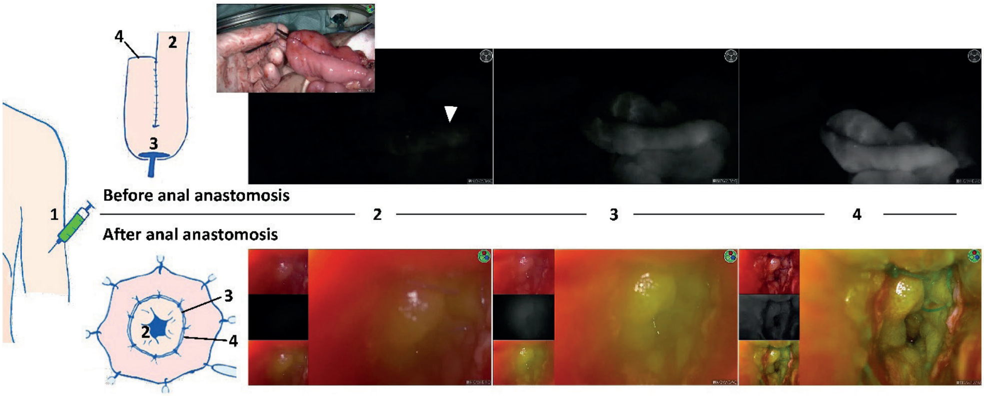

Figure 2: Time-points to assess time to fluorescent enhancement during ileal pouch-anal anastomosis. **Before IPAA reconstruction**, the J-pouch was examined and the following time-points were recorded during FA: 1. time of ICG injection (ICGi), 2. time of fluorescent signal at the inlet of the pouch (inlet), 3. at the planned anastomotic site (anvil), and 4. at the blind loop of the J-pouch (blind loop). **After ileoanal anastomotic reconstruction**, the anastomosis was evaluated transanally and FA time-points included: 1. time of ICG injection (ICGi), 2. time of first fluorescent signal of the mucosa (first signal), 3. time of fluorescence of the pouch at the anal anastomotic site (pouch-anal anastomosis), and 4. of the distal cuff at the anal anastomotic site (distal cuff-anal anastomosis).

Statistical analysis

All categorical data were presented as number of cases and percentages, whilst continuous data were shown as either mean ±standard deviation or as median and interquartile range (IQR) or total range, depending on data distribution. Categorical variables were compared using a χ^2 test or Fisher's exact test. Comparison of continuous variables was done with a t-test or Mann-Whitney U test, according to distribution. A p-value ≤0.05 was considered statistically significant. Time values were reported as median and IQR and were primarily assessed for patients with or without vascular ligation, and secondary for patients with or without change in management or anastomotic leakage. Time values including 'distal cuff-anal anastomosis' were not included in the comparison for vascular ligation. Time values were compared between groups using the Mann-Whitney U test. A p-value ≤0.05 was considered statistically significant. Univariate logistic regression analysis was performed to evaluate predictive time values for anastomotic leakage. When analysis revealed a P-value below 0.2 [14], a receiver operating characteristic (ROC) curve was produced. When the ROC-curve generated an area under de curve (AUC) above 0.7, a cut-off value was produced with high specificity using Youden's statistics. Correlations between time values and hemodynamic parameters were assessed by calculating the Spearman's rank correlation coefficient ρ. A P-value ≤0.05 was considered statistically significant.

Data were analyzed using the Statistical Package for Social Sciences (SPSS) (IBM Statistics, IBM Corp., Armonk, NY, USA), version 26.0.

RESULTS

In total 42 patients underwent IPAA during the study period, four of whom were excluded because of redo IPAA (n=1), non FA-guided IPAA (n=2) or another FA imaging platform (n=1). Thus, 38 patients were included (55.3% was male , median age 45 years [IQR 24-51]) (Table 1). The majority of patients (89.5%) underwent IPAA for ulcerative colitis (UC). Other diagnosis included Crohn's disease (n=1), familial adenomatous polyposis (n=1), Lynch syndrome (n=1), and Lynch syndrome in combination with MUTYH-associated polyposis (n=1). Comorbidities are shown in Table 1. The majority of patients (89.5%) underwent a modified-2-stage, this and other operative details are shown in Table 1.

Primary outcome

During IPAA, vascular ligation was performed in 15 of 38 patients (39.5%). In three of these cases, the ileocolic arcade was ligated, in 10 interconnecting branches, and in two a combination. FA was performed before and after ileoanal anastomosis in 29 patients (76.3%), in 6 patients (15.8%) only before and in 3 patients (7.9%) only after. Time values for the entire cohort and comparison for vascular ligation are shown in Table 2. Time values before anastomosis with ICGi as t=0 were prolonged, although not significantly, in patients with vascular ligation. No differences were observed for time values once ICG was observed in the pouch (times with inlet or anvil as t=0). After anastomosis, no time differences were observed, except for a longer (non-significant) time interval between ICG injection and first signal.

Table 1: Baseline characteristics and operative details

	FA-guided IPAA (N=38)	Vascular ligation (n=15)	No vascular ligation (n=23)
Male sex	21 (55.3)	11 (73.3)	10 (43.5)
Age (years) *median IQR*	45 (24-51)	42 (22-58)	45 (25-51)
BMI (kg/m2) *median IQR*	24.6 (21.5-27.6)	23.5 (21.5-26.9)	24.7 (21.4-29.3)
ASA classification (≤2)	38 (100)	15 (100)	23 (100)
Smoker (active)	6 (15.8)	4 (26.7)	2 (8.7)
Comorbidity*	5 (13.2)	2 (13.3)	3 (13.0)
Cardiovascular	0 (0)	0 (0)	0 (0)
Pulmonary	4 (10.5)	2 (13.3)	2 (8.7)
Diabetes	1 (2.6)	0 (0)	1 (4.3)
Diagnosis			
Ulcerative Colitis	34 (89.5)	12 (80.0)	22 (95.7)
Other	4 (10.5)	3 (20.0)	1 (4.3)
Stage procedure			
1-stage	1 (2.6)	1 (6.7)	0 (0)
2-stage	1 (2.6)	1 (6.7)	0 (0)
Modified 2-stage	34 (89.5)	11 (73.3)	23 (100)
Other	2 (5.3)	2 (13.3)	0 (0)
Immunomodulating medication**	4 (10.5)	2 (13.3)	2 (8.7)
Abdominal approach			
Laparoscopy***	32 (84.2)	15 (100)	17 (73.9)
Open	6 (15.8)	0 (0)	6 (21.6)
Conversion	2 (5.3)	2 (13.3)	0 (0)
Construction anastomosis			
Hand-sewn	1 (2.6)	1 (6.7)	0 (0)
Stapled	37 (97.4)	14 (93.3)	23 (100)
Additional lengthening manoeuvres			
Transverse peritoneal incisions	31 (81.6)	15 (100)	16 (69.6)
Vascular ligation	15 (39.5)	15 (100)	0 (0)
Vascular ligation specification			
Ileocolic arcade	3 (7.9)	3 (20.0)	-
Interconnecting branches	10 (26.3)	10 (66.7)	-
Combination of ileocolic arcade and interconnecting branches	2 (5.3)	2 (13.3)	-
Intraoperative complications****	1 (2.6)	1 (6.7)	0 (0)

Data is shown in n (%), unless stated otherwise.
ASA American Society of Anesthesiologists classification, AMC Amsterdam University Medical Centres location Academic Medical Centre, BMI body-mass index, FA Fluorescence Angiography, IPAA ileal pouch-anal anastomosis, IQR interquartile range
*Vascular comorbidity: brain infarction, myocardial infarction, or peripheral vascular disease. Pulmonary comorbidity: asthma or COPD. Diabetes: type 1 or 2.
** Mesalazine, or biological within 3 months before surgery.
*** Includes single/multi-port and hand-assisted.
**** Complications: bleeding (>500cc)

Table 2: Time to fluorescent enhancement: time values for patients with or without vascular ligation.

	t=0	End	Overall (n=38)	Vascular ligation (n=15)	No vascular ligation (n=23)	P-value
			Time to fluorescence (sec)			
Before anastomosis*	ICG injection	Inlet	20 (15-31)	24 (17-34)	19 (14-27)	0.294
		Anvil	28 (20-34)	31 (26-36)	26 (19-31)	0.253
		Blind loop	31 (23-52)	35 (28-52)	25 (21-50)	0.150
	Inlet	Anvil	3 (2-6)	3 (2-5)	4 (2-7)	0.393
		Blind loop	6 (4-14)	6 (2-20)	5 (4-13)	0.961
	Anvil	Blind loop	2 (0-4)	2 (0-6)	2 (0-5)	0.584
After anastomosis**	ICG injection	First signal	25 (20-36)	28 (25-34)	22 (19-38)	0.345
		Pouch-anal anastomosis	40 (24-45)	40 (30-40)	40 (23-51)	0.797
	First signal	Pouch-anal anastomosis	4 (2-10)	4 (2-12)	3 (1-19)	0.913

Data is shown as median and interquartile range. ICG: indocyanine green
* Measurements for 33/35 cases: 15 patients with and 18 patients without vascular ligation
** Measurements for 29/32 cases: 9 patients with and 20 patients without vascular ligation

Secondary outcomes

FA findings led to change in management in seven patients (18.4%) (table 3), due to absence of ICG fluorescence in parts of the pouch in six cases and to delayed ICG fluorescence in one. Absence of ICG fluorescence was noticed in a small area of the pouch (<1cm of bowel) in four cases. In two patients, the non-fluorescent part was at the blind loop after pouch construction and was additionally resected. In the two other patients, the non-fluorescent area was in close proximity to the anvil or at the longitudinal stapler line, and was reinforced by sutures. In 2 patients, absence of fluorescence in a segment of terminal ileum (10cm and 25cm) led to selection of a more proximal loop for pouch creation. Intact but delayed ICG fluorescence was noticed in one case between anvil and blind loop (33 seconds) and an ileostomy was created.

Change in management occurred more often after vascular ligation (6/15 (40.0%) vs 1/23 (4.3%); P=0.010) (Table 3). In case of ligation of the ileocolic arcade, change in management occurred in one out of three cases in which additional resection of the blind loop was performed. In case of ligation of interconnecting branches, change in management occurred in four out of ten cases and included suture reinforcement (2/4), additional resection of the blind loop (1/4) or ileostomy creation (1/4). When ligation of both ileocolic arcade and interconnecting branches was performed, 1 out of 2 patients required pouch reconstruction using a more proximal loop. In the latter case, a new pouch was reconstructed after absence of fluorescence in the entire pouch subsequently to ligation of the ileocolic arcade. For adequate length of the new pouch, interconnecting branches were additionally ligated. However, in this case, no intact arcade was present and only segmental branches, leading to an additional resection of 25cm of small bowel. The pouch was created with ICG-perfused small bowel and anastomosed under acceptable tension. No significant differences were found for time values between patients with or without change of management (data not shown).

Table 3: Change in management due to fluorescence angiography in patients with or without vascular ligation

	Vascular ligation (N=15)	**No vascular ligation (N=23)**
No change in management	9 (60.0)	22 (95.7)
Change in management	6 (40.0)	1 (4.3)
Suture reinforcement*	2/6 (33.3)	0/1 (0)
Additional bowel resection	2/6 (33.3)	0/1 (0)
Selection of a more proximal loop	1/6 (16.7)	1/1 (100)
Creation of ileostomy	1/6 (16.7)	0/1 (0)

Data is shown in n (%) or n/n (%), unless otherwise stated
*Excludes routinely performed anastomotic reinforcement

Median additional operative time owing to FA was 3 minutes (IQR 2-3). Time values were not correlated to hemodynamic parameters ($P>0.05$), except for heart rate that was inversely correlated to time value ICGi-inlet ($P=0.024$).

Median postoperative hospital stay was 6 days (IQR 6-14 days). Anastomotic leakage was observed in 6 patients (15.8%). All anastomotic defects were located on the circular anastomosis without signs of ischaemia or retraction. In 5 of 6 leaks, patients required reoperation to create an ileostomy making it a Grade C leak. For management of anastomotic leakage, 4 patients underwent EVAC and 2 had immediate transanal closure of the anastomotic defect. Of the 5 patients that received a secondary ileostomy, 4 had stoma closure after a median of 177 days (total range 131-323) after IPAA, and one patient is still undergoing EVAC therapy.

With regard to the long term results, 83% of patients with an anastomotic leakage (5/6) had a functional anastomosis after a median follow up of 28 months (IQR 24-33 months). The only patient with a stoma still in situ concerned a patient with UC and dysplasia, who had already undergone neoadjuvant chemoradiation and a low anterior resection complicated by a chronic leak, for which the patient underwent a resection of the leaking anastomosis with IPAA.

There was no mortality observed in this cohort. Occurrence of anastomotic leakage did not significantly differ between patients with or without vascular ligation (2/15 (13.3%) vs 4/23 (17.4%), respectively; P=1.000). Two anastomotic leaks in patients with vascular ligation occurred after ligation of interconnecting branches, one of which was combined with ligation of the ileocolic arcade. Anastomotic leakage was observed in 2 of 7 patients with a change in management (28.6%), compared to 4 of 31 (12.9%) when the procedure remained unchanged (P=0.302).

Comparison of time values in patients with or without anastomotic leakage are shown in Table 4. Time values including transit time through the pouch were non-significantly prolonged in patients with anastomotic leakage (anvil-blind loop, time values to pouch-anal anastomosis). Time from ICGi to pouch-anal anastomosis was predictive for anastomotic leakage (P=0.135, AUC=0.734). A cut-off value of 53 seconds was derived to predict anastomotic leakage (specificity 100%, sensitivity 50%, positive predictive value 100%, and negative predictive value 89%).

Table 4: Time to fluorescent enhancement: times values for patients with or without anastomotic leakage.

	t=0	End	Anastomotic leakage (N=6)	No anastomotic leakage (N=32)	P-value
			Time to fluorescence (sec)		
Before anastomosis*	ICG injection	Inlet	20 (15-38)	20 (15-27)	0.763
		Anvil	30 (17-42)	28 (23-32)	0.970
		Blind loop	39 (23-50)	29 (23-52)	0.749
	Inlet	Anvil	3 (2-4)	3 (2-7)	0.693
		Blind loop	9 (3-20)	5 (4-14)	0.655
	Anvil	Blind loop	6 (1-16)	2 (0-3)	0.247
After anastomosis**	ICG injection	First signal	29 (11-44)	25 (20-35)	0.644
		Pouch-anal anastomosis	47 (31-77)	40 (23-40)	0.135
		Distal cuff-anal anastomosis	49 (37-78)	41 (32-51)	0.348
	First signal	Pouch-anal anastomosis	8 (2-40)	3 (2-12)	0.444
		Distal cuff-anal anastomosis	13 (5-41)	14 (5-25)	0.893
	Pouch-anal anastomosis	Distal cuff-anal anastomosis	2 (0-8)	4 (0-13)	0.470

Data is shown as median and interquartile range.
* Measurements for 33/35 cases: 5 patients with and 28 patients without anastomotic leakage
** Measurements for 29/32 cases: 5 patients with and 24 patients without anastomotic leakage
ICG= indocyanine green

In one case, mucosal ischaemia of the blind loop was observed by endoscopy, after ligation of interconnecting branches without stoma creation (Figure 3). Time values were 92 seconds for ICGi-blind loop and 64 sec for anvil-blind loop. No anastomotic leakage occurred, the mucosa seemed to re-epithelialize over time and the pouch was preserved. In the case of intact but delayed ICG fluorescence between anvil and blind loop (33 seconds) after ligation of interconnecting branches leading to primary ileostomy, no anastomotic leakage occurred.

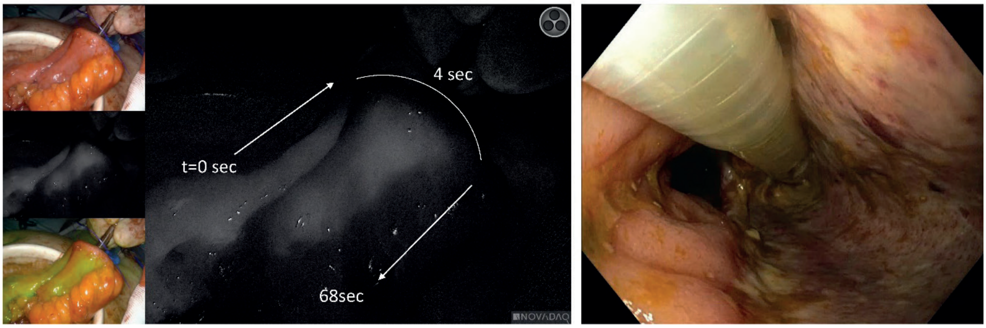

Figure 3: A case with intact but delayed fluorescence and mucosal ischaemia of the blind loop

DISCUSSION

In this study, FA-guided IPAA was described and FA characteristics were evaluated in ileoanal pouches with intact vascularisation as opposed to pouches where lengthening measures required vascular ligation. For the quantitative FA parameter time to fluorescent enhancement, time values were prolonged in patients with vascular ligation, without reaching statistical significance.

FA is of potential added clinical value during IPAA, especially after vascular ligation [8]. Vascular ligation might cause inflow (arterial) or outflow (venous) problems. FA displays problems in arterial flow as absence of ICG in the pouch [8]. Time values were assessed for small bowel parts that were perfused by ICG, translating into intact arterial flow. No significant differences were noticed for time values between patients with or without vascular ligation, although a trend towards prolonged time from ICG injection to first signal was noticed. Time values might therefore indicate redirection of arterial flow through the arcade, or presence of venous outflow obstruction. Increased resistance in the venous network might explain the delayed flow in case of venous outflow obstruction. Therefore, FA during IPAA might enable differentiation between an inflow problem (no ICG fluorescence), an outflow problem (delayed, but intact ICG flow) and adequate perfusion (rapid ICG flow).

When evaluated in a larger group of patients, one might be able to correlate the degree of delayed flow with patient outcomes, including anastomotic leakage and ischaemia. However, this correlation might be less profound for the pouch as compared to conduits that have a single artery supplying tissue perfusion, e.g. the gastric conduit after esophagectomy or the descending colon after low anterior resection [15, 16]. Small bowel showing intact, but delayed ICG fluorescence might still be used for IPAA, as additional resection of this part might further compromise the balance between perfusion and lengthening. However, these cases may benefit from a 3-stage, instead of a modified 2-stage procedure [12].

Absence of ICG signal in parts of the pouch in 6 cases resulted in a change of management in this study to ascertain IPAA reconstruction with ICG-perfused small bowel. Change in management included additional resection or selecting a more proximal small bowel loop for all types of vascular ligation. Ligation of both the ileocolic trunk as well as interconnecting branches should probably be avoided, especially when no arcade is present and the bowel is vascularised by segmental branches. In this study, this resulted in creation of a new pouch and resection of 25cm of non-vital terminal ileum. Anastomotic leakage within the vascular ligation group was only observed after ligation of interconnecting branches, in one combined with ileocolic arcade ligation, suggesting more severe perfusion problems after ligation of interconnecting branches. However, anastomotic leakage might also occur because of traction caused by insufficient reach after optimal mesenteric lengthening.

Anastomotic leakage secondary to perfusion restriction might be prevented by optimisation of perfusion under guidance of FA. In a case-matched study in 64 patients [8], only one leak occurred when FA was not applied. Anastomotic leakage rate of 15.8% as found in the present study is similar to that in a historic cohort without use of FA that also included patients from our centre (±17%) [1]. Interestingly, vascular ligation was more frequently performed when FA was applied (47%) than in a historic control cohort (16%) [8]. In the present cohort, vascular ligation was also regularly performed (39.5%). This might be explained by change in surgical attitude, i.e. becoming more aggressive towards vessel ligation and not accepting minor traction on the anastomosis. However, FA could also provide a sense of security when vascular ligation is performed, because perfusion can be checked more objectively. Especially after vessel ligation, it is important to check perfusion by FA as this led to significantly more cases of change in management in this study. Although not routinely done in this cohort, perfusion should ideally be checked using FA before creation of the pouch.

In this study, one fluorescence imaging system with standard settings was used with a standard ICG dose. It is unknown how these findings relate to a setting with a different imaging system and ICG dose. In future studies, calibration of imaging systems is mandatory to identify differences in fluorescence read-out. Furthermore, in this study the fluorescent signal was still interpreted subjectively. To asses separate (inflow) fluorescence parameters of FA more objectively, software that is able to produce fluorescence-time curves is a promising tool for future research (NTR trialregister.nl, NL8653) [10]. An advantage of the curves is that outflow can also be quantified, hopefully enabling to report on (the possible impact of) venous congestion.

Correlation with hemodynamic parameters was evaluated, and only heart rate was significantly correlated. The inverse correlation seems plausible, as time values between ICG injection and arrival at the pouch might prolong when the heart rate decreases. It is important to further study the association between hemodynamics and FA, as FA assessment and its threshold are ideally independent of the patient's hemodynamic state. Besides mean arterial pressure, heart rate and noradrenaline usage, other potential important parameters to take into account are cardiac output [17], viscosity (haematocrit) and the patient's temperature. In the future, prediction models created by conventional statistics or by the use of artificial intelligence might take both patient characteristics and FA thresholds into account, which probably allow for more precise prediction of patient outcomes.

Limitations of this study include a small population as no power calculation was performed, retrospective collection of patient and operative data, and a low number of events of vascular ligation and anastomotic leakage. However, this was a explorative study and although patient data were collected retrospectively, vascular ligation was often reported, and when not, it could be checked on surgical recordings. Because of the retrospective nature of this study, patients related outcome measures were not captured. Prospective studies are warranted to include these functional outcomes. Correction for the multifactorial aetiology of anastomotic leakage and stratifying for possible confounders was not possible in this study owing to a low absolute number of events, and this might have led to biased results. Redo pouches were not included in this cohort, however this is an interesting population to verify perfusion and a potential focus for further research to elucidate the role of FA in pouch surgery.

However, this is amongst the first studies reporting on FA-guided IPAA, and to our knowledge the first that evaluated a quantitative FA value.

Results from this study support that FA can differentiate between arterial (no ICG fluorescence) and venous (intact but delayed ICG fluorescence) problems or adequate perfusion (rapid ICG flow). A larger prospective cohort must be conducted to identify potential thresholds for predicting patient outcomes.

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CHAPTER 7

Understanding fluorescence time curves during ileal pouch-anal anastomosis with or without vascular ligation

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ABSTRACT

Background: Intraoperative indocyanine green fluorescence angiography (ICG-FA) may be of added value during pouch surgery, in particular after vascular ligations as lengthening maneuver. The aim was to determine quantitative perfusion parameters within the efferent/afferent loop and explore the impact of vascular ligation. Perfusion parameters were also compared in patients with and without anastomotic leakage (AL).

Methods: All consenting patients that underwent FA-guided ileal pouch-anal anastomosis (IPAA) between July 2020 and December 2021 were included. After intravenous bolus injection of 0.1mg/kg ICG, the near-infrared camera (Stryker Aim 1688) registered the fluorescence intensity over time. Quantitative analysis of ICG-FA from standardized regions of interests on the pouch was performed using software. Fluorescence parameters were extracted for inflow (T_0, T_{max}, F_{max}, slope, Time-to-peak) and outflow ($T_{90\%}$ and $T_{80\%}$). Change of management related to FA findings and AL rates were recorded.

Results: Twenty-one patients were included, three patients (14%) required vascular ligation to obtain additional length, by ligating terminal ileal branches in two and the ileocolic artery (ICA) in one patient. In nine patients the ICA was already ligated during subtotal colectomy. ICG-FA triggered a change of management in 19% of patients (n=4/21), all of them had impaired vascular supply (ligated ileocolic/ terminal ileal branches). Overall, patients with intact vascular supply had similar perfusion patterns for the afferent and efferent loop. Pouches with ICA ligation had longer T_{max} in both afferent as efferent loop than pouches with intact ICA (afferent 51 and efferent 53 versus 41 and 43 seconds respectively). Mean slope of the efferent loop diminished in ICA ligated patients 1.5(IQR 0.8-4.4) versus 2.2(1.3-3.6) in ICA intact patients.

Conclusion: Quantitative analysis of ICG-FA perfusion during IPAA is feasible and reflects the ligation of the supplying vessels.

INTRODUCTION

Ileal pouch- anal anastomosis (IPAA) helps to restore continuity after proctocolectomy for patients with ulcerative colitis, familial adenomatous polyposis and well selected patients with Crohn's colitis(1). After pouch surgery, a feared complication is anastomotic leakage (AL) which can occur in up to 15% of patients (2, 3). A traction-free, well-vascularized anastomosis is essential for anastomotic healing, and in pouch surgery these two factors need to be carefully balanced. In order to have a tension free anastomosis, lengthening manoeuvres may require vascular ligation(4) of the ileocolic artery(ICA) or ileal arterial branches. In most patients the ICA is already compromised at initial subtotal colectomy, and further vascular ligations may even have a bigger impact.

Intraoperative fluorescence angiography using indocyanine green (ICG-FA) is widely applied to assess tissue perfusion and could contribute to the prevention of AL secondary to perfusion restriction (5, 6). During IPAA, ICG-FA may be of added value as it can guide safe vascular ligations without increasing the incidence of AL (7, 8). However, the interpretation of ICG-FA remains mostly subjective, and quantification of ICG-FA remains a challenge (9, 10). First efforts in quantifying the fluorescence signal during IPAA surgery support that time from ICG administration to fluorescent enhancement of the afferent and efferent loop may be prolonged in patients with vascular ligation(7). Outflow on the other hand may also provide valuable information, as outflow problems are correlated to venous congestion contributing to ischemia (11). Taking this into account, it is important to focus on both inflow as outflow parameters.

The objective of the present pilot study is to determine quantitative fluorescent parameters to assess in- and outflow in relation to vascular ligation during IPAA surgery. Intraoperative change of management related to ICG-FA and AL were recorded.

MATERIALS AND METHODS

Study design

This case series has been reported in line with the PROCESS Guideline(12). In this single center pilot study, we included all consenting patients that underwent FA-guided IPAA in Amsterdam UMC from July 2020 until December 2021.

Patients were included when they met the following criteria: 18 years or older, proctocolectomy or completion proctectomy with (redo) IPAA for inflammatory bowel disease or inherited colorectal cancer disorders. Patients were excluded in case of allergy to ICG, iodide or sodium iodide. ICG-FA data were recorded in a prospectively maintained database, along with patient data from the electronic patient system.

The Institutional Review Board of the Amsterdam University Medical Centres (UMC), location Academic Medical Centre (AMC), approved the study protocol and confirmed that the Medical Research lnvolving Human Subjects Act (WMO) did not apply.

Surgical procedure

Different strategies for restorative proctocolectomy with IPAA were applied, including 1 and modified-2- stage procedures (13). The modified 2-stage procedure was the standard approach after prior subtotal colectomy for refractory disease. In patients who had their subtotal colectomy at Amsterdam Medical Centres, the ileocolic arcade was preserved as a routine. In patients referred from other units, the ileocolic arcade was mostly not preserved, and this was verified through the operative notes and postoperative abdominal CT if available.

Completion proctectomy and IPAA were performed by a combined abdominal and transanal minimally invasive approach as described previously (11). Standard lengthening manoeuvres consisted of dividing all adhesions, mobilization of the terminal ileal mesentery to the level of the duodenum and transverse peritoneal incisions on both sides of the small bowel mesentery. The yardstick for sufficient length was that the apex of the pouch should reach 1-2 cm below the pubic bone. If length was considered insufficient, the ICA and/or interconnecting terminal ileal branches were ligated (Figure 1). After securing sufficient length, the J-pouch was constructed by a side-to-side ileal anastomosis of 10 cm length using a linear stapler. A double purse string single staple anastomosis was performed as a routine with suture reinforcement. A diverting ileostomy was only created in case of technical problems (e.g. positive reverse leak test or subjective feeling of tension on the anastomosis) or aberrant ICG-FA findings (i.e. delayed fluorescence enhancement based on subjective interpretation of the surgeon).

Standardised fluorescent assessment

Perfusion of the pouch was assessed extracorporeally before connection of anvil and stapler for the anastomosis. The operating table was placed in a neutral position, the laparoscopic Stryker 1688 camera system (Stryker, Kalamazoo, MI, U.S.A.), 30 degree optic was placed in a fixed position 9 cm perpendicular from the anvil in the top of the pouch. All light in the operation room was switched off to minimize external light reflection. ICG (Verdye, Diagnostic Green; 0.1mg/kg/bolus) was injected peripherally as a bolus directly in the iv catheter of the left arm without iv extension. Starting with the moment of ICG injection, perfusion was captured in a continuous video recording for 200 seconds.

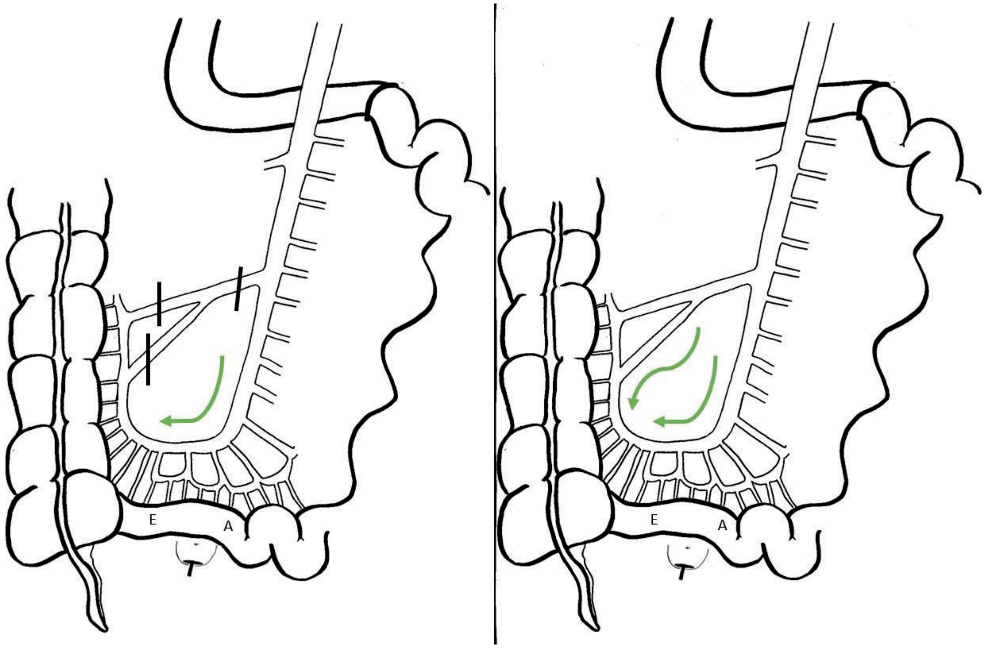

Figure 1. Route of ICG in case of ligation of the ileocolic artery (left) and an intact ileocolic artery (right) with E representing the efferent and A the afferent loop of the pouch. Adapted with permission from Slooter et al (7).

Quantification of fluorescent imaging

In order to achieve objective quantification, the raw ICG- FA video data were analysed post hoc by tailor made software written in Python (COPYRIGHT)**.** After loading the video into the software, size was calibrated using a measuring tape which was placed in the frame. Subsequently, a circular region of interests (ROI) with a diameter of 1 cm was placed in the middle of the pouch body, both on the afferent and efferent loop (Figure 2). The software subsequently extracted the mean intensity within the ROI for every frame and plotted the ICG in- and outflow in a fluorescence–time curve.

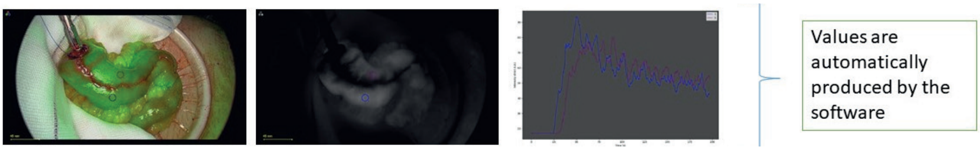

Figure 2. J-pouch and example how the ROI selection is made and curve generated.

A slightly modified version of the arterial input function reported by Elliott et al. was fitted to the curve to reduce the influence of noise on the calculated parameters (14). From this fit, the following parameters were extracted (Figure 3): Influx time point (t0): the time point at which the fit started, thereby increasing to above baseline intensity, F_{max}: maximal intensity in arbitrary units (AU), T_{max}: time in seconds from ICG administration until F_{max} has been reached., time-to-peak (ttp); time in seconds from τo until F_{max} has been reached, mean slope: mean rate at which the fluorescence intensity increased between t0 and T_{max} (AU/s), $T_{90\%}$: time in seconds after F_{max} until fluorescence intensity has dropped to 90% of F_{max} and $T_{80\%}$: time in seconds after F_{max} until fluorescence intensity has dropped to 80% of F_{max}.

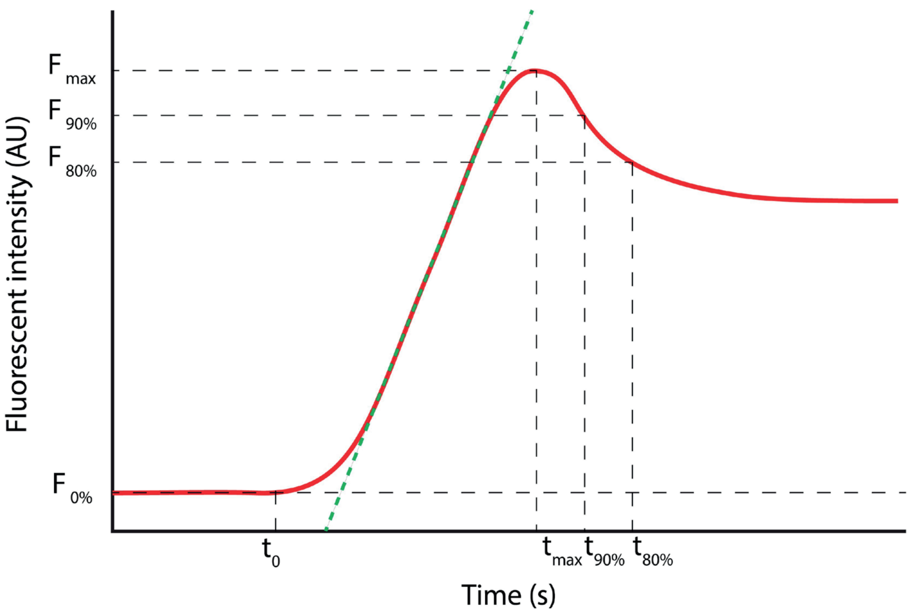

Figure 3. Fluorescent parameters: Influx time point (t0): the time point at which the fluorescence intensity in the ROI was statistically significantly larger than the background, F_{max}: maximal intensity in arbitrary units (AU), t_{max}: time in at which the background-corrected fluorescence intensity reached F_{max}, time-to-peak (ttp): T_{max} - t_0, the green line represents the mean slope: rate at which the fluorescence intensity increased (AU/s), $t_{90\%}$: time in seconds after F_{max} until 90% of F_{max} has been reached, $t_{80\%}$: time in seconds after F_{max} until 80% of F_{max} has been reached

Outcomes

The primary outcome was to determine quantitative perfusion parameters during IPAA within the efferent/afferent loop and explore the impact of lengthening measures requiring vascular ligation or previous inadvertent interruption of the ileocolic arcade. Perfusion parameters in patients with AL were also compared to those without.

Secondary outcomes included change in management due to FA, AL within 90 days and reinterventions due to AL. Change in management by FA was defined as every measure taken based on the results of FA only; i.e suture reinforcement of hypo-perfused regions, additional resections or preserving the pouch and creating an ileostomy. Interpretation of FA was mainly based on presence and absence of fluorescent signal in parts of the pouch. AL was recorded when an anastomotic defect was objectified by CT-scan or during endoscopy and was graded according to impact on clinical management similar to Sahami et al (3).

Statistics

Patient baseline characteristics and imaging characteristics are summarized using simple descriptive statistics. All categorical data will be presented as number of cases and percentages, whilst continuous data will be shown as either mean ± standard deviation or as median and interquartile range (IQR), depending on the data distribution. Data was analyzed using the Statistical Package for Social Sciences (SPSS) of IBM Statistics, version 26.0, or the latest version.

RESULTS

Baseline characteristics

In total, 21 patients were included in this study with a mean age of 40.5 ±11.3 years at time of IPAA. Half of the patients were male (52.4%). Patient characteristics are outlined in Table 1.

Operative characteristics

Operative characteristics are outlined in Table 2. The abdominal approach was in all except two patients via laparoscopy, requiring conversion into a laparotomy in one patient due to the extensiveness of dense adhesions. All patients underwent transanal minimally invasive surgery for the proctectomy, rectal cuff mobilization and double purse string single stapled anastomosis.

Table 1. Baseline characteristics

	IPAA (N=21)	AL (N=3)	No AL (N=18)
Gender, male	11 (52.4)	1/3	10/18
Age (years) mean+SD	40.5 +11.3	37.3+11.0	41.0+11.6
BMI (kg/m^2) mean+SD	25.8 +4.9	25.4 +4.1	25.9 +5.1
ASA classification (≤2)	18 (85.7)	2/3	16/18
Smoker (active)	1 (4.8)	0	1/18
Comorbidity*			
Vascular	0	0	0
Diabetes Mellitus	2 (9.5)	0	2/18
Diagnosis			
Ulcerative Colitis #	19 (90.5)	3/3	16/18
FAP	2 (9.5)	0	2/18
Medication for UC			
None	16/19	3/3	13/16
Mesalazine	2/19	0	2/16
Biologicals	1/19	0	1/16

Data is shown in n (%), unless otherwise stated, ASA , BMI body-mass index, IPAA ileal pouch-anal anastomosis, *Vascular comorbidity: brain infraction, myocardial infarction, or peripheral vascular disease. Diabetes Mellitus: type 1 or 2. # of whom one had secondary sigmoid carcinoma and one multifocal dysplasia, FAP: Familial adenomatous polyposis, UC: ulcerative Colitis

Vascular ligation

In almost half of the patients the ICA had already been ligated during the previous subtotal colectomy. During IPAA, intraoperative vessel ligation was performed in three patients to obtain sufficient reach for anastomosis, consisting of ligation of the ICA in one patient and interconnecting terminal ileal branches in two patients. Both patients with ligation of interconnecting terminal ileal branches had intact ICA.

FLUORESCENCE OUTCOMES

Vascular ligation group

In Table 3 the fluorescent parameters are summarized for patients with an intact or interrupted ICA. In patients without vascular ligation time values were similar for the afferent and efferent small bowel loops. When comparing the ICA ligated to intact ICA pouches, the time to achieve maximum fluorescent intensity (T_{max}) was 10 seconds longer in both the afferent as efferent loop of the pouch (afferent 51 and efferent 53 versus 41 and 43 seconds respectively). In case of ICA ligation the mean slope of the efferent loop was less steep 1.5 AU/sec (IQR 0.8-4.4) versus 2.2 AU/sec (IQR 1.3-3.6) without ligation. Regarding the outflow parameters: longer time intervals were observed to reach 80% of F_{max} in the ligation group (10 versus 16 sec respectively).

Table 2. Operative characteristics

	FA-guided IPAA (n=21)
Prior surgery definite ileocolic vessel ligation	9 (42.9)
Stage procedure	
1- stage	1 (4.8)
2- stage	1 (4.8)
Modified 2-stage	14 (66.7)
3-stage	4 (23.8)
Other*	1 (4.8)
Abdominal approach	
Laparoscopy	19 (90.5)
Open	2 (9.5)
Transanal approach	
TAMIS	21 (100)
Abdominal conversion	1 (4.8)
Mobilisation	
Mesenteric incisions	21 (100)
Intraoperative vessel ligation	3 (9.6)
Ileocolic vessel ligation	1 (4.8)
Interconnecting terminal branches	2 (4.8)
Construction anastomosis	
Hand-sewn	0
Stapled	21 (100)
Size stapler	
28 mm	0
29 mm	4 (19)
31 mm	1 (4.8)
32 mm	16 (76.2)
Median distance to DL in cm (IQR)	2 (1-2)
Operative time	240 (230-213)
Intraoperative complications*	0

Data is shown in n (%) or n/n), unless otherwise stated, * redo pouch due to FAP overgrowth in the initial pouch, TAMIS; Transanal Minimally Invasive Surgery**,** DL: dentate line
Intraoperative complications included: bleeding >0.5L, iatrogenic ureteral injury, serosal laesion, bowel perforation

In Figure 4 curves based on the median values among the two groups are represented, despite a difference in fluorescence intensity the curves of the afferent and efferent loops of the two groups have similar shapes during in- and outflow.

Both patients in whom the interconnecting terminal ileal branches were ligated had macroscopic blue colorization of the efferent loop during the surgery. In one patient, T_{max} in both the afferent as efferent loop was prolonged (see Supplementary Table 1) with T_{max} of 67 seconds for efferent loop, but the bowel loops showed clear fluorescence enhancement (F_{max} 84 for afferent and 71 for efferent loop). In both patients, outflow was prolonged with $T_{80\%}$ in the afferent loop of 13 and in the efferent loop of 36 seconds for one patient and. 23 and 71 seconds for the other

Table 3. Fluorescent parameters for patients with an intact ileocolic arcade and the ileocolic artery ligated during prior surgery or intraoperatively

Fluorescence parameter	ICA intact (n=11)	ICA ligated (n=10)
	Afferent loop	
	Inflow parameters	
t0 (sec)	29 (23- 35)	27 (16-51)
t_{max} (sec)	41 (36-58)	51 (31-71)
ttp (sec)	17 (12-24)	17 (8-36)
F_{max} (AU)	46 (39-57)	49 (33-97)
Slope (AU/sec)	2.4 (2.2-3.5)	2.1 (1.4-3.1)
Outflow parameters		
$t_{90\%}$ (sec)	5 (5-10)	6 (5-10)
$t_{80\%}$ (sec)	10 (8-20)	14 (9-20)
Efferent loop		
	Inflow parameters	
t0 (sec)	30 (24-35)	31 (24-71)
t_{max} (sec)	43 (36-65)	53 (34-64)
ttp (sec)	20 (9-24)	17 (10-28)
F_{max} (AU)	40 (32-71)	37 (25-77)
Slope (AU/sec)	2.2 (1.3-3.6)	1.5 (0.8-4.4)
	Outflow parameters	
$t_{90\%}$ (sec)	6 (5-11)	8 (5-17)
$t_{80\%}$ (sec)	10 (7-18)	16 (9-31)

Abbreviations: ICA: ileocolic artery, sec: seconds, ttp: time-to-peak, AU: arbitrary units, slope: mean slope

Change of management due to ICG-FA assessment

Based on qualitative assessment of the ICG-FA, change of management was opted in four out of 21 patients (19%). Of these, two patients had prior ICA ligation and two patients necessitated intraoperative ligation of the interconnecting terminal ileal branches to obtain more length. One patient with prior ICA ligation had delayed fluorescent enhancement of the entire pouch, with no fluorescent enhancement in the apex of the pouch. This region was inverted by sutures. In retrospect, flat slopes in both the afferent as efferent loop (0.75 and 0.64) were observed. This patient developed an AL on postoperative day 16. In the second patient with prior ICA ligation, there was a delayed fluorescent enhancement of the efferent loop of the pouch. The anastomosis was constructed, and a protective ileostomy was created, switching from a planned modified 2-stage into a 3-stage procedure. In one patient after ligation of the interconnecting terminal branches, a delayed enhancement during ICG-FA was observed in the apex of the pouch, which was not observed by white light assessment, therefore this hypoperfused area was inverted by sutures. In the other patient after ligation of the interconnecting terminal ileal branches, the pouch body discolored gradually in white light, but subsequent ICG-FA showed uniform and rapid enhancement. The operative plan was changes from a 1-stage into a 2-stage procedure. The latter three patients had an uncomplicated postoperative course.

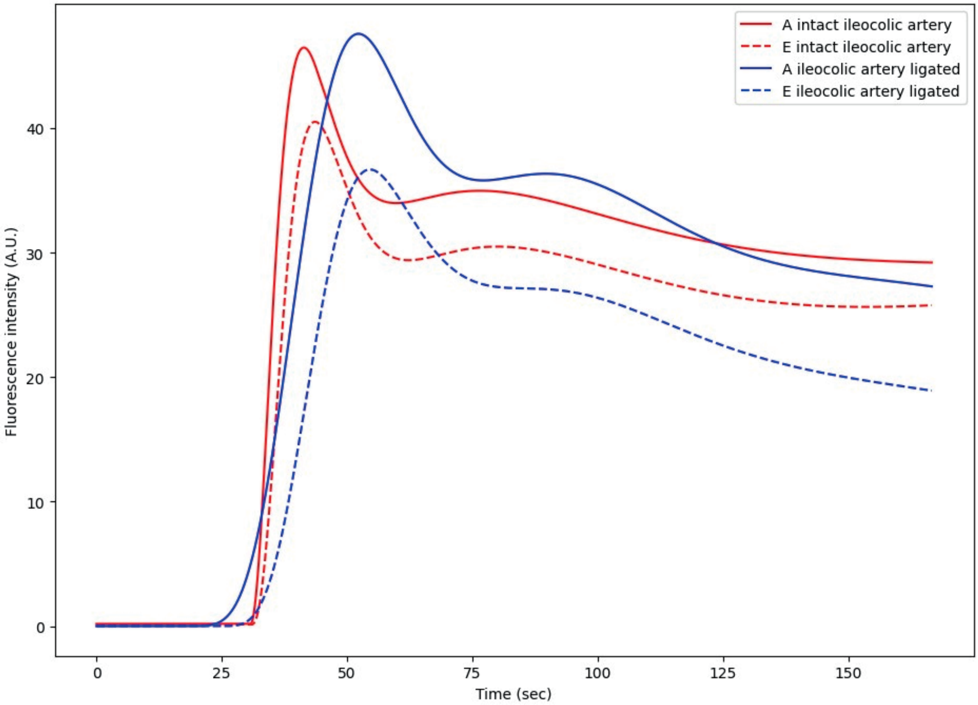

Figure 4. Curves based on the median value of fluorescence parameters of the group with and without ligation of the ileocolic arcade in the afferent and efferent loop

Postoperative outcomes

Fluorescence parameters are summarized in Table 4, in which the results are also shown for patients with or without AL seperately. AL was observed in three out of 21 patients (14%), all located at the circular anastomosis and diagnosed on postoperative day 5, 12 and 16. All patients did not have an ileostomy at moment of diagnosis. Two of the AL were diagnosed by endoscopic examination and the remaining one by CT scan. All patients were treated by creating an ileostomy and subsequent Endo-SPONGE® (B. Braun Surgical S.A., Barcelona, Spain) vacuum assisted closure (EVAC) procedures (15). All ileostomies were reversed within 1 year, without long term sequelae.

Longer time values were observed in these few patients for both in- as outflow parameters with respect to the afferent as efferent loop (see Table 3). The mean slope in the afferent loop was less steep in the AL group (1.4 versus 2.4 AU/sec).

Table 4. An overview of the different fluorescent parameters for the overall group, and a comparison of fluorescent parameters in patients with and without anastomotic leakage.

Fluorescence parameter	Total (n=21)	No AL (n=18)	AL (n=3)*
	Afferent loop		
	Inflow parameters		
t0 (sec)	25 (16-36)	26 (16-36)	38 (30-43)
t_{max} (sec)	47 (35-62)	44 (34-65)	49 (38-58)
ttp (sec)	17 (12-26)	16 (11-30)	20 (15-20)
F_{max} (AU)	56 (35-59)	51 (39-65)	32 (21-57)
Slope (AU/sec)	2.4 (1.6- 3.3)	2.4 (1.8-3.5)	1.4(0.8-2.5)
Outflow parameters			
$t_{90\%}$ (sec)	7 (6-11)	6 (5-9)	10 (8-13)
$t_{80\%}$ (sec)	12 (9- 21)	10 (8-19)	20 (18-23)
	Efferent loop		
	Inflow parameters		
t0 (sec)	27 (22-34)	29 (24-42)	33 (31-39)
t_{max} (sec)	49 (36-63)	44 (36-65)	51 (43-57)
ttp (sec)	17 (10-25)	17 (9-25)	22 (17-26)
F_{max} (AU)	40 (33-72)	39 (25-72)	47 (33-53)
Slope (AU/sec)	1.9 (1.1- 4.0)	1.6 (1.2-4.6)	2.2 (0.6-3.0)
	Outflow parameters		
$t_{90\%}$ (sec)	7 (5-13)	7(5-12)	8 (5-11)
$t_{80\%}$ (sec)	12 (9- 21)	12 (7-20)	15 (11-22)

Abbreviations: sec: seconds, ttp: time-to-peak, AU: arbitrary units, AL: anastomotic leakage, slope: mean slope
All numbers are medians and interquartile ranges between brackets. *signifies given median and range between brackets

DISCUSSION

By quantifying ICG-FA of 21 patients undergoing IPAA surgery, we were able to determine quantitative in- and outflow parameters within the pouch and explore the impact of lengthening measures requiring vascular ligation or previous inadvertent interruption of the ICA. In patients without vascular ligation of the ICA perfusion parameters between afferent and efferent loops were similar. However in patients with vascular ligation of the ICA both in- and outflow time values were prolonged and the mean slope was less steep in the efferent loop of the pouch.

This study supports prior results, patients without vascular ligation show rapid in and outflow similarly in both afferent and efferent loop. In case of ligation, changes are observed predominantly in the efferent loop with in- and outflow. This might be due to redirection of arterial flow through the arcade or potential venous obstruction. By contrast in case of AL, changes are also seen, but particularly in the afferent loop. ICG-FA is a promising tool to demonstrate adequate perfusion in gastrointestinal surgery(16). This technique is potentially of added value during IPAA surgery, especially after vascular ligation (7, 8, 11, 17). However, it remains challenging to differentiate between inflow (arterial) or outflow (venous) problems. Prior work indicates that it might be categorized in inflow problem (no ICG fluorescence), an outflow problem (delayed, but intact ICG flow) and adequate perfusion (rapid ICG flow) (7). However, the use and interpretation of ICG-FA enhancement depends on subjective interpretation and in- and outflow might affect each other.

This study shows that changes are visible in the shape of the curve and quantification parameters in the event of vascular ligation. Despite the fact that the curves in this study were not generated in real time, the clinical application for employing ICG-FA during IPAA might lie there. It can be challenging to determine intraoperatively whether the ICA is still intact. Particularly in patients with visceral obesity and in those cases where the arcade has been interrupted by ligation the descending branch of the ICA. In these patients ICG-FA can be applied to explore the integrity of the ICA and if needed to assess whether additional ligation of the interconnecting terminal ileal branches is possible. It is important to pay attention to keep the ICA intact when performing the colectomy since this might compromise perfusion and endanger the pouch's (specifically the efferent loop's) perfusion.

This is the first study to report on quantitative parameters of fluorescent time curves in IPAA surgery. All measurements were performed in a standardized manner and similar conditions. This produced valuable in and outflow ICG fluorescence data not reported before. The current study created new knowledge on pouch perfusion in general and explored the effect of lengthening measures on quantitative pouch perfusion patterns. The described technique is reproducible and will lead to a more objective interpretation of fluorescence angiography. A limitation of the study is that the cohort is too small to draw any firm conclusions regarding quantitative parameters and anastomotic leakage. However trends appear to be evident in the enhancement curve of the mainly the afferent loop of the pouch. If a quantitative threshold can be determined, this may select high risk patients for AL. Larger prospective trials should be carried out enabling multivariate analysis to identify a fluorescent threshold that may predict anastomotic leakage. This might influence clinical decision making intra- or postoperatively. For example changing a modified 2-stage into a 3- stage procedure or by taking pre-emptive measures postoperatively; for instance performing an early pouchoscopy for anastomotic inspection or pre-emptive endoSPONGE placement (11).

Besides, one fluorescence imaging system with standard settings was used. It is unknown how these findings relate to a setting with a different imaging system. In future studies, calibration of imaging systems is needed to identify differences in fluorescence read-out. Furthermore, in this study the fluorescent signal was still interpreted subjectively for intraoperative decision making.

In conclusion, this study explored the effect of vascular ligation on pouch perfusion using quantitative ICG- FA. Evident changes in perfusion were found after ligation, mainly in the efferent loop of the pouch. ICG-FA can detect previous vascular ligation and might guide surgeons during clinical decision making intra- or postoperatively in IPAA.

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SUPPLEMENTARY MATERIAL

Supplementary Table 1. Fluorescence parameters of the patients with ligation of the interconnecting terminal ileal branches.

	Pt 1	Pt 2
Afferent loop		
Inflow parameters		
t0 (sec)	24	23
t_{max} (sec)	33	53
ttp (sec)	41	84
F_{max} (AU)	8.5	29
Slope (AU/sec)	2.8	2.3
Outflow parameters		
$t_{90\%}$ (sec)	7	14
$t_{80\%}$ (sec)	13	23
Efferent loop		
Inflow parameters		
t0 (sec)	26	32
t_{max} (sec)	36	67
ttp (sec)	41	71
F_{max} (AU)	11	35
Slope (AU/sec)	2.3	1.5
Outflow parameters		
$t_{90\%}$ (sec)	14	36
$t_{80\%}$ (sec)	36	71

Abbreviations: sec: seconds, ttp: time-to-peak, AU: arbitrary units, AL: anastomotic leakage, slope: mean slope

CHAPTER 8

Perfusion assessment by fluorescence time curves in esophagectomy with gastric conduit reconstruction: a prospective clinical study

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ABSTRACT

Background: Intraoperative perfusion assessment with indocyanine green fluorescence angiography (ICG-FA) may reduce postoperative anastomotic leakage rates after esophagectomy with gastric conduit reconstruction. This study evaluated quantitative parameters derived from fluorescence time curves to determine a threshold for adequate perfusion and predict postoperative anastomotic complications.

Methods: This prospective cohort study included consecutive patients who underwent FA-guided esophagectomy with gastric conduit reconstruction between August 2020 and February 2022. After intravenous bolus injection of 0.05 mg/kg ICG, fluorescence intensity was registered over time by PINPOINT camera (Stryker, USA). Fluorescent angiograms were quantitatively analyzed at a region of interest of 1 cm diameter at the anastomotic site on the conduit using tailor made software. Extracted fluorescence parameters were both inflow (T_0, T_{max}, F_{max}, slope, Time-to-peak) as outflow parameters ($T_{90\%}$ and $T_{80\%}$). Anastomotic complications including anastomotic leakage (AL) and strictures were documented. Fluorescence parameters in patients with AL were compared to those without AL.

Results: One hundred and three patients (81 male, 65.7 $\pm$ 9.9 years) were included, the majority of whom (88%) underwent an Ivor Lewis procedure. AL occurred in 19% of patients (n=20/103). Both time-to-peak as T_{max} were significantly longer for the AL group in comparison to the non-AL group (39 sec vs. 26 sec, p=0.04 and 65 vs. 51 seconds, p=0.03 respectively). Slope was 1.0 (IQR 0.3-2.5) and 1.7 (IQR 1.0-3.0) for the AL and non-AL group (p=0.11). Outflow was longer in the AL group, although not significantly, $T_{90\%}$ 30 versus 15 seconds respectively, p=0.20). Univariate analysis indicated that T_{max} was predictive for AL (p=0.10, area under the curve 0.71) and a cut-off value of 97 seconds was derived, with a specificity of 92%.

Conclusion: This study demonstrated quantitative parameters and identified a fluorescent threshold which can be used for intraoperative decision making and to identify high-risk patients for AL during esophagectomy with gastric conduit reconstruction.

INTRODUCTION

Esophagectomy with gastric conduit reconstruction is an essential part of multimodal curative treatment of resectable esophageal cancer (1). Anastomotic leakage (AL) remains a life-threatening complication with an incidence of 7-30 %(2). The most common risk factors for AL of the esophagogastrostomy are torsion of or tension on the anastomosis, location of anastomosis, surgeon experience, active smoking and corticosteroid therapy (3, 4). Another important risk factor is poor blood supply at the anastomotic site. The gastric conduit is especially at risk as it mainly relies on the right gastroepiploic artery and right gastric artery for its blood supply (5). Among these risk factors, only perfusion and anastomotic tension/torsion can be intervened upon intraoperatively (6). However, intraoperative evaluation of gastrointestinal perfusion is challenging. Studies on this subject are lacking uniformity in approach, reliability and objectivity.

Indocyanine green fluorescence angiography (ICG-FA) is a promising tool to demonstrate adequate perfusion. Although, at this moment the use of this technique contends with similar shortcomings as previous intraoperative tools with regard to subjectivity and inter-user variability(7). Possibly partly due to these factors, studies show inconsistent results of the effect of ICG-FA on anastomotic leakage rates (8-11).

Ideally, a quantitative threshold for the fluorescence signal will be identified to predict adequate perfusion and postoperative outcomes. In order to establish a threshold, numerous research teams have been searching for quantifiable fluorescence parameters; from relatively simple quantification methods, such as time to fluorescence, to more complex methods such as fluorescence time curves (12, 13). However, all of these studies were retrospectively executed or had small sample sizes.

This study evaluates various parameters derived from fluorescence time curves as a quantitative value for ICG-FA and aims to determine a threshold to predict anastomotic complications in patients undergoing esophagectomy with gastric conduit reconstruction.

METHODS

Study design

In this single-centre prospective study, we included consecutive patients that underwent esophagectomy in Amsterdam UMC from August 2020 until February 2022.

Patients were included when they met the following criteria: 18 years or older and esophagectomy with gastric conduit reconstruction (Ivor Lewis or McKeown procedure). Exclusion criteria were: no informed consent, robot assisted procedures or allergy to ICG, iodide or sodium iodide. FA data were recorded in a prospectively maintained database. Patient data were extracted from a prospectively maintained database. The Institutional Review Board of the Amsterdam UMC location University of Amsterdam, approved the study protocol and confirmed that the Medical Research lnvolving Human Subjects Act (WMO) did not apply.

Surgical procedure

Before surgery, patients standardly received neoadjuvant treatment, usually consisting of chemoradiotherapy or perioperative chemotherapy (14, 15). Based on the primary tumor location and the radiation field, patients underwent either an Ivor Lewis or a McKeown procedure, as previously described(16). In brief, after mobilization of the esophagus, and intrathoracic and abdominal lymphadenectomy, ligation of the left gastric artery, right gastric artery at the angulus of the stomach, the left gastro-epiploic artery and the short gastric vessels was performed. A 3-4cm wide gastric tube was constructed. In Ivor Lewis esophagectomy, an intrathoracic anastomosis was created with a stapled anastomosis. The anastomosis was covered by an omental wrap and mediastinal pleural flap(17).

During the abdominal phase of the McKeown procedure, the gastric conduit was constructed through a small upper abdominal midline laparotomy when a minimally invasive approach was followed. Consequently, a left cervical incision was made, the gastric conduit was brought up to the cervical region through the prevertebral route and a hand-sewn or cervical anastomosis was created, and wrapped with omentum.

Standardised fluorescence assessment

ICG-FA was performed both before and after creation of the anastomosis, after the gastric conduit was brought up into the thorax (Ivor Lewis procedure) or exteriorly through the abdominal incision (McKeown procedure). Before ICG-FA, the planned anastomotic site of the gastric conduit was determined by visual inspection and measuring the needed gastric conduit length which was marked.

During the McKeown procedure an estimation was made on the predicted gastric conduit length; this point was marked during assessment. Subsequently, the camera was fixed in a laparoscopic holder 9 cm from the planned anastomotic site.

All surrounding light was turned off. ICG-FA was performed after administration of ICG (0.05 mg/kg/bolus) through a peripheral infusion cannula and FA images were captured for 200 seconds. Post anastomotic assessment was performed, in which the laparoscopic camera was fixed 6 cm from the anastomosis in a laparoscopic holder and FA was captured for 200 seconds. This distance was chosen for a more optimal view of the gastric conduit after anastomosis.

The laparoscopic PINPOINT camera (Stryker, Kalamazoo, MI, USA) was used to detect ICG. Based on the subjective interpretation of the fluorescence enhancement ICG-FA assessment, the surgeon was allowed to prompt change in surgical management. Change in management included extra mobilization or higher pull up of the gastric conduit, or choosing a more proximal anastomotic site with additional resection of the gastric conduit.

Quantification of fluorescent imaging

In order to achieve objective quantification, the raw FA data were analysed by tailor made software written in Python on basis of a gray-scale analysis**.** After loading the video into the software, size was calibrated using a measuring tape which was placed in the frame. Subsequently, a circular region of interests (ROI) with a diameter of 1 cm was placed in the midline of the gastric conduit at the planned anastomotic site. Subsequently, the software extracted the mean intensity within the ROI for every frame and plotted the ICG in- and outflow in a fluorescence time curve(Figure 1).

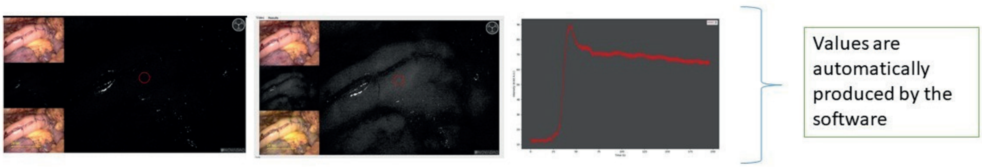

Figure 1. Represents region of interest (ROI) selection and how the fluorescence time curve is produced.

A slightly modified version of the arterial input function reported by Elliott et al. was fitted to the curve to reduce the influence of noise on the calculated parameters (18). From this fit, the following parameters were extracted (Figure 2): Influx time point (t0): the time point at which the fluorescence intensity in the ROI was statistically significantly larger than in the background, F_{max}: maximal intensity in arbitrary units (AU) , T_{max}: time in seconds from ICG administration until F_{max} has been reached, time-to-peak (ttp); time in seconds from t0 until F_{max} has been reached. Mean slope from t0 until F_{max}: rate at which the fluorescence intensity increased (AU/s), $T_{90\%}$: time in seconds after F_{max} until 90% of F_{max} has been reached, $T_{80\%}$: time in seconds after F_{max} until 80% of F_{max} has been reached.

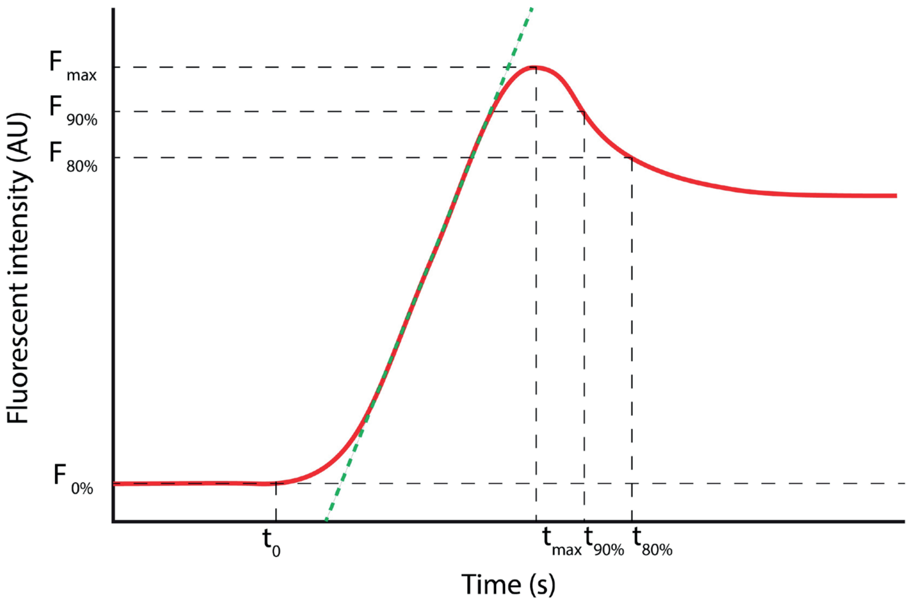

Figure 2. Fluorescence parameters
Influx time point (t0): the time point at which the fluorescence intensity in the ROI was statistically significantly larger than the background, F_{max}: maximal intensity in arbitrary units (AU), T_{max}: time in at which the background-corrected fluorescence intensity reached F_{max}, time-to-peak (ttp): T_{max} - t_0, the green line represents the mean slope: rate at which the fluorescence intensity increased (AU/s), $T_{90\%}$: time in seconds until 90% of F_{max} has been reached, $T_{80\%}$: time in seconds until 80% of F_{max} has been reached

Outcomes and definitions

The primary outcome was the fluorescence parameter the mean slope in relation to AL. Secondary outcomes included other fluorescence parameters, AL within 90 days, reinterventions due to AL, 90-day mortality, change of management due to the ICG-FA assessment. Postoperative anastomotic complications included AL, graft necrosis and anastomotic stricture. AL was recorded when an anastomotic defect was objectified by CT-scan, during endoscopy or during reoperation. AL and graft necrosis were defined according to the Esophagectomy Complications Consensus Group classification (19), and complications were classified according to the Clavien–Dindo (CD) score (20). Clinically relevant benign strictures were defined as a score for dysphagia ≥2 and treatment by ≥1 dilatation.

Sample size calculation

In a pilot study in 22 patients undergoing esophagectomy with gastric conduit reconstruction, the mean slope of ICG-FA was quantitatively measured. In the group without AL (n=18) the mean slope was 2.0 (±2.41) compared to 0.2 (±0.07) in the group with AL (n=4). (21). To find a statistical difference in the slope at a significance level of 0.05 and with a power of 80%, the least count of the group with AL should be at least 17 patients.

In a one year period since the introduction of FA in the Amsterdam UMC, location AMC, the anastomotic leak rate was 14%. To achieve inclusion of at least 17 patients with a leak, in total 122 patients should be included, taking a possible dropout due to technical failures as well of 15% at least 135 patients should be included.

Statistics

Patient characteristics are summarized using descriptive statistics. Categorical data are presented as number of cases and percentages, whilst continuous data are shown as either mean ± standard deviation or as median and interquartile range (IQR), depending on the data distribution. Fluorescence parameters are reported in median (IQR) and were compared between patients with or without anastomotic complications using the Mann–Whitney U test. A P-value <0.05 was considered statistically significant.

Univariate logistic regression was performed to define a predictive value for fluorescence parameters for AL. When fluorescence parameters had a P-value <0.2, a receiver operating characteristic (ROC)-curve was generated (22). When the ROC-curve yielded an area under the curve (AUC) above 0.7, a cut-off value was produced with high specificity and positive predictive value. Specificity was calculated using the Youden's statistics, after which the positive predictive value was calculated for every specificity.

Data was analyzed using the Statistical Package for Social Sciences (SPSS) of IBM Statistics, version 26.0.

RESULTS

Baseline and operative characteristics

One-hundred-forty patients underwent esophagectomy with primary gastric conduit reconstruction from August 2020 to February 2022. One-hundred-eight of these patients underwent ICG-FA during surgery and 103 were included in this analysis (Figure 3).

Baseline and surgical details are shown in Table 1. The mean age was 66±9.9 years. The majority of patients was male (79%), received neoadjuvant chemoradiation (85%) and had an adenocarcinoma (81%). The surgical procedure was an Ivor Lewis procedure in 88% of the patients. All procedures were performed (partially) minimally invasively and no conversions were required.

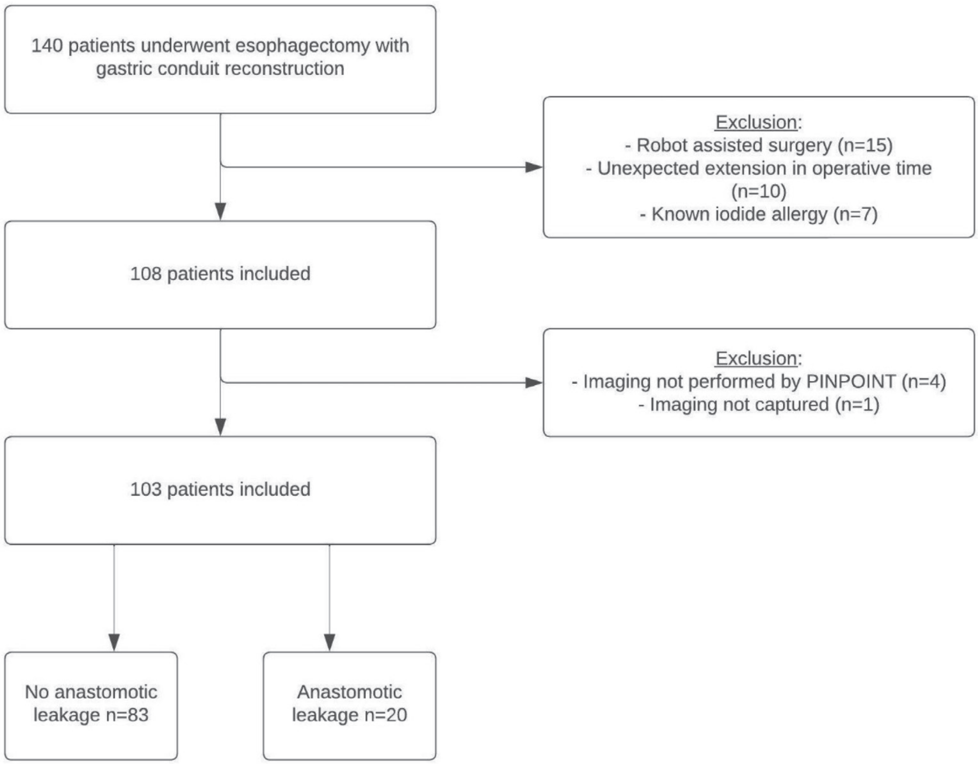

Figure 3. Flowchart of included patients

Postoperative outcomes

Anastomotic leakage occurred in 20 out of 103 patients (19%). AL rates were 14 out of 91 patients (15%) for intrathoracic and 6 out of 12 (50%) for cervical anastomoses. One patient in the change of management group had AL (n=1/3, 33%). For 11 out of 20 patients (55%) with AL, the CD score was ≧3. Reoperation was required for 5 out of 20 patients (25%), including of creation of a new anastomosis in two patients, resection of the gastric conduit with an esophagostomy in the neck in two patients and a video-assisted thoracoscopic surgery to decorticate empyema in the thorax in one patient. An anastomotic stricture occurred in 11 out of 103 patients (11%), of whom none had AL.

Fluorescence parameters for AL patients were also calculated for ROIs 2 cm more proximally on the gastric conduit to compare perfusion if extra mobilization is feasible (Table 4). All parameters improved by changing the anastomotic site into a location more proximal on the gastric conduit: T_{max} 55 (IQR 39-100) versus 65 (44-121) seconds and mean slope 1.0 (IQR 0.3-2.5) and 2.3 (IQR 0.5-3.5).

Table 1. Baseline and operative characteristics

	All patients (n=103)	**No AL (n=83)**	**AL (n=20)**
Age (years) *mean ±SD*	65.7+9.9	65.2+10.5	67.8+7.0
Gender, male	81 (79)	65 (78)	16 (80)
BMI (kg/m2) *mean ±SD*	26.3+4.0	26.1+3.8	26.9+4.7
Weight loss (kg) at clinical presentation	1 (0-5)	1 (0-5)	1 (0-5)
ASA ≥3	33 (32)	25 (28)	8 (40)
Smoker, *active*	19 (19)	15 (18)	4 (21)
Comorbidity			
Pulmonary	11 (10)	10 (12)	1 (5)
Cardiac	31 (30)	22 (27)	9 (45)
Diabetes Mellitus	17 (17)	11 (13)	6 (30)
Tumor histology			
Adenocarcinoma	81 (79)	68 (82)	13 (65)
Squamous cell carcinoma	15 (15)	9 (11)	6 (30)
Gastric tumor: adenocarcinoma	6 (6)	5 (6)	1 (5)
Neuro-endocrine tumor	1 (1)	1 (1)	0
Immunosuppressant use			
Steroids	5 (5)	3 (4)	2 (10)
Immunosuppressants	4 (4)	4 (5)	0
Tumor stage			
cT3	89 (86)	72 (87)	17 (85)
cN+	56 (54)	43 (52)	13 (65)
Neoadjuvant Treatment			
Chemoradiation CROSS	87 (84)	71 (86)	19 (95)
Definitive chemoradiation	3 (3)	3 (4)	0
Chemotherapy, FLOT	4 (4)	4 (5)	0
None	9 (9)	8 (10)	1 (5)
Surgical procedure			
Ivor Lewis	91(88)	77 (85)	14 (15)
McKeown	12 (12)	6 (50)	6 (50)
Approach			
Minimally invasive adominal	4 (4)	4 (100)	0
Minimally invasive thorax	6 (6)	5 (83)	1 (17)
Minimally invasive adominal and thorax	93 (90)	74 (80)	19 (20)
Conversion	0	0	0
Intraoperative complications*	1	0	1
Estimated blood loss	200 (100-450)	200 (100-475)	300 (150-438)
Operative time (min) *mean ±SD*	412±71	403±72	454±55

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Table 2. Fluorescent parameters at anastomotic site of AL patients

	t0	F_{max}	T_{max}	mean slope
Anastomotic site	25 (19-28)	56 (34-80)	65 (44-121)	1.0 (0.3-2.5)
2 cm more proximal	22 (14-29)	67 (43-84)	55 (39-100)	2.3 (0.5-3.5)

ICG- FA

Overall, For the pre-anastomotic assessment, overall inflow parameters after ICG injection were 22 seconds (IQR) for t0 and 51 seconds (IQR) for Fmax. The mean slope was 1.7 (0.8-3.0) for all patients. In terms of outflow, a median of 15 seconds (IQR 10-36) until reaching 90% and 34 seconds until reaching 80% of Fmax (IQR 18-79) was found.

An overview of fluorescence parameters in patients with and without AL are shown in Table 3. The mean slope tended to be less steep during both pre anastomotic as post anastomotic assessment for the AL group without reaching statistical significance (median of 1.0 versus 1.7, p=0.11 and 1.3 versus 1.0 p=0.76).

Table 3. Fluorescent parameters

	Pre anastomotic assessment			Post anastomotic assessment		
Parameter	No AL	AL	p Value	No AL	AL	p Value
T0 (sec)	21 (14-26)	25 (19-28)	0.24	16 (11-23)	24 (11-30)	0.09
Ttp (sec)	26 (19-40)	39 (25-97)	0.04	32 (23-50)	34 (21-50)	0.84
T_{max} (sec)	51 (37-67)	65 (44-122)	0.03	50 (36-79)	58 (46-81)	0.47
F_{max} (AU)	60 (48-74)	56 (34-80)	0.56	71 (52-86)	62 (56-80)	0.47
Slope(AU/sec)	1.7 (1.0-3.0)	1.0 (0.3-2.5)	0.11	1.7 (0.7-2.2)	1.3 (0.7-1.7)	0.76
$T_{90\%}$ (sec)	15 (9-30)	30 (12-41)	0.21	21 (10-42)	33 (15-72)	0.17
$T_{80\%}$ (sec)	33 (17-65)	82 (22-111)	0.20	61 (18-91)	71 (49-103)	0.44

Both time values ttp and T_{max} were longer during pre-anastomotic assessment for the AL group in comparison to the non-AL group (39 sec vs. 26 sec, p=0.04 and 65 vs. 51 seconds, p=0.03 respectively).

Although not significant, outflow time values during pre both assessments, were longer for the AL group compared to the non-AL group ($T_{80\%}$ 82 vs. 33 seconds p=0.21 during pre-anastomotic assessment and 71 versus 61 seconds, p=0.44 during post anastomotic assessment). Correspondingly, time values until inflow (t0) of fluorescence during the post anastomotic assessment tended to be longer too without reaching statistical significance (24 versus 16 seconds, p=0.09).

Based on subjective ICG-FA interpretation, the surgical team opted for a change of anastomotic site to a clearer fluorescent region 2 to 5 cm more proximal in the conduit in three out of 103 (3%) patients, requiring extra mobilization of the gastric conduit.

Univariate analysis was carried out for fluorescence parameters shown in Table 4, T_{max} was predictive for anastomotic leakage (*P* = 0.10, AUC = 0.71) and a cut-off value of 97 seconds was derived with a specificity of 92%.

Table 4. Univariate cox proportional hazards regression analysis of anastomotic leakage

Variables	HR (95% CI)	P value
Pre anastomotic ttp	1.81(0.66-5.00)	0.25
Pre anastomotic T_{max}	2.39 (0.84-6.82)	0.10
Pre anastomotic slope	0.84 (0.32-2.24)	0.73

DISCUSSION

This study prospectively investigated quantification of ICG-FA by analyzing fluorescence time curves and how it relates to occurrence of AL in patients undergoing esophagectomy with gastric conduit reconstruction. A significant difference was observed in terms of time until reaching maximal intensity (T_{max}) in patients with and without AL during pre anastomotic assessment. This could be an important parameter which can influence intraoperative decision making by predicting anastomotic leakage after esophagectomy with gastric conduit reconstruction.

To our knowledge this is the first prospective cohort study to evaluate perfusion with fluorescence time curves in this patient group in a standardized setup. Nevertheless the phenomenon of quantifying the fluorescence signal in patients undergoing esophagectomy is not new. Measuring time to fluorescence enhancement has already been described as an effective 'timing' fluorescence parameter with thresholds established around 90 seconds until fluorescent enhancement (13, 23). Absence of fluorescence may suggest arterial insufficiency, whereas a delay in fluorescence in- or outflow may signify venous congestion. These conditions may cause ischemia. However, it is known that when only using subjective visual interpretation of ICG-FA, surgeons overestimate the perfusion compared with quantitative analysis (24). The slope of the curve is described as having the best clinical performance in identifying AL patients (25, 26). This study was therefore powered on the mean slope of the curve, however this did not reach statistical significance.

Research on ICG-FA quantification, tends to focus mainly on inflow parameters whilst defining outflow parameters remains challenging. Moreover, the inflow and outflow of the gastric conduit could affect one and another. For example, severe venous congestion of the gastric conduit can cause reduction of inflow. Our results may emphasize this by longer time values observed during post-anastomotic assessment until the inflow of ICG (t0). This might explain the less profound differences seen during the post-anastomotic assessment between the AL and non-AL group. Taking this into consideration, it is difficult to distinguish between in- and outflow and it is of paramount importance to not only focus on inflow but also on outflow parameters.

Objective fluorescence interpretation by quantitative parameters can help the surgeon intraoperatively; in the patients with AL the perfusion parameters were better 2 cm more proximally, if deemed possible the surgeon could mobilize the gastric conduit more in order to make the anastomosis more proximal. Nevertheless, we know that patients with a change of management (i.e. trimming the gastric conduit) also have high percentages of AL, also in this series, potentially explained by tension on the anastomosis and generally a less perfused gastric conduit(27). For this reason, ICG- FA might be of more value for determining the postoperative policies than intraoperatively during esophagectomy; namely to select high-risk patients for strict postoperative monitoring: early endoscopy with preemptive endoluminal vacuum-assisted therapy in the form of a VACstent or endosponge placement(28). On the other hand, in low-risk patients with good perfusion oral nutrition may be initiated on short notice. In this way, perfusion assessment can be used to better tailor the postoperative course. This approach could reduce length of hospitalization and resources needed to treat complications.

Nevertheless this study is also limited, even with the use of ICG-FA, the AL rate was high, especially in patients undergoing McKeown procedures, which might be explained by the selection of patients for a McKeown procedure at our unit, as these were all patients with extended radiation fields because of higher tumor locations or lymph node metastases located higher up in the mediastinum (29). Although this study examined quantitative values, these values were not yet acted upon. If intervened upon the fluorescent threshold of 97 seconds found in this study, eight AL might have been avoided. Yet, the occurrence of AL involves many different factors not corrected for in this study. A prospective trial focusing on interpretation by quantitative threshold as determined in this study with also taking the multifactorial etiology of AL would be the next step in validating this threshold.

In this study, only one fluorescence imaging device was used, it is not known how these results relate to other imaging devices as camera settings differ between different manufacturers.

Light distribution may differ and this impacts fluorescence intensity in the same field of view. It is of importance to address these aspects in future studies on perfusion assessment using ICG fluorescence imaging to achieve reliable quantification for all systems. In the future, fluorescence time curves should be compared between multiple imaging systems and software programs in a standardized setting, for instance by using a phantom. Artificial intelligence could help with the prediction of patient outcomes, while combining FA videos, these imaging characteristics, and patient data(30). The strength of this study lies in the fact that ICG-FA was performed prospectively in a standardized manner, making it unique in its reproducibility.

In conclusion, quantification of ICG- FA is feasible. Patients with a longer interval from ICG administration until reaching maximum intensity have an increased risk of AL enabling the early identification of high-risk patients for anastomotic leakage in whom extra mobilization of the gastric conduit or postoperative preemptive measures may be taken. In this fashion ICG-FA might tailor the intra- and postoperative course of patients undergoing esophagectomy with gastric conduit reconstruction. Objective interpretation of ICG-FA should be applied in conjunction with calibration of imaging devices in order to achieve reliable quantification and implement it broadly. A prospective trial focusing on interpretation by quantitative threshold as determined in this study with also taking the multifactorial etiology of AL would be the next step in validating this threshold.

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CHAPTER 9

Investigating and compensating for periphery-center effect among commercial near infrared imaging systems using an indocyanine green phantom

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ABSTRACT

Near infrared imaging (NIR) camera systems have been clinically deployed to visualize intravenous injected indocyanine green (ICG) spreading through the vascular bed, thereby creating the ability to assess tissue perfusion. While standardization is key to make fluorescence angiography (FA) comparable and reproducible, optical characteristics like field illumination homogeneity are often not considered. Therefore the aim of this study is to investigate light distribution and the center-periphery effect among five different NIR imaging devices in an indocyanine green phantom. A 13 × 13 cm fluorescence phantom was created by diluting ICG in Intralipid (representing 0.1 mg/kg dose in an 80 kg reference male), to evaluate the overall spatial collection efficiency with fluorescent modalities of five different NIR camera systems using a 0-degree laparoscope. The fluorescence signal from the phantom was quantified at a fixed distance of 16 cm using tailor-made software in Python. The results showed considerable variability in regard to light distribution among the five camera systems, especially toward the periphery of the field of view. In conclusion, NIR signal distribution varies between different systems and within the same displayed image. The fluorescence intensity diminishes peripherally away from the center of the field of view. These optical phenomena need to be considered when clinically interpreting the signal and in the development of computational fluorescence quantification.

INTRODUCTION

Easier access to intra-operative near infrared (NIR) imaging has resulted in widespread use of this technology, allowing surgeons to see beyond the visual spectrum [1]. As an emerging optical imaging technique, NIR imaging has already shown clinical benefits in various surgical practices. NIR camera systems have been deployed to visualize intravenous injected indocyanine green (ICG) spreading through the vascular bed, thereby creating the ability to assess tissue perfusion, demarcate tumor tissue, and visualize vital structures [2,3]. When bound to blood plasma, ICG has a peak spectral absorption of around 800 nm and emits fluorescence at longer wavelengths [4].

In gastrointestinal surgery, indocyanine green fluorescence angiography (ICG-FA) has mainly been used to tackle perfusion-related complications, such as anastomotic leakage [5,6]. However, several studies report variable results in reducing the anastomotic leakage rates by using ICG-FA [5–8]. This may be due to the inter-user variation in interpretation of the FA signal, which remains mainly subjective using visual assessment only and is therefore associated with a considerable learning curve [9,10]. However, while clinical use of fluorescence imaging systems is rapidly growing, the appropriate knowledge for reliable image interpretation is lagging. Essential in overcoming these challenges for broad effective implementation of ICG-FA, is standardization of fluorescence assessments to make them more comparable and reproducible. Standardization and protocolization enable the possibility of quantifying the fluorescence signal, which is an important focus of research in this field [11].

When standardizing the fluorescence measurement, tracer administration (dosage, volume, infusion rate), working distance, and ambient light are often taken into consideration [12]. To accurately interpret and quantify the fluorescence signal being displayed, a thorough understanding of the underlying physics is necessary. Factors such as distance, movement, and the relationship between the center and periphery can all have a significant effect on the intensity of the signal. These factors have received little attention by clinicians while it directly influences the fluorescence signal and may hamper correct interpretation. In clinical practice, for instance, the bowel located in the center may show more fluorescent intensity than a more proximal segment located in the periphery of the field of view (Figure 1) [13].

For other medical imaging modalities, universal standards are described to benchmark their performance. In order to do so for NIR imaging, solid tissue-mimicking phantoms have been developed to characterize NIR imaging systems [14,15], however, these papers have not yet been translated into applicable solutions for interpretation by clinicians. Moreover, so far, parameters such as the illumination homogeneity, the resolution, or the dependency of fluorescence intensity on tissue optical properties are not generally comprehensively addressed in the phantoms built. The studies that do address inhomogeneities of light distribution plot the intensity measurements only for a few locations (i.e., five reflective wells placed in the corners and center of the phantom), therefore, it is not possible to perform a correction of the recorded pixel data [16]. To better understand this periphery-center effect, which is observed in clinical practice, and promote awareness among clinicians and the potential consequences on fluorescent parameters, we investigated the light distribution within the field of view of five different commercial NIR imaging devices using a fluorescent phantom. We aimed to correct the data for illumination field distribution and light collection aberration known as vignetting to facilitate objective quantitative comparison of fluorescence in a flat field between systems.

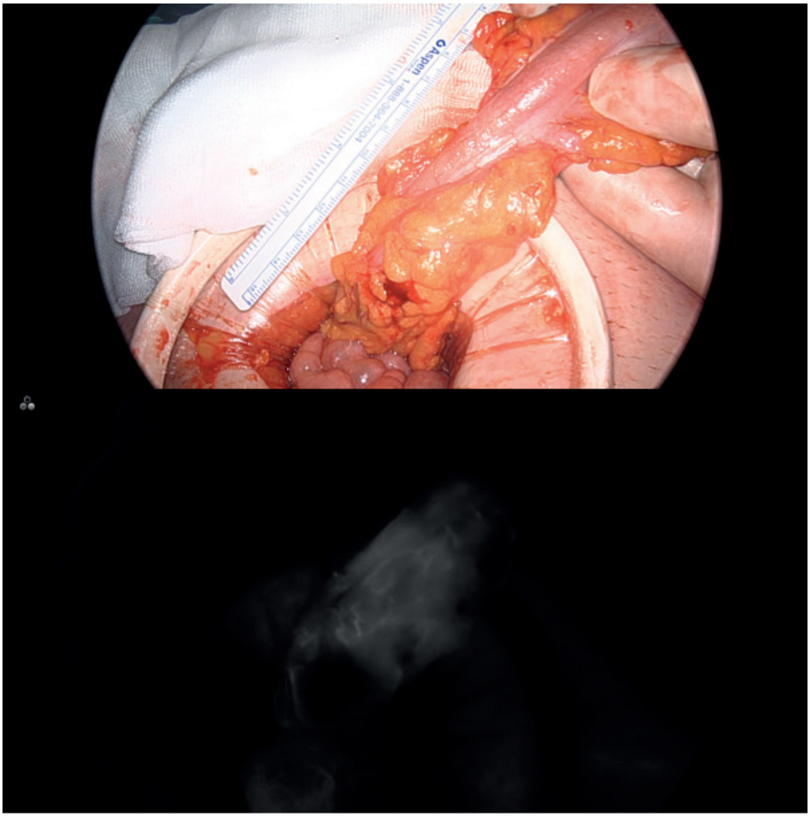


Figure 1. A segment of colon during a transanal total mesorectal excision. The top image is the white light image and the image below, the corresponding fluorescent image, demonstrating less fluorescent enhancement at a more proximal bowel segment (see blue arrow).

METHODS

Phantom Preparation

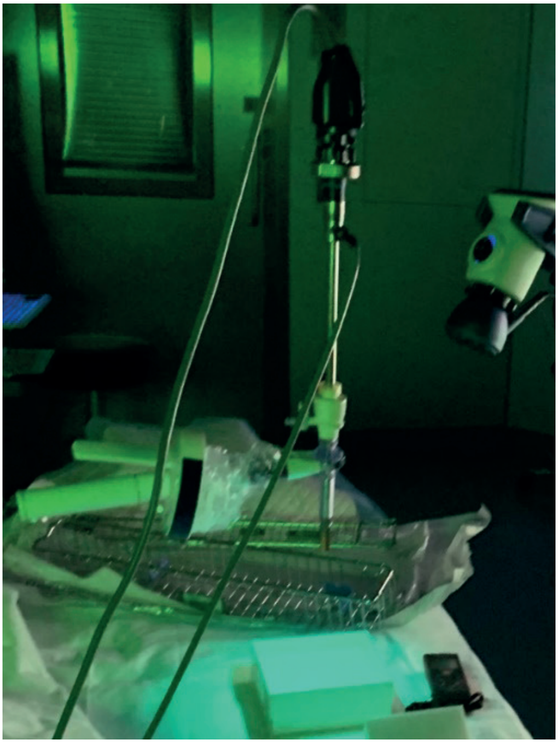
The phantom was created in a container of 13 × 13 cm, with a height of 6 cm. In total, 0.5 L of fluorescent phantom was created, resulting in a homogenous dilution within the container of 13 × 13 × 3.8 cm. The phantom was manufactured by heating 230 mL MilliQ ultrapure water with 20 g agarose (Sigma Aldrich, *St. Louis, MO, USA,* A9539) to generate a 4% agarose dilution. After the dilution was cooled to 60 °C, 250 mL of 20% stock Intralipid (Fesenius Kabi, *Bad Homburg,* Germany) was added to create a 10% Intralipid concentration, mimicking light scattering by tissue. A total of 285 µg ICG (Verdye, Diagnostic Green, Aschheim, Germany) was added to the mixture, and stirred for 10 min at 60 °C. The ICG concentration was calculated based on an individual of 80 kg, with 7 L blood [17]. The administered concentration of ICG we use in our clinical protocol is 0,1 mg/kg patient weight. With 7 L blood, the administered amount would correspond to 8 mg; for our phantom, this would result in 570 µg ICG. Several phantoms were prepared with different ICG concentrations, and the phantom with a concentration of 285 µg ICG was used as we obtained a perfectly homogeneous distribution.

NIR System Assessment

Five different clinical NIR camera systems (see Supplementary Table S1) were assessed using the set-up shown in Figure 2. These systems were: (1) Intuitive Surgical Inc. (*Sunnyvale, CA, USA*), XI Firefly, (2) Olympus (Tokyo, Japan), Visera Elite II, (3) Stryker (*Kalamazoo, MI, USA*) (Novadaq), AIM laparoscope, (4) Quest Medical Imaging (Wieringerwerf, The Netherlands), Quest Spectrum, (5) Stryker, Stryker 1688.

Fluorescent Assessment with the Phantom

IRB approval or written consent was not necessary as these assessments did not involve patients or patient characteristics. In theater, under fluorescent angiography conditions (dimmed surrounding light) the phantom was placed on an operating table. The laparoscope was fixed onto a mechanical holding arm (MOFIXX laparoscope holder, Alphatron Surgical, Rotterdam, The Netherlands) at a distance of 16 cm from the phantom surface, ensuring a stable position throughout the experiment. The distance was measured with a laser distance measurement system (Leica Distro D2, Leica Geosystems, *St. Gallen, Switzerland*). In this manner, the camera was fixated in the middle of the field of view (FoV). The recorded videos were transferred to a laptop for analysis.



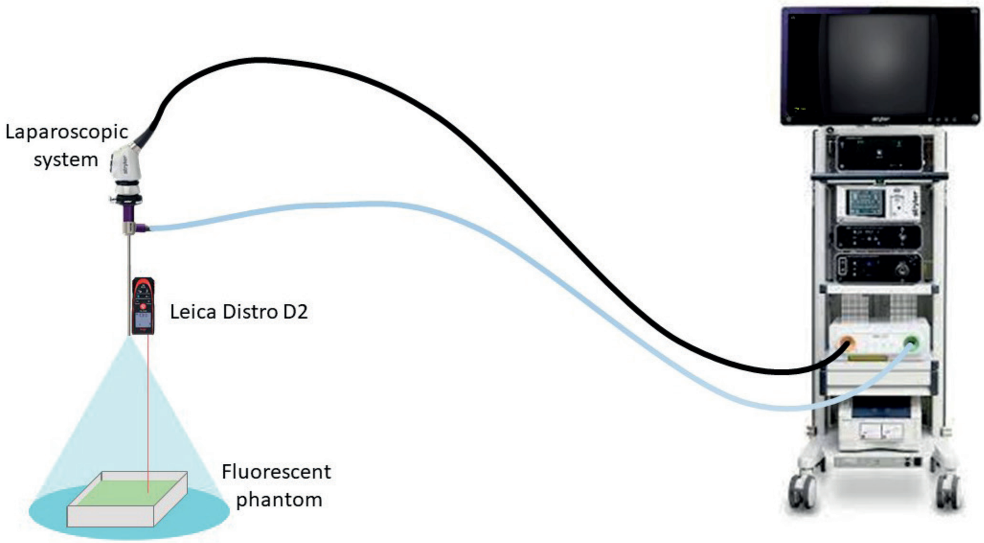


Figure 2. Experimental set-ups. The image at the left represents the phantom placed at 0-degrees with the endoscopic camera fixated at 16 cm.

Signal Quantification

Regions of interest (ROIs) in the video recordings of the phantom were analyzed by tailor-made software using Python v3.8 programming language (Python Software Foundation, https://www.python.org/, accessed on 10 September 2022). After calibrating the surface area in the video image using the known measurements of the phantom (see Supplementary Figure S1), a grid of 23 × 23 segments with a segment size of 5 mm was projected on the data within the phantom. While running the software the mean fluorescence intensity was calculated within each cell. The percentage of fluorescence signal loss (FSL) in the FoV was calculated by

$$FSL = 1 - \frac{F_{low}}{F_{\mathbf{high}}} \times 100\%$$

in which F_{low} denotes the lowest fluorescent intensity in an ROI and F_{high} the highest.

For an objective quantitative comparison of fluorescence between systems, it is important to correct the data for influences, such as the point spread function of the used optics, illumination differences, and camera sensitivity of each individual system. This can be achieved using a flat-field correction known in microscopy. To that end, data from the phantom measurements can correct each system using a FIJI (open source imaging process software, version 2.0.0-rc-56/1.51 h, https://imagej.net/, accessed on 15 October 2022) pixel-by-pixel based implemented flat-field correction function as described by Schindelin et al. [18,19].

$$i2\ new = \frac{i1}{\mathrm{i2}} \times\ k1 + k2$$

In which i1 is the original image, i2 is the phantom image, k1 is the mean intensity of the phantom image and k2 the mean intensity of a dark image (in our case left to 0). We used as an example a phantom measurement of the light distribution measured by a Stryker 1688 imaging device and a fluorescence angiogram acquired during a colon resection by the Stryker 1688.

RESULTS

Light Distribution

A large variability in light distribution was seen within each camera system; the highest intensity was observed in the middle, with FSL toward the periphery of the image. In Figure 3 the light distribution was shown with the orientation of the phantom of the *x*-axis and normalized fluorescence intensity on the *y*-axis in order to portray the signal loss. This signal loss toward the periphery of the FoV was especially observed with the Firefly system (up to 60% loss at the periphery of the FoV) and the Stryker 1688. When the phantom was placed in the middle, the light intensity distribution was skewed to the right with 40% loss to the left edges.

Table 1. Percentage of fluorescence signal loss per imaging device

Imaging Device	Highest Intensity (AU)	Lowest Intensity (AU)	FSL%
Firefly	114	23	80
Olympus	86	57	34
Pinpoint	174	76	57
Quest	175	107	39
Stryker	107	26	76

Correction

Correction of the original data for influences such as the point spread function of the optics, illumination differences, and camera sensitivity was achieved by employing a flat-field correction executed in FIJI. Figure 5 shows the acquired phantom data of the Stryker 1688 camera on a clinically obtained fluorescent image of a segment of colon during a transanal total mesorectal excision at the top left, with a red line indicating the location of the intensity distribution shown in the adjacent graph. Both adjacent graphs depict the intensity distribution and Locations 1 and 2 before and after correction.

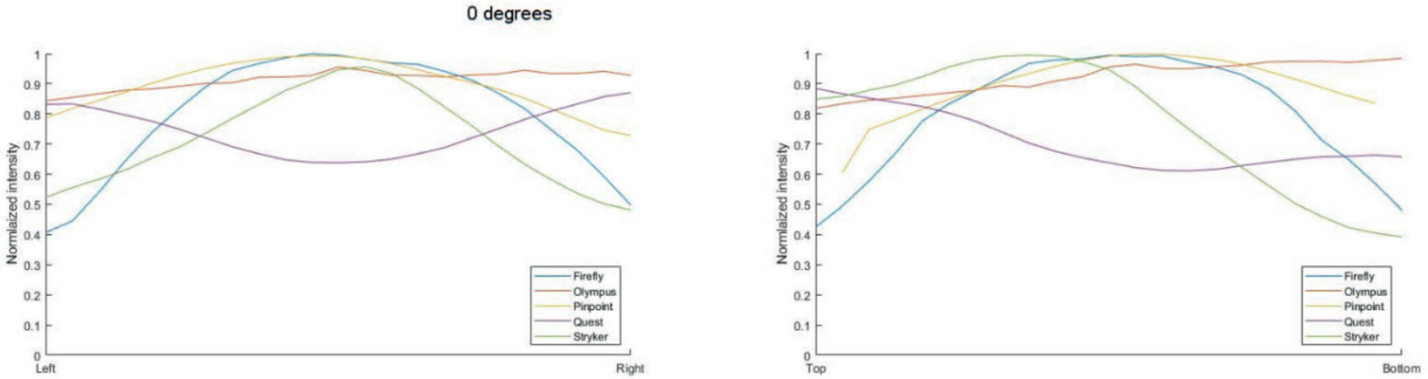


Figure 3. Four longitudinal cross-sections of the light distribution. On the *y*-axes, normalized intensity (maximum fluorescent intensity set at 100% and background noise at 0) is shown and on the *x*-axes the orientation of the phantom, which takes 13 cm from left to right. The top two images show the light distribution with the phantom placed at a zero degree.

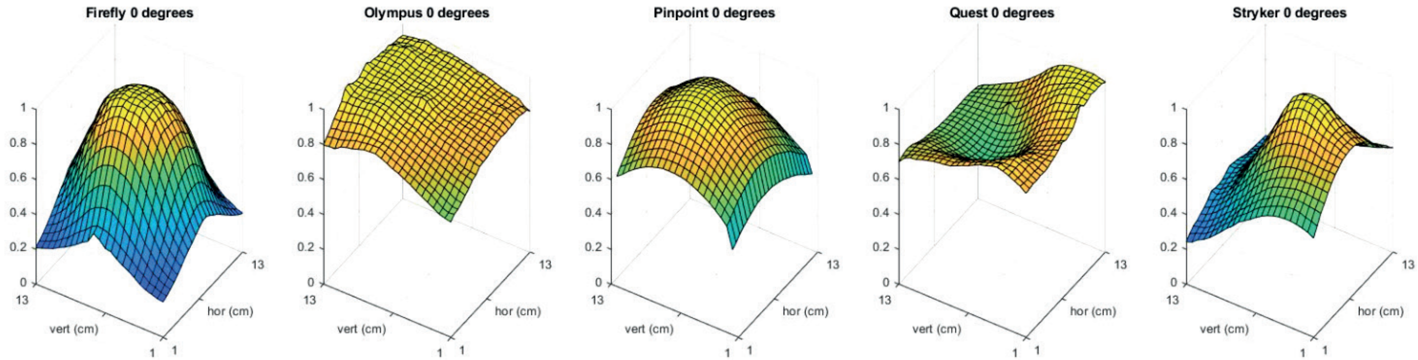


Figure 4. 3D representation of the light distribution among the five different cameras.

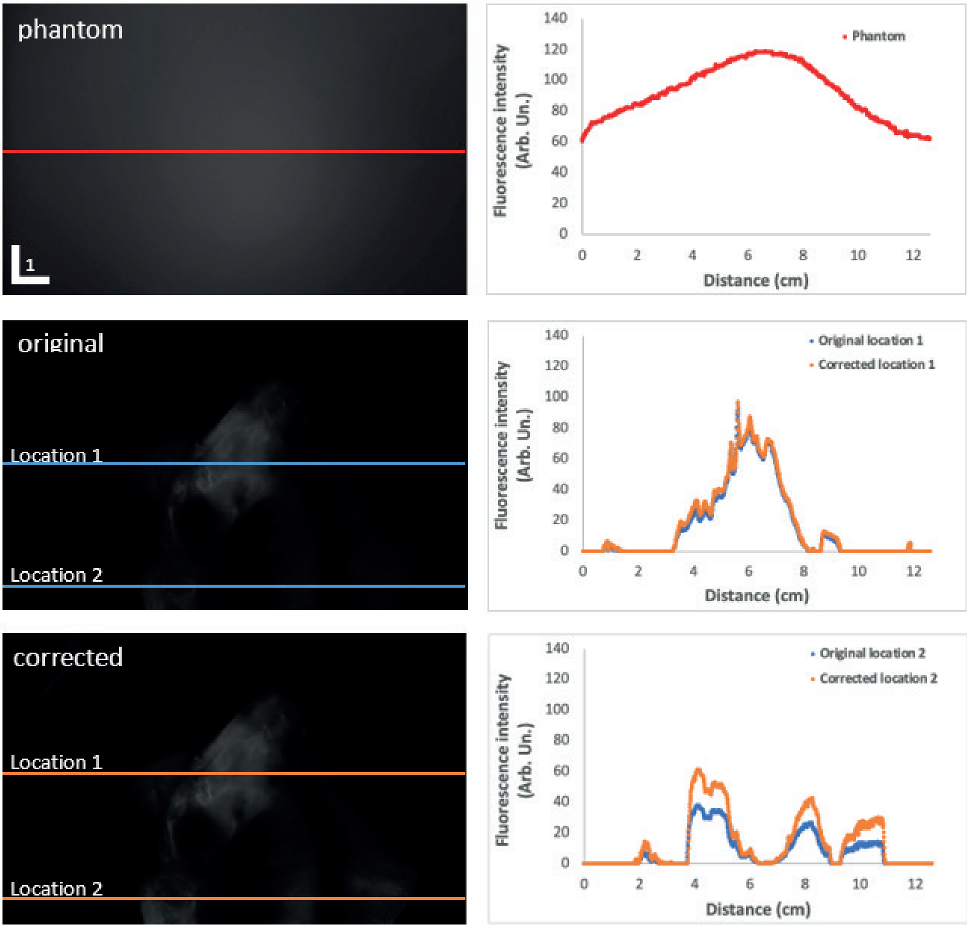


Figure 5. Top left image showing the phantom using the Stryker 1688 camera. The red line indicates the position of the adjacent graph with a fluorescent intensity distribution. The middle and lowest images both show the fluorescent image of a segment of colon during a transanal total mesorectal excision before and after correction. The blue and orange lines indicate the location on the intensity distributions plotted in the two adjacent graphs for the central and peripheral part of the image both before (blue)and after (orange) correction. The corrected result is therefore a more realistic representation of the fluorescence distribution in the tissue.

DISCUSSION

The goals of improving fluorescent assessments and their interpretation are similar to those in science in general; achieving objectivity, reproducibility, and comparability. In this study, a fluorescence imaging standard was used that incorporated ICG to test the center-periphery effect of five commercially available imaging systems indicated for use with ICG. The results of this study demonstrate a considerable variation in light distribution within the FoV; with decreasing fluorescence intensity toward the periphery down to 60% in relation to the highest intensity. Among the five different commercially available NIR camera systems, considerable variability exists regarding fluorescence intensity and sensitivity. These features should be considered and if possible corrected for while interpreting the fluorescent signal clinically and selecting ROIs for quantification.

Recent reviews have stated that inflow parameters have superior clinical performance over intensity parameters, due to immunity to changes in camera distance and angulation [12,20]. Our findings emphasize these results, as dynamic flow parameters are less likely to be affected by the ROI selection and thus inhomogeneous illumination fields. Despite the fact that for quantification the camera is kept stable in terms of distance, movement due to breathing or peristalsis is problematic and challenging to eliminate. Furthermore, by utilizing normalization and correction for the light distribution, one could modify the *slope* parameter to be based on relative changes in fluorescence intensity, significantly reducing the impact of several of the above-mentioned challenges that affect the measurement and differences in camera systems.

This study addresses the periphery-center effect in the flat field only and does not take different distances or the morphology of the tissue into account. In this study, it was decided to standardize the distance and optical properties to remove the confounding effects which light scattering and absorption can have on fluorescence. These factors require other, more sophisticated solutions. The aim of this study was to quantify the impact of the periphery-center effect in the flat field and to correct it as a first step.

Recent work has demonstrated that significant variations in performance between NIR cameras exist, with each camera system being used at different distances and speeds of movement [21]. The results indicated in this study were focused on defining the ideal optical distance (FoV) and distance per camera demonstrating that each device has its own ideal set-up.

Our results demonstrate that there are significant variations among different camera systems. It is likely that other camera systems not included in our testing would also exhibit these differences. This makes it challenging to establish consistent fluorescent parameter thresholds across different camera systems. It is important to note that most commercial systems are designed primarily to provide surgeons with information about perfusion, rather than to quantify the signal or for inter-system compatibility. Currently the control over system parameters such as gain, camera integration time, and illumination intensity is limited. However, recent developments such as manual gain settings, protocols for fluorescent assessments that include tracer dosage, and standardization of distance aim to quantify and calibrate the results to some extent in the future. As shown in this study, the periphery-center effect impacts quantification outcomes if one is not aware of this while choosing ROIs (i.e., the fluorescent intensity may decrease significantly in the periphery, also represented by the FSL%). In clinical use, even though the camera is likely to be focused on the ROI at its center, one should take this into account and possibly correct for it. As the number of commercially available optical imaging systems has greatly increased, this technology is now being used by more inexperienced surgeons who occasionally lack knowledge of the fundamental principles and pitfalls of optical imaging, making it difficult to interpret imaging data in a way that is accurate, precise, reproducible, and reliable. Raising awareness that using and comprehending optical imaging modalities requires training and is, therefore, a learning curve, could lead to the organic beginning of this new class of trained surgeons; the interventional imaging surgeon. This is not novel because it is comparable to traditional imaging techniques, which today each have their own class of medical professionals, namely the nuclear physician and the radiologist.

However, being able to compare fluorescent thresholds between patients and/or systems is a future goal as well as a challenge. The flat field corrected illumination differences and optical behavior of the NIR imaging devices in these studies can be incorporated together with patient data in (deep learning) algorithms to automate quantitative/artificial intelligent ICG perfusion angiogram classifications to facilitate its interpretation for all clinicians, not only the prior mentioned interventional imaging experts. These algorithms incorporated in robotic or laparoscopic consoles might propose resection lines after NIR assessment on the live tissue based on patient-, optical-, fluorescent characteristics.

This study is limited first for not truly mimicking the clinical situation, as the phantom is entirely flat. However, correcting for different angulation, depth, and tissue morphologies is hard to summarize in one formula. Second, it was conducted using an ICG phantom, however, both the methodology as the message of this study apply to other fluorescent tracers of the same emission peak. In addition, during this study we chose to perform all the assessments with one fixed distance so as to have the entire phantom in the FoV. To achieve this, a distance of 16 cm was set, however, during laparoscopy, especially in patients with a low BMI, a smaller distance is conventional and usually in the range of 10 cm. That said, the scope of this paper was not to mimic clinical use but to demonstrate the light distribution and impact of angulation. Ideally, a fluorescent phantom offers comprehensive information on multiple systems' parameters with only one snapshot, but this phantom only addresses illumination and camera sensitivity. This study is also limited in assessing only the commercial camera systems we had at our disposal, whereas clinical practice is dependent on the fluorescence systems hospitals have available.

In conclusion, there was a considerable center-periphery effect within an FoV with sometimes not even peak intensity in the middle of the FoV, and this differs among systems. Other phantoms with only a few wells do not capture these illumination differences entirely, these features should be considered and if possible corrected for while interpreting the fluorescent signal clinically and before selecting ROIs for quantification

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SUPPLEMENTARY MATERIAL

Supplementary Table 1. Table demonstrating features of camera systems tested in this experiment. Data of user manuals, communication with company representatives or previously published assessments. – denotes that data was not available or obtainable through previously mentioned methods.

	Company	**Intuitive Surgical Inc.**	**Olympus**	**Stryker (Novadaq)**	**Quest Medical Imaging**	**Stryker**
Product	System	XI Firefly	Visera Elite II	AIM and SPY fluorescence	Quest Spectrum	Stryker 1688
	Lap/ open	Laparoscopic	Laparoscopic	Laparoscopic	Open	Laparoscopic
	Camera	XI Firefly	CH-S200-XZ-EB	Pinpoint	Quest Spectrum handheld	AIM platform
Illumination/ Excitation	Light Source	Laser	IR Xenon Bulb	Laser	Laser	Laser
	Excitation Wavelength	803 nm	710-790nm	805nm	780nm (ICG mode)	808nm
	Operation Mode	Continuous	Continuous	Continuous	Continuous	Continuous
	NIR Source power output	-	300W Bulb	2mW	-	2mW
Fluorescence collection	Collection wavelength	800 nm	810-920 nm	825-850 nm	800 nm (ICG mode)	805-830 nm
	Sensor type	CCD	CMOS (x3)	CCD (x2)	CCD (x3)	CMOS
	Integration Time	Realtime	Realtime	Realtime	Realtime	Real time
	Image overlay	Yes	Yes	Yes	Yes	Yes
	Variable gain setting	No	No	No	Yes	Yes

CHAPTER 10

Iatrogenic injury of the urinary tract during salvage procedures for pelvic sepsis- experience of a national referral centre

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ABSTRACT

Aim: This study aimed to determine the incidence, consequences and outcomes of iatrogenic urinary tract injury (IUI) during salvage surgery for pelvic sepsis.

Method: Patients who underwent salvage surgery for pelvic sepsis after prior low anterior resection or Hartmann's procedure for rectal cancer in the period between 2010 and 2020 were retrospectively reviewed. The primary endpoint was the incidence of IUI. Secondary endpoints were timing of diagnosis (intra- versus postoperative), reinterventions related to the IUI and healing of IUI.

Results: In total 126 consecutive patients were included, and IUI occurred in 13 patients (10%). A ureteric injury occurred in eight patients, bladder injury in four patients and a urethral injury in one patient. The injury was diagnosed postoperatively in 63% (n=8/13) with a median duration between surgery and diagnosis of the IUI of 10 days (IQR 6-15). The median number of reinterventions was five (range 1-31) in the group with a postoperative diagnosis and one (range 0-1) in the group with an intraoperative diagnosis. Four patients required a surgical reintervention, all concerning injuries diagnosed postoperatively. At the end of follow-up, 85% of patients (n=11/13) had a healed IUI.

Conclusion: IUI are not uncommon in salvage procedures for pelvic sepsis, even in an experienced tertiary referral centre. Most injuries were diagnosed postoperatively which affects the severity of these complications, emphasizing the need to improve intraoperative diagnostic modalities.

What does this paper add to literature

Iatrogenic urinary tract injuries (IUI) during salvage surgery for pelvic sepsis are associated with high morbidity depending on the location and timing of diagnosis. This is the first large observational study on this topic, which demonstrates the relatively high incidence, the often late diagnosis, and the frequent need for reinterventions.

INTRODUCTION

Pelvic sepsis might develop if an anastomotic leakage (AL) persists after a low anterior resection (LAR) or in case of blow-out of the rectal stump after low Hartmann's procedure[1]. This is a complex problem as patients with pelvic sepsis are often subject to multiple interventions (endoscopic, radiologic and surgical) to obtain local control. Salvage procedures for pelvic sepsis are a surgical challenge due to inflammatory-, radiation- and surgical induced fibrotic scarring and altered anatomical planes, and associated with high perioperative morbidity rates[2]. In particular, such salvage procedures for pelvic sepsis might be prone to IUI[3].

IUI occur in approximately 0.3-1.7 % of elective colorectal surgeries. Despite the relatively low incidence, IUI are still considered a feared complication[3, 4]. These injuries are associated with significant morbidity due to several risks including urinoma and fistula formation and urinary tract infection with possible loss of renal function. The outcomes depend on location of the injury and timing of diagnosis[4, 5]. Often, IUI are recognized postoperatively and may require a temporary diverting nephrostomy and secondary surgery at a later stage[6].

Data on the occurrence of IUI after redo abdominal and pelvic surgery, and in particular salvage management for pelvic sepsis is lacking. We hypothesized that major salvage surgery for pelvic sepsis is associated with a higher incidence of IUI with more often postoperative diagnosis related to the difficult intraoperative identification in the irradiated, inflamed and fibrotic operative field. The aim of this single centre, retrospective study is to evaluate the incidence, consequences and healing of IUI in major salvage surgery for pelvic sepsis after a LAR or Hartmann's procedure.

METHODS

Patients

All consecutive patients undergoing major salvage surgery between January 2010 and January 2020 after prior LAR or Hartmann's procedure for rectal cancer were included. Those patients were treated for acute or chronic pelvic sepsis at a single tertiary referral centre (the Amsterdam University Medical Centres (AUMC) – location AMC). Pelvic sepsis was defined as uncontrolled persisting inflammation within the pelvic cavity following AL, including leakage from a rectal remnant after primary low Hartmann's procedure or dismantled anastomosis. Pelvic sepsis was diagnosed during physical examination, endoscopy, radiological imaging, or a combination of diagnostic modalities, and defined as chronic when sepsis was still present 12 months following the index procedure. Major salvage surgery included fistula excision, omentoplasty, muscle- or fasciocutaneous flap, redo colo-anal anastomosis, end colostomy with takedown of the anastomosis and intersphincteric resection of rectal stump.

The primary endpoint was the incidence of IUI. Secondary outcomes included timing of diagnosis of the injury (intra- versus postoperative), diagnostic modality, injury related re-interventions and percentage of patients with healed IUI. IUI were considered to be healed if there were no clinical symptoms related to the urinary tract and continuity with unimpeded flow based on contrast imaging.

The study has been approved by the medical ethical committee of the AUMC – location AMC (reference number W21_099 # 21.112).

Data collection

Patient and treatment characteristics were retrospectively collected from medical charts and stored in an electronic database. Preoperative patient demographics, body mass index, medical and surgical history, and radiation therapy were reviewed. Operative records were reviewed for placement of preoperative ureteral stents, operative time, operative technique, and extent of intra-operative adhesions. IUI were reviewed for location of injury, timing of diagnosis, clinical presentation, diagnostic modality, and management following Clavien Dindo classification[7].

Statistical analysis

Categorical data were compared using the Chi-Squared test, or the Fisher exact test when appropriate, and were presented as numbers and proportions. Numerical data were compared using the independent *t* test or Man-Whitney *U* test according to distribution. The outcomes were reported as means with standard deviation (SD) or medians with interquartile range (IQR). The median number of re-interventions per patient were reported with IQR, as well as the range to represent inter-individual variability. The statistical significance level was set at a *P*-value of < 0.05. IBM SPSS Statistics for Windows (v.26.0, IBM Corp., Armonk, New York, USA) was used for the statistical analyses.

RESULTS

Baseline characteristics

In total, 126 consecutive patients underwent salvage surgery for pelvic sepsis, of whom 73% (n=92/126) were male. Mean age was 62.5 years (± SD 11). The index procedure for rectal cancer consisted of a LAR in 91% (n=115/126) of the patients and 94% (n=118/126) of patients had undergone neoadjuvant (chemo)radiotherapy. At our centre, 82 patients (65%) underwent major pelvic surgical interventions related to leakage of the anastomosis or rectal remnant prior to salvage surgery, ranging between one and 28 interventions (median 1, IQR 1-2), with 44 patients (35%) who underwent non-surgical interventions (range 0-5, median 0, IQR 0-1). The pelvic anatomy at time of salvage surgery and other baseline characteristics are outlined in Table 1. Median time between index procedure and salvage surgery was 26 months (IQR 14-65).

Table 1. Baseline characteristics

	n=126
Sex, male	92/126 (73)
Age at time of salvage, mean ± SD (years)	62.5 ± 11.0
BMI, mean ± SD (kg/m2)	25.6 ± 3.6
ASA classification	
ASA I	25/126 (20)
ASA II	76/126 (60)
ASA III	23/126 (18)
ASA IV	2/126 (2)
Active smoker	20/126 (16)
Diabetes mellitus type II	20/126 (16)
Neo-adjuvant therapy	
None	8/126 (6)
Short-course radiotherapy only	59/126 (47)
Long-course radiotherapy only	1/126 (1)
Radiotherapy only, type unknown	7/126 (6)
Short-course radiotherapy followed by chemotherapy	5/126 (4)
Chemoradiotherapy	46/126 (37)
Index surgery	
Low anterior resection	115/126 (91)
Hartmann procedure	11/126 (9)
Pelvic status before salvage	
Rectal extirpation	3/126 (2)
Anastomosis in situ	92/126 (73)
Primary Hartmann	10/126 (8)
Secondary Hartmann	21/126 (17)
Time between salvage surgery and last date of follow-up, months, median (IQR)	48 (23-72)

Descriptive statistics are presented in proportions, unless otherwise stated'. Abbreviations: SD: standard deviation, BMI: body mass index, ASA: American Society of Anaesthesiology, IQR: interquartile range

Prior to the salvage surgery, 4% (n=5/126) of the patients had a urinary complication. Three patients had stenosis of the ureter, two of them requiring endoscopic stent placement and the other patient underwent five times a radiological nephrostomy placement. Two patients had a fistula from the urethra to the colon and rectum, one of them resulting in a bladderneck stenosis, requiring an endoscopic bladder neck incision.

Intraoperative characteristics

In two patients (1.5%), a prophylactic ureteral stent was inserted pre-operatively. Both these patients had a history of urinary complications before salvage treatment in our institution: both had unilateral ureteric obstruction related to pelvic sepsis, with progressive hydronephrosis in one of these patients. A suprapubic catheter was inserted uncomplicatedly intraoperatively in 65% of the patients (n= 82/126), 78% (n=64/82) of them were male. Of the 11 patients with a Hartmann's procedure as index procedure, (74%) eight underwent an intersphincteric resection of the rectal stump and the three remaining patients had restoration of continuity as salvage surgery. Of 115 patients with a LAR as index procedure, redo colo-anal anastomosis was performed in 47% (n=54/115) of patients, intersphincteric resection of the rectal stump after prior take down of the anastomosis in 17 % (n=21/115), and intersphincteric resection of the leaking anastomosis and creation of and end colostomy in 35% (n=40/115).

In most patients (94%, n=119/126), a combined abdominoperineal approach was pursued, while an isolated abdominal or perineal approach was used in two (2%) and five (4%) patients, respectively. For the abdominal part of the procedure, a minimally invasive approach by laparoscopy was performed in 58% of cases (n=70/120), and by TAMIS in 56% (n=70/124) for the perineal approach. Conversion from laparoscopy to a midline laparotomy was necessary in three patients (4%) due to dense adhesions. Extensive adhesiolysis was necessary in 36% (n=45/126) of the patients. The ureters were identified intraoperatively in 29 % (n=36/126) of the patients with ureterolysis in 22 patients. Median operative time was 373 minutes (IQR 297-500) in the group with an IUI, compared to 292 minutes (IQR 241- 342) in the group without an IUI. There were no other intraoperative complications.

Iatrogenic urinary tract injuries

An IUI occurred during salvage surgery in 13 patients (10%). In none of the patients with a prior urological complication, an IUI occurred during salvage surgery. All patients with a IUI had radiotherapy as neoadjuvant treatment. Of these patients, a unilateral ureteric injury occurred in seven patients, bilateral ureteric injury in one patient, bladder injury in four patients and a urethral injury in one patient. The damage to either ureter, bladder or urethra was noticed intraoperatively in five patients. The diagnostic modality used to detect IUI postoperatively in the other eight patients is specified in Table 2.

Table 2. Characteristics of patients with iatrogenic urinary tract injury

Patient	Year salvage	Type of injury	Procedure	Abdominal approach	Perineal approach	Time of diagnosis	Symptoms	Diagnostic modality	Initial management
1.	2015	Distal left ureter	Redo anastomosis	Open	Open	POD 6	Fever, abdominal pain	Elevated creatinine in fluid	-
2.	2014	Bladder	Take down anastomosis, end colostomy	Open	Open	POD 4	Leakage of urine from wound	CT IVP	-
3.	2020	Urethral	Redo anastomosis	Open	TAMIS	Intraoperatively	n/a	Gel leakage through TUC	Primary repair over urethral catheter
4.	2014	Bladder	Intersphincteric completion proctectomy with omentoplasty	Open	Open	POD 15	Leakage of urine from anal wound	CT scan	-
5.	2016	Distal left ureter	Interpshincteric resection rectal stump	Open	Open	POD 12	Abdominal pain, pyrexia	CT IVP	-
6.	2017	Distal left ureter	Intersphincteric completion proctectomy	Laparoscopic	TAMIS	Intraoperatively	n/a	Identification ureter	Re-insertion ureter by psoas hitch
7.	2019	Bladder-urethra transition	Intersphincteric resection rectal stump	Open	TAMIS	POD 8	Fever, increased drain output	CT scan	-
8.	2019	Bladder, trigonum	Intersphincteric resection rectal stump	Open	Open	Intraoperatively	n/a	Entry to bladder	Primary repair and SPC
9.	2014	Distal right ureter	Redo anastomosis	Open	Open	Intraoperatively	n/a	Identification ureter	Re-insertion ureter by oversuturing over stent
10.	2016	Distal right ureter	Redo anastomosis	Laparoscopic	TAMIS	POD 18	Abdominal pain, leakage of urine from anal wound	CT scan	-
11.	2016	Bilateral ureter	Redo anastomosis	Laparoscopic	TAMIS	POD 13	Urinary retention	CT scan	-
12.	2018	Distal left ureter	Redo anastomosis	Laparoscopic	TAMIS	POD 6	Urinary retention	CT scan	-
13.	2011	Middle right ureter	Intersphincteric resection rectal stump	Open	Open	Intraoperatively	n/a	Identification ureter	Primary repair

Abbrevations: TAMIS: transanal minimally invasive surgery, POD: postoperative day, n/a: not applicable, CT IVP: CT Intravenous pyelography, SPC: suprapubic catheter

Table 3. Reinterventions related to the IUI

Patient	Location injury	Moment of diagnosis	Reintervention			CD score	Healed EFU
			Radiologic	Surgical	Endoscopic		
1.	Distal left ureter	Postoperatively	Nephrostomy tube (2)	Ileocystoplasty	Dilatation and stent placement	IIIb	Yes
2.	Bladder	Postoperatively	Nephrostomy tube (4)	-		IIIa	Yes
3.	Urethral	Intraoperatively	-	-	-	-	Yes
4.	Bladder	Postoperatively	Nephrostomy tube (30)		Nephrostomy tube (1)	IIIa	No
5.	Distal left ureter	Postoperatively	Nephrostomy tube (2)	Reimplantation of the left ureter in psoas hitch	Stent placement (2)	IIIb	Yes
6.	Distal left ureter	Intraoperatively	-	-	Removement stent	IIIa	No
7.	Bladder-urethra transition	Postoperatively	-	-	-	II	Yes
8.	Bladder, trigonum	Intraoperatively	-	-	-	-	Yes
9.	Distal right ureter	Intraoperatively	-	-	Removement stent	IIIa	Yes
10.	Distal right ureter	Postoperatively	Nephrostomy tube (7)	Uretero-plasty with Boari flap	Removement stent (1)	IIIb	Yes
11.	Bilateral ureter	Postoperatively	Nephrostomy tube (4)	Ileal interposition ureter	-	IIIb	Yes
12.	Distal left ureter	Postoperatively	Nephrostomy tube (1)	-	-	IIIa	Yes
13.	Middle right ureter	Intraoperatively	-	-	-	-	Yes

Abbrevations: CD: Clavien Dindo score, EFU: end of follow up. Number between brackets represents amount of performed procedures.

In all patients with ureteric injuries, a ureterolysis was performed intraoperatively, and resulted in direct damage to the ureter in three patients (patient 6, 9, 13). These injuries were recognized intraoperatively, and required re-insertion of the ureter in two patients, while one injury could be repaired by primary suture. The other five iatrogenic ureter injuries were picked up between postoperative day six to postoperative day 18 (patient 1, 5, 10-12), and were either a missed injury or secondary to ischaemia following the ureterolysis. One entry into the bladder was recognised intraoperatively and was repaired by a primary two-layer closure. In one patient (patient 3) a urethral injury occurred, that was immediately closed over a transurethral catheter. Median duration between surgery and diagnosis of the IUI in patients with postoperative detection was 10 days (IQR 6-15).

Follow up iatrogenic injuries

Six patients did not require any further reintervention outside endoscopic removal of ureteric stents (patient 3,6-9,13), and IUI was intraoperatively detected and managed in five of them(Table 3). Four patients with postoperatively detected ureteric injuries needed nephrostomy tubes as initial management (patient 5,10-12), and subsequent ureteric reimplantation procedures in three patients; an ileal interposition for the patient with a bilateral ureteric injury, one psoas hitch and one Boari flap procedure. One patient had a stent placed after unsuccessful endoscopic dilatation of a ureteric stricture and eventually had a reconstruction by an ileal interposition (patient 1). Of patients with a bladder injury, two out of three patients with a postoperative diagnosis (patient 2, 4) required bilateral nephrostomy tubes to control urine leakage.

For all patients with IUI, the median number of overall reinterventions was one (range 0-31, IQR 1-5). Patients with a postoperative diagnosis of the IUI had a median number of overall reinterventions of five (range 1-31) and patients with intraoperative diagnosis had a median of one reintervention (range 0-1). All radiologic and surgical reinterventions were performed in patients with postoperative detection of the injury. Readmission related to the IUI occurred in 46% (n=6/13), with a median admission length of 11 days (range 2-13).

At the end of follow-up, 85% of patients (n=11/13) had a healed IUI. The median duration from the occurrence of the IUI until healing was eight months (IQR 1-16). Patients with intraoperative diagnosis had a median time to healing of one month (IQR 1-9), whereas patients with postoperative diagnosis had a median time to healing of 8 months (IQR 7-60). There were two patients (patient 4 and 6) with persisting problems of IUI; one (patient 4) still has nephrostomy tubes in situ due to stenosis of the ureters without reconstruction options with a healed injury of the bladder on radiological imaging, and the other patient (patient

6) has persistent obstruction symptoms without obstruction objectified by imaging. There was no mortality associated with the IUI. None of the IUI led to chronic kidney problems.

DISCUSSION

The present study reveals that IUI occurs in 10% of the patients undergoing salvage surgery for pelvic sepsis after prior LAR or Hartmann's procedure for rectal cancer with almost always neoadjuvant radiotherapy. The majority were diagnosed postoperatively with a median delay of 10 days with subsequent need for radiological and surgical reinterventions, while intraoperatively detected injuries did not require such reinterventions. Eventually, most patients did not have long-term sequelae related to the IUI.

In the current literature, IUI are portrayed as a rare complication, but this scarcely available data only reflects primary, elective surgery[3, 4, 6, 8]. So far, no studies have reported the incidence during complex abdominal or pelvic redo surgery. The substantially higher incidence after redo surgery compared to primary colorectal surgery is likely explained by a combination of factors that complicate the pelvic dissection, such as extensive scar tissue related to radiotherapy, previous surgery and chronic inflammation, as well as altered anatomy.

In nearly two third of the patients the injury was recognized postoperatively. This is in line with prior studies which report that 50-70% of IUI are identified postoperatively[9, 10]. Similar to other studies, these patients typically present with flank or abdominal pain, fever, ileus and/or urinary discharge via the anal canal, perineal wound or pelvic drain. The diagnosis of IUI, if not recognized intraoperatively, is usually several days postoperative, although reports on timing are inconsistent[8, 11 12]. We found that IUI were diagnosed after a median period of 10 days in this setting of salvage surgery (IQR 6-15). The relatively long interval suggests that the pathophysiological mechanism of postoperatively detected leakage might often be ischaemia, rather than a full thickness injury with direct urinary leakage. Perfusion of the ureters might have been already compromised by previous radiotherapy, and the use of diathermia and sealing devices during salvage surgery might result in secondary necrosis.

As expected, we detected a clear difference in morbidity between IUI detected during or after surgery in favour of the former group, as reflected by the median number of reintervention and the type of reinterventions. Intraoperative identification of the urological structures in close proximity to the field of dissection is essential to prevent injury. Furthermore, intraoperative detection of potential injury is key for immediate repair and is known to result in better long-term outcomes[12]. However, identification of the ureter is most often achieved by visual inspection and palpation, which can both be challenging during minimal invasive surgery, especially in this specific patient population with extensive fibrosis. Furthermore, posterior displacement of pelvic organs typically occurs after primary or secondary Hartmann's procedures. This will hamper correct identification of the distal part of the ureters and vesico-ureteric junctions. If restoration of continuity is aimed for during salvage surgery, dissection of the bladder and ureters might be necessary to create enough space for the colon to reach the rectal remnant. Clearly, in this setting of redo pelvic surgery for pelvic sepsis, there is a need for techniques to improve the visualization of the urinary tract.

Prophylactic ureteral stenting (PUS) has gained popularity in the last couple of years with the purpose of preventing ureteral injuries[13]. However, no guidelines support its efficacy, as most studies show no benefit in the use of PUS in the incidence of IUI[14, 15]. By way of contrast, the use of PUS itself is demonstrated to be associated with high rates of iatrogenic urinary tract injury[16]. Even though there might not be a role for PUS to prevent IUI in primary surgery, it can still be a helpful tool to visualize the urological tract during redo surgery and ensure early recognition of IUI. However, one must be aware that ureteral stents are not always palpable in fibrotic tissue and do not prevent bladder and urethral injuries, neither do they influence the risk of ischaemic perforations with late urinary leakage.

A potential safer alternative for intraoperative visualization of the entire urological tract (not limited to the ureters) is near-infrared fluorescence imaging. Proof of concept studies suggest a promising future, being able to identify 22% (n=14/62) of ureters that were not visible in white light[17]. Near-infrared fluorescence showed the ureter to be in a different location than expected in 16% (n=10/62) of the cases. From currently available fluorescent dyes, methylene blue is the best option that is readily available for fluorescence imaging of the ureter owing to its simple method of administration (intravenously) and efficacy[18]. However the main limitation of methylene blue is the low excitation coefficient, which may hamper visualization of the urological tract in fibrotic tissue. An experimental near infrared agent, ZW800-1, is promising for ureter detection in the future[19]. Phase I-II studies show a good safety profile of ZW800-1 in patients with normal renal function, and detection of ureters is possible with low dosages. A further advantage of ZW800-1 is that its excitation and emission spectrum overlaps with that of indocyanine green (ICG), a clinically available and frequently used fluorescent agent. ZW800-1 can therefore be visualized with the same imaging systems at 800nm. Visualization of the urological tract via near-infrared fluorescence imaging, may also prevent the need for ureterolysis, which in our series led to direct injury in three patients and devascularization with delayed stenosis or leakage in five patients.

A substantial limitation of this study is its retrospective design. Patients were prospectively included, but specific data on IUI were retrieved retrospectively. For this reason, there were no established moments for measuring renal function (i.e. creatinine). In addition, the study is limited due to the low absolute number of events of IUI, which prevents us to detect independent predictors.

In conclusion, this is the first study presenting the incidence of IUI in a large cohort of patients undergoing redo pelvic surgery for pelvic sepsis with often prior radiotherapy. Results from this study support that IUI is a more frequent complication during salvage surgery with an incidence of 10%, as compared to primary colorectal resection. With regard to implications for clinical practice, our findings demonstrate that awareness of potential IUI is warranted during this type of surgery and patients can be counselled on the expected course and outcome. In addition, our findings outline the need for other intraoperative diagnostic modalities to assist in recognition of the urological tract in this complex patient group. PUS might help visualize the ureter, however fluorescence imaging might have the most value as it has the potential to visualize the whole urinary tract.

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CHAPTER 11

Summary

SUMMARY

In every field of science, humankind is advancing at an astounding pace. Surprisingly, from the beginning of medicine, the current standard for reliable perfusion assessment has not altered much; estimated from the color of the serosal surface, pulsation and bleeding from the marginal arteries. This is quite surprising as proper perfusion is a crucial component of organ function and wound healing and hence plays a key role in reducing mortality and morbidity across a wide range of diseases. For this reason, the need to "visualize" perfusion has never been more urgent.

It is important to understand that imaging-based perfusion evaluation has no therapeutic value on its own, but it can be used as a so-called 'red flag' diagnostic tool. While using imaging within gastrointestinal surgery, it is the surgeon's responsibility to: 1. use standardized imaging, 2. accurately evaluate the images and 3. take reasonable action upon these images. A well-weighted and imaging data-based shift in clinical outcome can only be foreseen when all three of these pillars are in place. As a result, perfusion assessment alone serves as an additional source of crucial real-time information that the surgeon may use while making decisions at critical moments during a procedure.

The aim of this thesis is to explore the current modus operandi for qualitative ICG-FA measurements and to achieve objective and reproducible ICG-FA assessments by defining a threshold for adequate perfusion in gastrointestinal surgery. In essence, it describes a journey towards quantifying tissue perfusion.

Chapter 1 provides a general introduction of ICG- FA in gastrointestinal surgery as well as the outline of this thesis.

Chapter 2 describes a multi-centre cohort study and the use and outcomes of ICG-FA in the acute setting. Although ICG-FA has been widely implemented in the clinical practice for elective surgery, the potential added value in the acute setting had barely been studied. Among 93 operations for acute bowel ischaemia, there is a change of management of 29%, resulting in bowel preservation in approximately one out of four patients. An overall reoperation rate of 12% is found, 29% in patients with a change of management versus 8% in those in whom there was no change. While there is no increase in unplanned reoperations between the groups, standards need to be set for the interpretation of FA images for this indication and the potential subsequent need for second-look surgeries.

Shifting towards the elective setting, in certain situations restoration of continuity after esophageal resection is not possible by gastric conduit reconstruction, and in this case

a colonic interposition might be an alternative. **Chapter 3** studies ICG-FA guided colonic interposition and its role with regard to postoperative anastomotic leakage. ICG-FA proves to be a safe and feasible technique to assess perfusion of the colonic segment and potentially assures the surgeon in the choice of the colonic segment for the interposition. This study shows that 20% of patients has a change in management due to the application of ICG. There are no significant differences in patients with or without ICG-FA in anastomotic leakage rates.

Chapter 4 details variability in interpretation of ICG enhanced fluorescence angiograms during the assessment of gastric conduit perfusion among surgeons during qualitative assessment. While there is a reduction in variance seen with mastery of the technique, fallibility of operator interpretation even occurred among expert uses in one case. This highlights the shortcoming of qualitative assessment of fluorescence and emphasizes the importance of quantifying the fluorescence signal.

During ileal pouch anal anastomosis (IPAA) surgery, it might be necessary to perform lengthening maneuvers that require vessel ligation in order to make the pouch reach the anus for creation of the anastomosis. Particularly in these cases, ICG-FA might be of value to rule out significant perfusion problems, and even distinguish arterial inflow from venous congestive problems. However, literature describing ICG-FA during IPAA is scarce, and change of management after ICG-FA has thus far not been recorded. Case reports outline in **chapter 5** that ICG- FA is of added value in the intraoperative decision making during IPAA surgery. In both cases, the pouch body gradually discolored but ICG-FA showed rapid fluorescent enhancement, resulting in creation of an ileostomy. As an anastomosis was pursued and the patients had an uncomplicated postoperative course, ICG-FA seems to be beneficial in IPAA surgery.

Considering the potential value of ICG-FA in IPAA surgery in the previous chapter, **chapter 6** continues studying quantification of ICG-FA**,** evaluating time to fluorescence during IPAA. Patients with or without vascular ligation as part of lengthening measures are compared. Time from ICG injection to arrival in the pouch is non-significantly prolonged in patients that underwent vascular ligation. Time values might therefore indicate redirection of arterial flow through the arcade, or presence of venous outflow obstruction. Increased resistance in the venous network might explain the delayed flow in case of venous outflow obstruction. Therefore, FA during IPAA might enable differentiation between an inflow problem (no ICG fluorescence), an outflow problem (delayed, but intact ICG flow) and adequate perfusion (rapid ICG flow)

In **chapter 7** the initiated path of quantification is continued. Quantitative in- and outflow parameters of the efferent/afferent loop are determined and the impact of lengthening measures requiring vascular ligation or previous inadvertent interruption of the ileocolic arcade, is explored. Overall in patients without vascular ligation, perfusion parameters between afferent and efferent loops were similar. In patients with vascular ligation of the ileocolic artery both in- and outflow time values are prolonged and in particular, the mean slope of the ICG curve of the efferent loop is less steep. This might be explained by rerouting of arterial flow through the arcade in case of vascular ligation. Due to the different characteristics of the ICG-FA curve, quantitative ICG-FA can identify prior vascular ligation and assist surgeons in intra- or postoperative decision making. This cohort was too small to calculate a fluorescent threshold associated with adequate perfusion.

Chapter 8 investigates fluorescence time curves in a large prospective case series. Multiple fluorescent parameters were explored, if they are correlated to the occurrence of anastomotic leakage in patients undergoing esophagectomy with gastric conduit reconstruction. There is a significant difference in terms of time until reaching maximal intensity T_{max} in patients with and without anastomotic leakage during pre-anastomotic assessment. This is an important parameter which can influence intraoperative decision making and may predict anastomotic leakage after esophagectomy with gastric conduit reconstruction.

The goal of fluorescent assessment is to obtain a diagnostic tool that is objective, reproducible, and comparable. When standardizing the fluorescence measurement, the body mass adjusted ICG dosage and a fixed distance to the tissue are often taken into consideration. However, optical factors such as light intensity distribution and sensitivity of the camera receive little attention. **Chapter 9** demonstrates a considerable variation in the light distribution within the field of view; a decreasing fluorescence intensity towards the periphery down to 60% of the highest intensity among five different commercially available near infrared camera systems is found. This chapters highlights the consequences on quantification of choosing region of interests in the periphery of the field of view. Correction of this important confounder is mandatory to achieve reliable and comparable fluorescent thresholds.

As previously mentioned, there are many different indications for near infrared imaging to enlighten the surgeon on making the invisible visible. **Chapter 10** entails patients undergoing salvage surgery for pelvic sepsis after rectal cancer, showing that this complex patient group is more prone to iatrogenic urinary tract injury, occurring in 10% of the patients. The surgery is quite complex and challenging due to inflammatory-, radiation- and surgically

induced fibrotic scarring. Iatrogenic urinary tract injuries are diagnosed postoperatively with subsequent need for multiple reinterventions, while intraoperative injuries do not require such reinterventions. This chapter outlines the need for intraoperative diagnostic modalities, such as near infrared imaging, to assist in recognition of the urological tract in this complex patient group.

CHAPTER 12

General discussion and future perspectives

GENERAL DISCUSSION AND FUTURE PERSPECTIVES

In this thesis, the modus operandi of qualitative indocyanine green fluorescence angiography (ICG-FA) measurements is explored and we aimed to obtain objective and reproducible ICG-FA assessments by defining a quantitative threshold for adequate tissue perfusion in the gastrointestinal tract during surgery.

The work described in chapters 2, 3 and 5 highlights the potential clinical relevance of ICG-FA, with a reported rate for change of management of 5 to 15% in the elective and up to 35% in the acute setting (1-3). Nevertheless this technique has not consistently shown a reduction of anastomotic leakage rates in recent literature. A recent meta-analysis for esophagectomy and gastric conduit reconstruction did not show a significant benefit for ICG-FA in reducing anastomotic leakage rates (4). On the other hand, a systematic review of 7735 patients did demonstrate a reduced leakage rate in colorectal surgery applying ICG (OR 0.39, $p<0.001$): one anastomotic leak could be prevented for every 23 colorectal resections involving a primary anastomosis (5). However, the camera systems and ICG dosages varied significantly across all included trials, demonstrating the current lack of standardization for ICG-FA. Moreover, the best available scientific evidence is based on retrospective and nonrandomized studies, lacking high-quality, prospective, randomized controlled trials that are adequately powered to show a reduction in anastomotic leak rate.

The rapid pace of technological advances in near infrared (NIR) imaging, make it difficult to study the actual efficacy. By the time reliable results are available, the used techniques are often outdated. Furthermore the subjective assessment of the fluorescent signal in the current ongoing randomized controlled trials such as IntAct and AVOID are a further weakness (6, 7). Still, the routine use of ICG-FA in day to day practice is evolving and in some units even considered standard of care (8). It is important to realize that the occurrence of anastomotic leakage is a multifactorial event and even perfusion related anastomotic leakage is dependent on a many different factors; such as hypothermia, hyperglycemia and intraoperative vasopressor use (9). Even if FA is associated with a reduction of anastomotic leakages, other factors will play a role as ICG-FA might only prevent leakages originating from inadequate perfusion. A combined strategy that deals with multiple peri- and intraoperative risk factors of anastomotic leakage might further lower its occurrence. This is explored in the IMARI and DOUBLE CHECK trial, multi-interventional perioperative programs that focus on multiple modifiable risk factors for anastomotic leakage, including inadequate perfusion, tension and the microbiome (10 and NCT05250882).

The full potential of fluorescence imaging can only be confirmed if the process to obtain a fluorescent angiogram is objective and standardized and therefore reproducible and comparable. ICG- FA has shown to be subject to interpretations by different observers and is also affected by the surgeon's level of experience with the technique (chapter 3 and (11)). In an effort to reduce this subjective component in surgical decision-making, quantifiable fluorescence based perfusion parameters must be developed.

Quantitative assessment of ICG-FA appears to be a promising method to identify patients at a high risk for anastomotic leakage. This can be achieved by time to first fluorescence or parameters established on fluorescence time curves (12 and chapter 6,7 and 8).Fluorescence time curves are specifically of interest, as they are able to show both in- and outflow characteristics of perfusion. In particular, *inflow* parameters (ttp, T_{max}, $T_{1/2max}$, T_0, mean slope) appear to be different between patients with and without anastomotic leakage (13-17). However, the accuracy of each parameter as a predictor of AL is inconsistent across studies. Impairment of venous outflow, leading to venous congestion may also play an intricate role in poor anastomotic healing. Nonetheless, only a few studies report how these outflow parameters change the fluorescent time curve and impact on patient outcomes.

As each patient may exhibit an individual fluorescence-time curve shape due to perfusion related characteristics but also patient demographics, large trials are needed to validate both in and outflow thresholds. The fact that ICG-FA's is on the verge of becoming standard of care, hampers the design of randomized controlled trials to validate quantification thresholds as surgeons will lose equipoise to randomize patients. These thresholds should therefore be validated in large prospective trials, comparing outcomes such as anastomotic leakage rates to comparable historic cohorts.

Technology savvy surgeons, dedicated to using optical imaging techniques have built on their experience since the emergence of these techniques. The experience of these early adopters, usually working in university or large teaching hospitals, is lacking in the majority of the current users , as the technique is now entering main stream practice. These inexperienced surgeons might not be aware of the fundamental optical imaging principles and pitfalls as also described in chapter 10, and as a result they are unable to provide an objective, accurate, reproducible, and reliable interpretation of imaging data. The experts may educate the residents by raising the knowledge that using and comprehending optical imaging modalities is susceptible to training and hence a learning curve. Quantification algorithms may also function as a tool to educate residents, as novel studies demonstrate that using quantification of ICG-FA may attribute to safer resections by novice surgeons up to the experienced surgeon level. In this study, novice surgeons were asked to diagnose non-ischemic bowel segments in a blinded setting (18). By providing this extra data, quantification algorithms helped inexperienced surgeons learn how to more accurately measure intraoperative perfusion.

In addition, real time quantitative ICG- FA could be incorporated in laparoscopic imaging devices or robotic platforms. It would be beneficial to extrapolate the ICG-FA time curves as shown in this thesis to full angiography maps for the whole surgical field in real time. This would help the surgeon in making decisions based on a fully quantitative perfusion overview and could delineate regions of reduced perfusion based on established cut-off values of the whole surgical field without losing time. In the future ICG-FA might be combined with other preoperative imaging modalities (computed tomography, magnetic resonance, ultrasonography) creating a true augmented reality; i.e. areal-time quantitative ICG-FA map could be superimposed on a previous acquired MRI or CT scan, which in turn guides the surgeon during surgery. With improved ICG-FA software, and established cut-off values, the system could be combined with machine learning to propose resection lines, projected on the live images of the operative view. However, uniformity in fluorescence imaging and obtained fluorescence parameters must be met. Artificial intelligence (AI) algorithms, particularly deep learning, have demonstrated remarkable results for medical purposes, in fields such as radiology and pathology, and for clinical cancer detection (19, 20). It could also help detect patients at risk for anastomotic leakage by combining patient 's characteristics and imaging device data with FA images. In this way, high risk patient may be identified preoperatively or before clinical deterioration, pre-emptive treatment could be considered and implemented. Such early identification and intervention can result in a reduction of the effect of the complication or even its prevention. A downside of the implementation of such a model, however, especially when a high sensitivity is desirable, is the risk of overtreatment. To achieve these machine learning models, It is essential to obtain the largest possible datasets from a reliable neural network with post-surgery follow-up, as the predictive performance of the models is more accurate for complications with higher occurrence rates and balanced data sets (21).

The clinical applications described in the present thesis were all related to gastrointestinal surgery, yet, the use of ICG-FA may also lie outside the surgical discipline, for instance in gastroenterology outpatient clinics. Early experiential reports describe AI and ICG-FA for applications in both endoscopic diagnosis (characterization of lesions) and endoscopic therapy (indicating and demarcating limits of early-stage cancers) as a real-time decision support tool. Cancer vascular architecture is significantly different in dysplasia compared to normal tissue, becoming increasingly disorganized with true malignancy. Identification of malignant tissue is important to guide biopsy taking or show the correct planes of dissection (22). Currently this mandates lesion sampling in the form of a biopsy guided by the operator's eye. Yet false negative rates of cancer detection in polyps >2cm have reported to be between 18 and 50% highlighting the need for improvement (23, 24). Furthermore, many advise against biopsy in cases potentially suitable for local excision as it may result in fibrosis and increase the difficulty of local endoscopic excision (25). There is the potential for automated digital pathological tissue classification intraoperatively even with a non-tissue selective agent such as ICG.

Based on neo-vascularization properties of tumor lesions, fluorescence-time curves can also be used for the detection of cancer, and ICG might function as a low-cost, universal marker for tumor imaging. ICG also shows promising results in the detection of colorectal liver metastases. ICG is exclusively cleared by the liver and immature hepatocytes; surrounding malignant liver cells are unable to excrete ICG into bile, leading to an accumulation of ICG and leaving a fluorescence rim (26). Also results of targeted fluorescence fluorophores are very encouraging to both image tumors (SGM-101, cRGD-ZW800-1, bevacizumab-800CW, and ONM-100) (27-30) as to image the ureter(ZW800-1, IS-001, and IRDye-800BK) (31-33).

At this moment, most clinically available near infrared systems are optimized for ICG at 830 nm. This wavelength is slightly too high for optimal imaging of most experimental fluorescent agents, which have peak emission wavelengths around 800 nm. To fully utilize the potential of this technology, the NIR system manufacturers need to facilitate systems in which adjustments to the required wavelengths are possible. This allows for a multi-step approach for instance during rectal surgery. First, the ureter can be imaged and identified using the technology. Then, by adjusting the wavelength, a different tracer can be utilized to visualize perfusion of the anastomosis. This multi-step approach enhances the diagnostic capabilities of the technology and provides the best outcomes for patients undergoing rectal surgery.

To further advance the use of fluorescent agents in surgery, extensive research and development has been carried out, resulting in the creation of a multitude of experimental agents. Currently, several of these agents are undergoing late-phase clinical trials to assess their efficacy. The most promising uses of these fluorescent agents include enhancing the precision of cancer removal during surgery, detecting previously undetected tumors, and imaging the ureter in high-risk cases. In order for these agents to become widely adopted in clinical practice, it is essential to show that their use results in a direct improvement in patient outcomes. This includes a change in surgical management, reduced surgical complications, increased survival rates, and a lower likelihood of cancer recurrence. The demonstration of these benefits through large, well-designed clinical trials is crucial in establishing the value of fluorescent agents in surgical procedures.

In conclusion, ICG-FA has proven to be a valuable tool in the field of gastrointestinal surgery. This technology provides real-time imaging of perfusion and has the potential to alter surgical decision-making during both elective and emergency surgical procedures. Qualitative interpretation of ICG-FA images can be challenging due to the inter-user variability and learning curve. To address these issues, real-time fluorescence time curves have been developed as a quantitative tool, which can help identify high-risk patients for anastomotic leakage. This information can then be used to tailor the intraoperative or postoperative course for patients and optimize outcomes.

While the first steps of calibrating the differences between various devices have been demonstrated, there is still a need for further advancements in this area and standards on image acquisition and analysis are paramount. The journey towards better use of ICG-FA will continue and further refinements in technology and techniques are required to fully realize its potential. By investing in these advances, the industry can help ensure that ICG-FA remains a valuable tool for surgical decision-making and helps to improve outcomes for patients undergoing surgery.

Given ICG-FA's widespread use, the focus now also needs to shift from designing randomized controlled trials to setting up large, prospective data sets with uniform quantitated fluorescence parameters to accurately guide surgeon and make a lasting impact on patient outcomes.

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APPENDICES

Nederlandse samenvatting

List of publications

List of contributing authors

PhD Portfolio

Dankwoord

Curriculum Vitae

NEDERLANDSE SAMENVATTING

Op elk gebied van de wetenschap worden grote stappen gezet. Verrassend genoeg is vanaf het begin van de geneeskunde de huidige behandelingsstandaard voor perfusiebeoordeling niet veranderd; dit wordt geschat aan de hand van de kleur de serosa en al dan niet aanwezig zijn van pulsaties. Met een toenemend besef dat een goede perfusie een cruciale component is van orgaanfunctie of wondgenezing en dus een sleutelrol speelt bij het terugdringen van mortaliteit en morbiditeit bij een groot aantal ingrepen, is de noodzaak om perfusie beter te “visualiseren” nog nooit zo urgent geweest.

Beeldvorming van de perfusie is van belang in veel verschillende medische disciplines, omdat de perfusie indicatief is voor de vitaliteit van het betreffende weefsel. Het is van cruciaal belang te begrijpen dat op beeldvorming gebaseerde perfusie-evaluatie op zichzelf geen therapeutische waarde heeft, maar wel kan worden gebruikt als een zogenaamd ‘*red flag’* diagnostisch hulpmiddel. Binnen de gastro-intestinale chirurgie, is het bij het gebruiken van beeldvorming de verantwoordelijkheid van de chirurg om: gestandaardiseerde beeldvorming te gebruiken, de beelden nauwkeurig te evalueren en toereikende maatregelen te nemen in het geval van een afwijkende meting. Een weloverwogen en op beeldvorming gebaseerde verandering van beleid is alleen mogelijk of zinvol wanneer alle drie deze pijlers aanwezig zijn. Op deze manier kan een deze beeldvorming van de perfusie gebruikt worden als een extra bron van *real time’* informatie, die de chirurg kan gebruiken bij het nemen van beslissingen op een kritiek moment tijdens de operatie.

Het doel van dit proefschrift is de modus operandi van kwalitatieve indocyanine groen fluorescentie angiografie (ICG-FA) metingen te onderzoeken en te komen tot objectieve en reproduceerbare ICG-FA beoordelingen door het definiëren van een drempelwaarde voor adequate perfusie bij gastro-intestinale chirurgie. In dit proefschrift wordt een reis naar het kwantificeren van weefselperfusie beschreven.

Hoofdstuk 1 geeft een algemene inleiding over ICG-FA bij gastro-intestinale chirurgie en de opzet van dit proefschrift.

Hoewel ICG-FA in de klinische setting al op grote schaal wordt toegepast voor electieve chirurgie, is de potentiële meerwaarde in de acute setting nog nauwelijks onderzocht. **Hoofdstuk 2** beschrijft een multicenter cohortstudie en het gebruik en de uitkomsten van ICG-FA in de acute setting. Bij 93 operaties voor acute darmischemie is er een verandering van beleid in 29% van de patiënten, wat resulteert in darmbehoud bij ongeveer één op de vier patiënten zonder een substantiële toename van ongeplande reoperaties. Dit is een belangrijk verbetering van uitkomsten, aangezien darmischemie vaak gepaard gaat met grote darmresecties en vele additionele reoperaties.

In de electieve setting, is herstel van continuïteit na slokdarmresectie in bepaalde situaties niet mogelijk middels een buismaagreconstructie, dan is een coloninterpositie een mogelijk alternatief voor renconstructie. **Hoofdstuk 3** onderzoekt of ICG-FA mogelijk is gedurende het herstellen van de continuïteit van het maagdarmstelsel middels een coloninterpositie en de mogelijke rol van ICG-FA met betrekking tot het voorkomen van naadlekkages. ICG-FA blijkt een veilige en haalbare techniek om de perfusie van de coloninterpositie te beoordelen en biedt de chirurg zekerheid bij de keuze van het colonsegment voor de interpositie. Uit deze studie blijkt dat bij 20% van de patiënten het operatieve beleid op basis van de ICG-FA meting is veranderd. Er zijn geen significante verschillen tussen patiënten met of zonder ICG-FA in het voorkomen van naadlekkages.

Hoofdstuk 4 beschrijft de variabiliteit in de interpretatie van ICG fluorescentie angiogrammen tussen verschillende chirurgen tijdens de kwalitatieve beoordeling van de buismaag doorbloeding. Hoewel de variatie afneemt naarmate men de techniek beter beheerst, is er in één casus nog steeds sprake van grote variabiliteit in interpretatie door experts op fluorescentie gebied. Dit onderstreept het belang van het bereiken van een objectieve maat van perfusie.

Echter kan kwalitatieve beoordeling van ICG-FA ook relevante veranderingen in beleid brengen. Tijdens operaties voor de ileo-anale pouch anastomose (IPAA) kan het nodig zijn lengtemaatregelen uit te voeren waarbij ligatie van vaten nodig is om lengte te verkrijgen voor de anastomose. Vooral in deze gevallen kan ICG-FA van waarde zijn om significante perfusieproblemen uit te sluiten. Literatuur over ICG-FA tijdens IPAA is echter schaars en verandering van beleid op geleide van ICG-FA is tot nu toe niet beschreven. In **hoofdstuk 5** wordt in een tweetal casussen besproken dat ICG-FA van toegevoegde waarde kan zijn de peroperatieve besluitvorming tijdens IPAA-chirurgie. In beide gevallen verkleurde de pouch geleidelijk blauw gedurende de ingreep, maar ICG-FA liet een snelle fluorescentie aankleuring zien, wat resulteerde in het aanleggen van de anastomose met een beschermend ileostoma. Aangezien er wel sprake van continuïteitsherstel is door het aanleggen van de anastomose, lijkt ICG-FA nuttig te zijn bij IPAA-chirurgie om mogelijk arteriële instroomproblemen te onderscheiden van veneuze congestieproblemen.

Gelet op de potentiële waarde van ICG-FA bij IPAA-chirurgie in het vorige hoofdstuk bij kwalitatieve beoordeling van de beelden, wordt in **hoofdstuk 6** voor het eerst kwantificatie van ICG-FA tijdens IPAA geëvalueerd. Tijd tot eerste fluorescentie in zowel de afferente als de efferente lis van de pouch wordt vergeleken tussen patiënten met of zonder vasculaire ligatie. De tijd van ICG-injectie tot aankomst in de pouch is verlengd, hoewel niet significant, bij patiënten die een vasculaire ligatie ondergaan.

In **hoofdstuk 7** wordt het ingeslagen pad van kwantificatie vervolgd en worden kwantitatieve in- en uitstroomparameters binnen de afferente en efferente lis bepaald. Het effect van vasculaire ligatie, danwel om peroperatief lengte te verkrijgen of een eerdere onbedoelde onderbreking van de arteria ileocolica, op de fluorescentie tijd curve wordt onderzocht. Bij patiënten zonder ligatie zijn de perfusieparameters tussen de afferente en efferente lis vergelijkbaar. Bij patiënten met vasculaire ligatie van de arteria ileocolica zijn zowel de in- als de uitstroomtijdwaarden verlengd en is de helling van de curve minder steil in de efferente lis. Dit zou kunnen komen vanwege een verandering in arteriële aanvoer via de arcade in het geval van vasculaire ligatie. Vanwege de verschillende kenmerken van de ICG-FA-curve kan kwantitatieve ICG-FA tijdens de operatie vasculaire ligatie identificeren en chirurgen assisteren bij beslissingen tijdens of na de operatie. Dit cohort is echter te klein om tot een fluorescente afkapwaarde te komen van adequate perfusie.

Hoofdstuk 8 onderzoekt in een grote prospectieve serie kwantificatie van perfusie bij patiënten die een slokdarmresectie met buismaagreconstructie ondergaan middels fluorescentietijdcurves, hierbij worden verschillende fluorescente parameters onderzocht of ze gerelateerd zijn aan het optreden van een naadlekkage. Er is een significant verschil in tijd tot het bereiken van de maximale intensiteit (T_{max}) bij patiënten met en zonder naadlekkage tijdens de beoordeling voor de anastomose. Dit is een belangrijke parameter die de peroperatieve besluitvorming kan beïnvloeden en mogelijk naadlekkages na slokdarmresecties met buismaagreconstructie kan voorspellen.

Zoals eerder vermeld, is het doel van een fluorescentiebeoordeling en de interpretatie ervan objectiviteit, reproduceerbaarheid en vergelijkbaarheid. Bij het standaardiseren van de fluorescentiemeting wordt vaak rekening gehouden met de voor de lichaamsmassa gecorrigeerde ICG-dosering en de vaste afstand van de camera tot het weefsel. Aan optische factoren zoals de verdeling van de lichtintensiteit, de gevoeligheid van de camera en de vignettering van het beeld als gevolg van de gebruikte optiek wordt echter weinig aandacht besteed. **Hoofdstuk 9** toont een aanzienlijke variatie in de lichtverdeling binnen het gezichtsveld van de camera; met afnemende fluorescentie-intensiteit binnen het beeld naar de periferie toe; tot 60% daling ten opzichte van de hoogste intensiteit bij vijf verschillende commercieel verkrijgbare nabij-infrarode camerasystemen. Dit hoofdstuk belicht de mogelijke gevolgen voor de kwantificering door het kiezen van interessegebieden in de periferie van het gezichtsveld indien hiervoor niet wordt gecorrigeerd.

Er zijn veel verschillende indicaties voor nabij-infrarode beeldvorming om het onzichtbare zichtbaar te maken. **Hoofdstuk 10** heeft betrekking op patiënten die een *salvage* operatie ondergaan voor sepsis van het bekken na rectumcarcinoom, waarbij wordt aangetoond dat deze complexe patiëntengroep vatbaarder is voor het optreden van iatrogeen urinewegletsel tot 10% van de patiënten. Deze operatie is een chirurgische uitdaging als gevolg van inflammatoire, bestralings- en chirurgisch geïnduceerde littekenvorming. Iatrogene letsels aan de urinewegen worden vaak postoperatief gediagnosticeerd en vereisen vervolgens meerdere re-interventies, terwijl dit bij peroperatief gediagnosticeerde letsels niet nodig is. Dit hoofdstuk schetst dus noodzaak van peroperatieve diagnostische modaliteiten, zoals nabij-infrarood beeldvorming, om te helpen bij het identificeren van de urinewegen en mogelijk direct herkennen van een letsel in deze complexe patiëntengroep.

Kortom, ICG-FA is een waardevol instrument gebleken voor gastro-intestinale chirurgie. Deze technologie maakt *real-time* beeldvorming van de perfusie mogelijk en kan de chirurgische besluitvorming bij zowel electieve als spoedoperaties veranderen. De kwalitatieve interpretatie van ICG-FA-beelden kan een uitdaging zijn vanwege de variabiliteit in interpretatie tussen gebruikers en gaat dus gepaard met een leercurve. Om deze problemen aan te pakken zijn *real-time* fluorescentietijdcurven ontwikkeld als kwantitatief instrument, welke bij kunnen dragen bij het identificeren van patiënten met een hoog risico op het ontwikkelen van een naadlekkage. Deze informatie kan vervolgens worden gebruikt om het per- of postoperatieve beloop van patiënten aan te passen en de behandeling te optimaliseren.

Hoewel de eerste stappen voor het kalibreren van de verschillen tussen diverse fluorescentie apparaten zijn gezet, is er nog steeds behoefte aan verdere optimalisatie op dit gebied en zijn uniforme standaarden voor beeldacquisitie en -analyse van groot belang. De reis naar een gestandaardiseerd gebruik van ICG-FA zal doorgaan en er zijn verdere verfijningen van deze techniek nodig om de potentie ervan volledig te realiseren.

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PhD period:	01-05-2020 – 31-12-2022
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Name PhD co-supervisors:	Dr. R. Hompes / Dr. D.M. de Bruin

1. PhD training		
	Year	**Workload (ECTS)**
General courses		
- Clinical Epidemiology: Observational Epidemiology, AUMC	2020	1.0
- Clinical Epidemiology: Randomized Clinical Trials, AUMC	2020	1.0
- Talents in PhD, Amsterdam UMC, Graduate School	2021	0.5
- Entrepreneurship in Health and Life Sciences, Graduate School	2021	1.0
- Project management, Graduate School	2021	1.0
- English scientific writing, Graduate School	2020	1.0
- Practical Biostatistics, AUMC	2020	1.0
- BROK, basic course Legislation and Organisation for Clinical Researchers.	2020	2.0
Seminars, workshops and master classes		
- Monthly Journal Club Surgery	2020-2022	2.0
- Weekly colorectal department seminars	2020-2022	1.0
- Digestive Diseases Grand Rounds, two weekly	2021-2022	1.0
Presentations at scientific congresses		
Oral presentations:		
The use of fluorescence angiography to assess bowel viability in the acute setting : an international, multi-centre case series		
- European Society of Coloproctology, virtual	2021	0.5
- European Association of Endoscopic Surgery, Krakow	2022	0.5
- Digestive Disease Week, San Diego	2022	0.5
- Chirurgendagen, Den Haag	2022	0.5
- Wetenschapsdag Amsterdam UMC, Amsterdam	2021	0.5
Fluorescence angiography in colonic interposition as reconstruction after esophageal resection		
- European Society for Diseases of Esophagus, Milan	2021	0.5

Evaluation of inter-user variability in indocyanine green fluorescence angiography to assess gastric conduit perfusion in esophageal cancer surgery		
- European Society for Diseases of Esophagus, Milan	2021	0.5
- European Association of Endoscopic Surgery, Krakow	2022	0.5
Perfusion assessment by fluorescence time curves in esophagectomy with gastric conduit reconstruction: a prospective clinical study	2022	0.5
- Wetenschapsdag Amsterdam UMC, Amsterdam	2023	0.5
- Digestive Disease Days, Velthoven		
Poster presentations:		
Understanding fluorescence time curves during ileal pouch-anal anastomosis with or without vascular ligation		
- European Society of Coloproctology, Dublin	2022	0.5
- Digestive Disease Days, Velthoven	2023	0.5
Investigating and compensating for periphery-center effect among commercial near infrared imaging systems using an indocyanine green phantom		
- European Society of Coloproctology, Dublin	2022	0.5
Iatrogenic injury of the urinary tract during salvage procedures for chronic pelvic sepsis –experience of a national referral centre		
- European Society of Coloproctology, Dublin	2022	0.5
(Inter)national conferences attended		
- Alpine Colorectal Meeting (ACM), Courchevel, France	2023	0.5
- Digestive Disease Days (DDD), Velthoven	2022	0.5
- Wetenschapsdag Amsterdam UMC, Amsterdam	2022	0.5
- European Society of Coloproctology(ESCP), Dublin, Ireland	2022	0.5
- Chirurgendagen, Den Haag	2022	0.5
- Digestive Disease Week (DDW), San Diego, The United States	2022	0.5
- European Association of Endoscopic Surgery (EAES), Krakow, Poland	2022	0.5
- European Society for Diseases of Esophagus (ESDE), Milan, Italy	2021	0.5
- Wetenschapsdag Amsterdam UMC, Amsterdam	2021	0.5
- European Society of Coloproctology (ESCP), virtual	2021	0.5
- Digestive Disease Days Symposium, virtual	2021	0.5

2. Teaching		
	Year	**Workload (ECTS)**
- Medical master students, lecture twice a year - Specialized (oncology) nurses, surgical lecture four times a year - Surgical nurse, surgical lecture four times a year	2020-2022 2020-2022 2020-2022	1.0 1.0 1.0
Other activities - Organising committee, *Dutch Fluorescence Guided Surgery symposium*, Bussum	2022	2.0

DANKWOORD

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Friends who cycle 12 hours together stay together? Lieve Art en Lies, toen ik me opgaf voor de D2D ride tijdens verveling in corona tijd, had ik niet gedacht dat ik er tot op de dag van vandaag slappe grappen, reisjes en gezelligheid aan over zou houden. Dank daarvoor!

Lieve Car, Chien, Hansie, Ier, Juul en Tine, lieve hockey, eindelijk de mogelijkheid jullie eens te bedanken voor de bijzondere vriendschap zonder dat er een paar flessen wijn in het spel zijn. Fietsen, vakanties in Italië, Aruba, Kaapstad of Indonesië, festivals, Sinterklaas vieringen, wijnreizen met jullie is het oprecht altijd feest, zelfs een rondje Markermeer in de derde versnelling. Er zijn weinig mensen die me zo aan het lachen kunnen maken, maar mij tegelijkertijd zo op mijn plek kunnen zetten. Daarnaast zijn jullie er door dik en dun voor mij geweest, dank daarvoor, jullie betekenen heel veel voor mij!

Queenies, avondjes met jullie één op één of met elkaar, blijven voelen als thuis komen, ook al hebben we elkaar lang niet gezien. Van blauwe bank op de Butjesstraat naar tafel in Italië; uitgebreid tafelen en oneindig praten is de rode draad van ons huis. Dank voor jullie steun en interesse!

Lieve buurgirls, jullie oprechte interesse is bijzonder, ook al zien we elkaar soms weinig. Lieve Suus, echte buuf inmiddels, zo fijn je nu letterlijk en figuurlijk zo dichtbij te hebben. Ik geniet van onze spontane koffietjes, sportlesjes of etentjes. Lies, jouw kwaliteit om écht te luisteren en door te vragen hoe ik me voel of ergens over denk, is iets wat ik ontzettend bewonder.

Cape Town girls, lieve Helena, Miem, Marie en Ran, mijn wetenschappelijke carrière begon in Kaapstad. Nog steeds denk ik terug aan een geweldige periode, mede en vooral door jullie. Stuk voor stuk zijn jullie zo gek als een deur, daarom zijn avondjes en avonturen met jullie fantastisch. Tegelijkertijd weet ik dat ik altijd bij jullie terecht kan.

Lieve Boon en Norps, wat was het een geweldige tijd op de JPH, etentjes, borrelen, FbF, samen op boevenpad in Amsterdam tot op duivenjacht op het balkon. Niet lang nadat ik op de JPH kwam te wonen, overleed mijn vader, de support en afleiding die jullie mij hebben geboden, is niet in woorden uit te drukken. Ik weet zeker dat onze band de basis is voor een levenslange vriendschap!

Lieve Pienie, where to start… Wij vonden elkaar tijdens de coschappen in Groningen in het schoppen tegen de gebaande paden. Nu zijn er weinig dingen waar wij elkaar niet in vinden. Ik kan met jou praten, lachen, mijn ei kwijt, eten, reizen, lay overs van 40 uur overleven zonder ruzie, vragen voor advies, maar ook feesten. Je bent echt een powermens- eerlijk, daadkrachtig, hart op de tong maar vooral ook lief en attent voor de mensen om je heen. Deze combinatie is bijzonder en waardeer ik ontzettend aan jou. Dank voor alles wat je in deze jaren voor me betekend hebt en nog gaat betekenen.

Lieve Char, Hannelotte, Truus &Truus, soms is het idioot te beseffen dat wij elkaar pas vier jaar kennen, maar onze vriendschap is misschien nu al het mooiste cadeau dat de chirurgie mij heeft gegeven! Vanaf het OLVG zijn wij onafscheidelijk geweest en volgde ik jou niet lang daarna het onderzoeksleven in. Het mooie vind ik dat er bij ons altijd veel gepraat en geborreld wordt, maar over werkmijlpalen hebben we het nauwelijks. Want ook hebben we beiden in deze paar jaar veel meegemaakt; dank voor de steun, luchtigheid en gezelligheid die je mij hebt geboden. Los van het feit dat je een inspirerend mens bent, (je ziet nooit beren op de weg, altijd optimistisch en attent) voel ik me bij jou thuis! Het kon niet anders dat jij vandaag ook naast mij stond!

Dan tot slot mijn lieve familie, lieve mam, dank voor de warmte en de onvoorwaardelijke liefde waarmee je ons hebt groot gebracht. De thuisbasis die jullie hebben gecreëerd, is de belangrijkste zekerheid in mijn leven. Bij jou voel ik me nooit teveel met mijn verhalen. Jouw oprechte interesse en het meegenieten in alles wat wij doen of waar wij mee bezig zijn, zijn ongekend. Jij zult dan ook waarschijnlijk de enige persoon zijn die dit boekje van voor tot achter zal lezen. Jouw secuur- en nauwkeurigheid geven mij sturing en door je ruimhartige vertrouwen en liefde ben ik de persoon geworden die ik nu ben, daarvoor is mijn dankbaarheid niet in woorden uit te drukken. Ik ben blij en trots dat je vandaag naast me staat.

Lieve Al en Hid, samen stedentrips, borrelen, marathons lopen, wonen het doet maar.. Zowel van Amsterdam naar Bussum rennen als de finish overkomen in Barcelona zijn twee van mijn meest trotse momenten. Niet om de prestatie an sich, maar om het feit dat ik dan opzij keek en besefte dat we dit samen deden. Met jullie is alles leuker! Hid, ik weet nog dat ik mijn eerste publicatie met jullie deelde en jij hem diezelfde avond al had gelezen. Jouw loyaliteit en interesse zijn inspirerend en hoe jij de meest complexe zaken simpel kan maken bijzonder. Ik weet dat jij altijd voor mij klaar staat. Lard, met jouw natuurlijke charisma en humor, kun jij andere mensen laten stralen. Voor twee amicale mensen, die beiden graag aan het woord zijn, hebben wij samen niet altijd woorden nodig; aan een half woord of oogopslag hebben wij genoeg. Maar tegelijkertijd weet jij een luisterend oor te bieden of advies te geven op momenten dat ik deze het allermeest nodig heb. Dit is voor mij van onschatbare waarde. Lieve josties, wat ben ik trots op onze band, ik besef steeds vaker dat deze niet vanzelfsprekend is.

Lieve pap, woorden schieten tekort om te beschrijven hoe jammer ik het vind dat jij dit alles niet meer mee kan maken. Deze laatste alinea van dit boek schrijf ik dan ook met een brok in mijn keel, want ja het zijn de laatste woorden van het boek, maar tegelijkertijd sluit ik hiermee de laatste periode in mijn leven af waar jij (letterlijk) deel van uitmaakte.

Gedurende deze promotietijd ben ik er nog meer achter gekomen hoe veel ik op jou lijk. Eigenschappen die mij zeker door deze periode hebben heen gesleept, maar ook soms ongelofelijk hebben tegen gewerkt zoals mijn extreme ongeduld. Maar toch ook dank daarvoor, want zonder wrijving, geen glans. Bedankt voor je oneindige vertrouwen in mij, je ongelofelijke trots, beiden zo onvoorwaardelijk en sterk dat ik deze tot op de dag van vandaag voel. Ik mis je ontzettend.

CURRICULUM VITAE

Hanneke (J.J.) Joosten is geboren op 2 april 1993. Ze groeide op in Bussum met haar ouders Roelof en Joke en twee broertjes Allard en Hidde. In 2011 behaalde zij haar Gymnasium diploma cum laude aan het Sint Vitus College en verhuisde zij in 2012, na een jaar te hebben gereisd in Zuid- Amerika naar Groningen voor haar medische opleiding aan de Rijksuniversiteit van Groningen. Na het behalen van haar bachelor in 2015, vertrok ze naar Kaapstad om onderzoek te doen in het kader van de wetenschappelijke stage op de afdeling traumachirurgie van het Groote Schuur Hospitaal.

In 2019 studeerde zij af en ging ze aan de slag als arts-assistent bij de chirurgie in het OLVG Oost Vervolgens startte zij onderzoek naar fluorescentie geleide chirurgie in het Amsterdam UMC. De wetenschappelijke resultaten zijn gebundeld in dit proefschrift. Hanneke had de eer om verschillende projecten gedurende haar promotietijd te presenteren op (inter) nationale congressen.

Momenteel is zij werkzaam als arts-assistent in het OLVG West en zal zij per 1 juli starten met de opleiding tot chirurg in Amsterdam.

Hanneke woont in Amsterdam en naast werk houdt ze van sporten (wielrennen, hardlopen, skiën en kitesurfen), koken en tijd te spenderen met vrienden en familie.