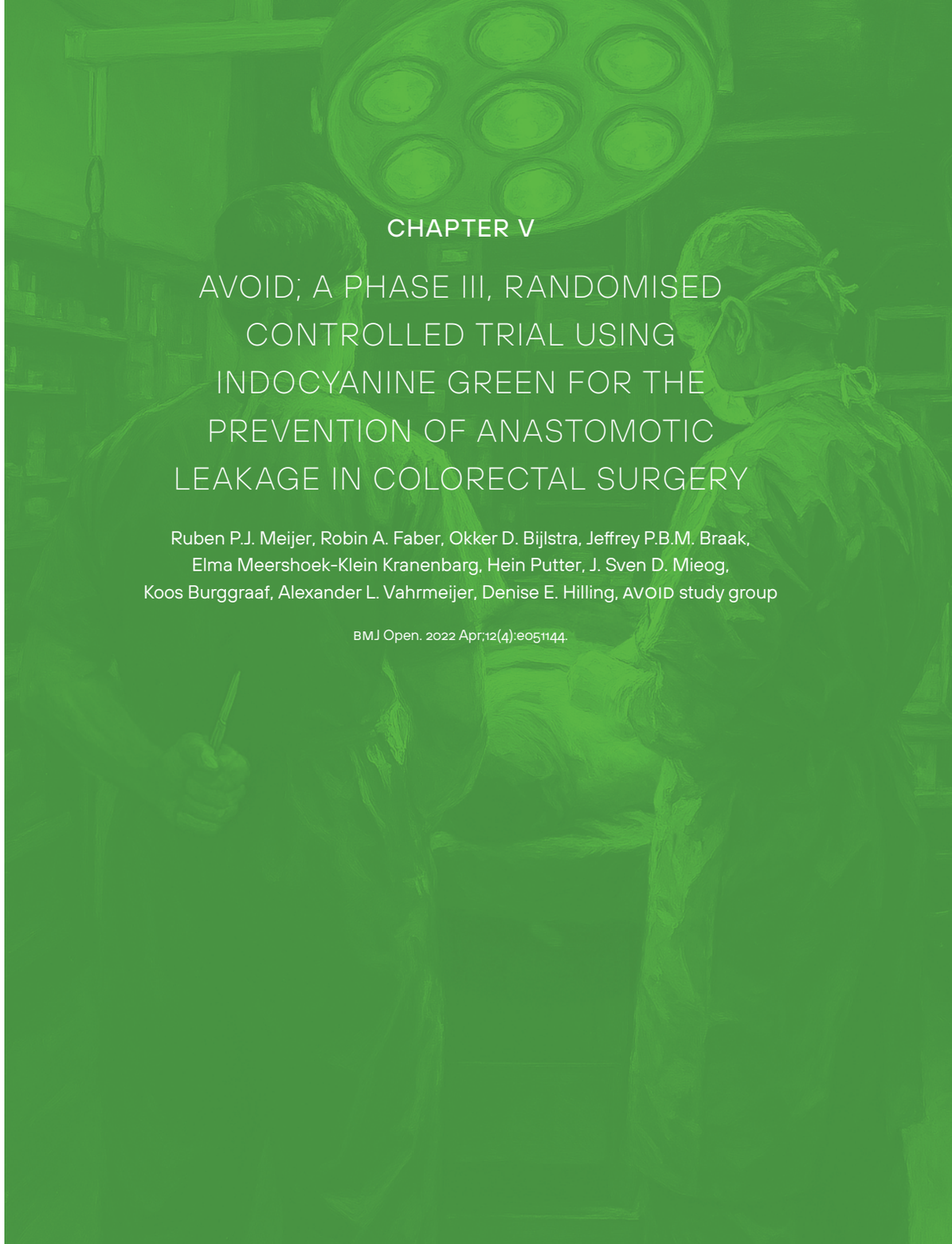
Near-infrared fluorescence imaging in colorectal cancer and its metastases

Meijer, R.P.J.



CHAPTER V

AVOID; A PHASE III, RANDOMISED CONTROLLED TRIAL USING INDOCYANINE GREEN FOR THE PREVENTION OF ANASTOMOTIC LEAKAGE IN COLORECTAL SURGERY

Ruben P.J. Meijer, Robin A. Faber, Okker D. Bijlstra, Jeffrey P.B.M. Braak,
Elma Meershoek-Klein Kranenbarg, Hein Putter, J. Sven D. Mieog,
Koos Burggraaf, Alexander L. Vahrmeijer, Denise E. Hilling, AVOID study group

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Abstract

INTRODUCTION Anastomotic leakage (AL) is one of the major complications after colorectal surgery. Compromised tissue perfusion at the anastomosis site increases the risk of AL. Several cohort studies have shown that indocyanine green (ICG) combined with fluorescent near-infrared imaging is a feasible and reproducible technique for real-time intraoperative imaging of tissue perfusion, leading to reduced leakage rates after colorectal resection. Unfortunately, these studies were not randomised. Therefore, we propose a randomised controlled trial to assess the value of ICG-guided surgery in reducing AL after colorectal surgery.

METHODS AND ANALYSIS A multicentre, randomised controlled clinical trial will be conducted to assess the benefit of ICG-guided surgery in preventing AL. A total of 978 patients scheduled for colorectal surgery will be included. Patients will be randomised between the Fluorescence Guided Bowel Anastomosis group and the Conventional Bowel Anastomosis group. The primary endpoint is clinically relevant AL (defined as requiring active therapeutic intervention or reoperation) within 90 days after surgery. Among the secondary endpoints are 30-day clinically relevant AL, all-cause postoperative complications, all-cause and AL-related mortality, surgical and non-surgical reinterventions, total surgical time, length of hospital stay and all-cause and AL-related readmittance.

ETHICS AND DISSEMINATION This protocol has been approved by the Medical Ethical Committee Leiden-Den Haag-Delft (METC-LDD) and is registered at ClinicalTrials.gov and trialregister.nl. The results of this study will be reported through peer-reviewed publications and conference presentations.

TRIAL REGISTRATION NUMBERS NCT04712032 and NL7502

Introduction

Anastomotic leakage (AL) is a major complication after colorectal surgery, accounting for considerable morbidity and mortality.[1-6] The incidence of AL in colorectal surgery ranges from 2.4 to 11% in colon cases and up to 23.3% in rectal cancer surgery.[4-15] The occurrence of AL often has a multifactorial cause, including risk factors such as tumour location, level of anastomosis, male gender, high ASA score, comorbidities, smoking, obesity and (neoadjuvant) radiotherapy.[3,4,6,11,13,14,16]

Most risk factors for AL can no longer be changed at the time of surgery. Therefore, it is important to focus on the few factors that can be influenced, such as compromised tissue perfusion at the anastomosis site. It has been reported that this factor significantly increases the risk of AL.[17-19] Perfusion is commonly assessed by palpating the mesenteric arterial pulsations, inspection of the bowel colour, and bleeding at the anastomosis sides. Other intraoperative tests to prove the integrity of the anastomosis are the air leak test and inspection of the resection doughnuts.[20] Though useful, these clinical assessments have proven to have a low predictive value for AL which emphasises the urge for a better diagnostic test.[21]

A promising diagnostic tool is intraoperative near-infrared (NIR) fluorescence imaging. This technique combines a fluorescent contrast agent, e.g. indocyanine green (ICG), and a dedicated NIR imaging system.[22] The intravenous injection of ICG has proven to be a feasible and reproducible application for real-time perfusion assessment.[23-25] ICG was introduced by Fox *et al.* in 1957 and is currently used for a variety of diagnostic indications.[26] Diluted and intravenously injected ICG, with a peak emission at 820 nm, is invisible for the naked eye and will therefore not interfere with the surgical field.[27] Moreover, it is cleared quickly by the liver and has low toxicity.[28]

Several cohort studies have investigated the benefit of NIR fluorescence imaging with ICG for intraoperative assessment of bowel perfusion. Some of these studies have shown that this technique enables clear visualisation of bowel perfusion within minutes after intravenous injection of ICG, resulting in reduced leakage rates and hospital stay.[29-32] Moreover, several systematic reviews support this promising results concerning the prevention of AL.[33-34] This has already led to the start of two randomised controlled trials (ICG-COLORAL; NCT03602677 and InTACT trial; ISCRN 13334746) which are currently recruiting patients. On the other hand, Kin *et al.* have shown no benefit by using ICG in preventing AL.[35] Major drawbacks of these cohort studies are that they were

not randomised and did not use clinically relevant AL as the primary endpoint. Therefore, we propose AVOID: '*Anastomotic leakage and Value Of Indocyanine green in Decreasing leakage rates*', a randomised controlled trial to investigate the benefit of intraoperative imaging with ICG for the reduction of AL rate in colorectal surgery.

Methods and analysis

PRIMARY AIM

The main objective of this study is to assess if ICG-guided perfusion assessment will result in a reduction of the AL rate within 90 days after surgery. ICG-guided perfusion assessment will be an adjunct to conventional laparoscopic imaging versus conventional laparoscopic imaging alone.

HYPOTHESIS

It is hypothesised that intraoperative assessment of bowel perfusion using NIR fluorescence imaging with ICG will lower the incidence of clinically relevant AL within 90 days after colorectal resection.

STUDY DESIGN

In this multicentre randomised controlled trial, patients will be allocated to two groups: the Fluorescence Guided Bowel Anastomosis group (FGBA) or the Conventional Bowel Anastomosis group (CBA). Patients in the FGBA group will receive at least one dose of 5 milligram ICG, up to a maximum of 3 doses, to assess bowel perfusion. Patients in the CBA group will not receive any study related interventions and will be treated according to standard of care. The allocated treatment result is not blinded for the surgeon performing the procedure. Patients will be unblinded after the procedure.

SETTING

This national study will take place in multiple academic and large teaching hospitals in the Netherlands. More Dutch hospitals will be added during the course of the study.

PARTICIPANTS

All patients scheduled for laparoscopic or robotic-assisted colorectal surgery (malignant and benign indications) with primary anastomosis will be screened for eligibility during multidisciplinary team meetings and, when eligible for participation, informed about the study by their attending physician. It will be emphasized that a patient can withdraw from the study at any given moment without having to offer any reason. The fundamental concepts outlined in the Declaration of Helsinki will be followed during the execution of the trial.[36]

SAMPLE SIZE CALCULATION

The power analysis was performed based on Dutch national AL percentages, derived from the Dutch ColoRectal Audit (DCRA).[37] It is hypothesized that the use of ICG will decrease the AL rate in colorectal surgery from 7 to 3%. With a significance of 0.0492 (adjusted for the interim analysis using the O'Brien-Flemming approach), power of 80%, drop-out of 5% and a control-intervention ratio of 1:1, a sample size of 978 (489:489) patients is needed.[38]

INCLUSION CRITERIA

In order to be eligible to participate in this study, a patient must meet all of the following criteria: aged 18 years and above, scheduled for laparoscopic or robotic-assisted colorectal resection with primary anastomosis, able to communicate in the Dutch language and willing to comply with the study restrictions, and signed informed consent prior to any study-mandated procedure.

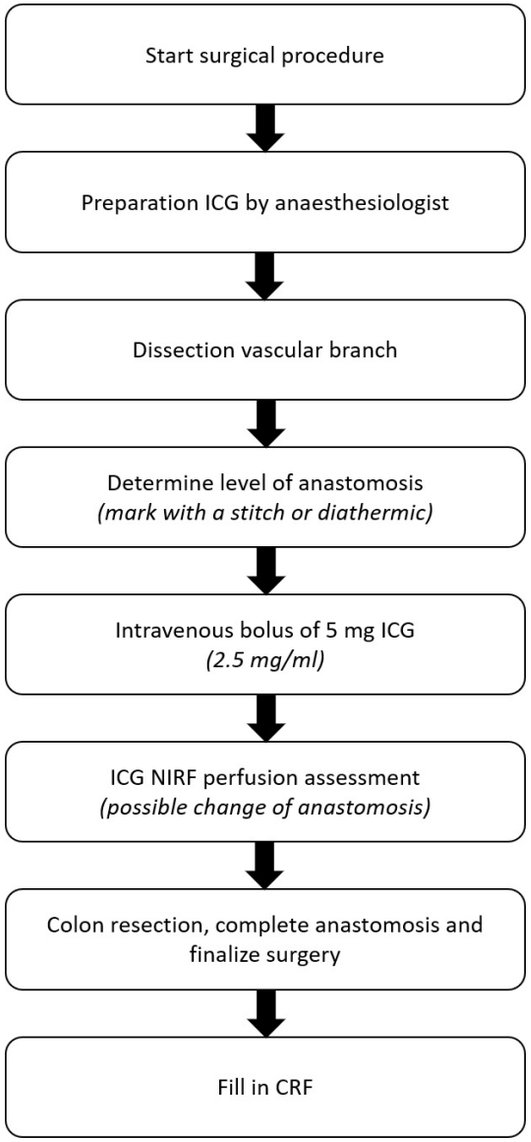
EXCLUSION CRITERIA

A potential patient who meets any of the following criteria will be excluded from participation in this study: known allergy or history of adverse reaction to ICG, iodine or iodine dyes, severe liver or kidney insufficiency, hyperthyroidism or a benign thyroid tumour, pregnant or breastfeeding women, scheduled for emergency surgery, palliative surgery or terminally ill, scheduled for a defunctioning stoma, taking phenobarbital, phenylbutazone, primidone, phenytoin, haloperidol, nitrofurantoin, and probenecid, or any other condition that the investigator considers to be potentially jeopardizing the patients well-being or the study objectives (following a detailed medical history and physical examination).

RANDOMISATION

After inclusion in the study (i.e., after written informed consent is obtained), patients will be randomised to the FGBA or the CBA group. Randomisation will be performed online via Castor EDC (Castor, Amsterdam, the Netherlands) with variable block sizes and stratified by institute. The allocated treatment result is not blinded for the surgeon performing the procedure. Patients will be unblinded after the surgical procedure.

FIGURE 1 Surgical flowchart.



Abbreviations: CRF, case report form; ICG, indocyanine green; NIRF, near-infrared fluorescence.

INTERVENTION

Patients in the CBA group will undergo laparoscopic or robotic colorectal resection according to standard of care using conventional methods to assess the integrity and viability of the anastomosis. Patients in the FGBA group will undergo the same standard of care surgical procedure as patients in the CBA group; however, in addition to the conventional methods, NIR fluorescence imaging with ICG will be performed to assess the bowel perfusion at the anastomosis side. All surgeries, in both arms, will be performed by an attending surgeon. NIR fluorescence imaging with ICG will be performed as follows (Figure 1): after dissection of the vascular branch, the preferred level of anastomoses (proximally and distally) will be highlighted by a stitch or diathermic mark in the adjacent mesocolon or mesorectum. Then, 5 mg ICG (2.5 mg/ml, Diagnostic Green, Aschheim, Germany), followed by 10 ml saline flush, will be injected intravenously by the anaesthesiologist. Within a few minutes, the anastomotic microvascularisation of both bowel ends will be assessed using the Olympus Medical Imaging Video System and Laparoscope (Olympus, Leiderdorp, the Netherlands) or Da Vinci Firefly (Intuitive Inc., Sunnyvale, CA, United States of America). The green overlay setting of these systems will be used for perfusion assessment. The level of resection and subsequent anastomosis may be changed accordingly (with the mesocolic stitch serving as the baseline). During the procedure, the ICG injection (5 mg) may be repeated for a second or third time with a 15 minute wash-out period between each administration. Repeated doses may be applicable when, for example, both anastomosis sides do not fit into the optical field, or when perfusion seems compromised after anastomosis finalisation. All injections, including the reason(s) for repeated injection(s), and the consequences of administration, will be documented in the case report form (CRF).

The 90-day follow-up is a standard of care follow-up moment in all participating hospitals. It will be done either by phone, by videoconference or in person, according to standard of care in the participating hospital. Patients who, for any reason, do not visit the hospital 90 days after resection, will be contacted by phone and asked for any postoperative complications or reinterventions.

OUTCOME MEASURES

PRIMARY OUTCOME

The primary outcome is the rate of clinically relevant AL within 90 days after surgery. This will be compared between the FGBA group using ICG for perfusion assessment and the standard of care surgery, CBA group. The definition

of clinically relevant AL is derived from the definition of Rahbari *et al.*[39] Grade B (requiring active therapeutic intervention but manageable without re-operation) and C AL (requiring re-operation) will be considered clinically relevant. There is no central study protocol for the detection of AL. No routine CT scans will be performed for AL assessment. Post-operative blood tests, radiologic assessment and subsequent assessment of AL will be based on local protocols and the judgement of the local surgical team.

SECONDARY OUTCOMES

30-day clinically relevant AL
30- and 90-day all-cause postoperative complications
30- and 90-day mortality; all-cause and AL related
30- and 90-day reinterventions; surgical and non-surgical
Total surgical time of primary surgery
Postoperative length of hospital stay; primary stay and readmittance within 90 days
Readmittance; all-cause and AL related

TRAINING

Prior to their first inclusion, surgeons and other involved hospital staff of the participating center will be trained during a site initiation visit by the principal investigator or one of the coordinating investigators. If needed, training with the Olympus Medical Imaging Video System and Laparoscope or Da Vinci Firefly will be provided by either Olympus or Intuitive. Surgeons are invited to observe surgical procedures, using NIR fluorescence imaging with ICG for intraoperative assessment of bowel perfusion, in the Leiden University Medical Centre (LUMC). One of the coordinating investigators, with a broad experience in fluorescence-guided surgery, will assist all participating surgeons during their first number of cases to ensure standardization of the technique.

This study is performed in collaboration with Olympus. In order to keep the study data as homogenous as possible, the use of camera system has been limited to the Olympus Medical Imaging Video System and the Da Vinci Firefly in case of robotic-assisted surgery.

DATA COLLECTION

A CRF will be filled in during surgery by trained local research staff. This CRF captures baseline characteristics, basic surgical data and study specific data. For patients in the FGBA group it will be documented whether the resection margins have been adjusted and, if so, which margin (distal or proximal margin) and the extent of adjustment in centimetres. In addition, in case of a non-planned de-functioning stoma, it will be recorded whether ICG-guidance contributed to this decision. All clinical data will be prospectively registered via an electronic CRF (ECRF) in a digital database of Castor EDC. We will not transfer or collect imaging data (video or pictures) for postoperative analysis.

DATA VALIDATION AND MANAGEMENT

Patient data will be registered coded and analysed by comparing the FGBA group with the CBA group. Only the local investigators will have access to local source data after informed consent is given. The research group from LUMC will have access to all coded data in the Castor EDC database.

STUDY TIMELINE

Patients have been included in the study from July 2020, starting in the LUMC. As per August 1st 2021, 352 patients were included in 6 different hospitals. With a mean inclusion rate of 40 patients per month the anticipated last inclusion will be in the final quarter of 2022. There is no maximum for the number of centres nor the number of inclusions per centre.

STATISTICAL ANALYSIS

The most recent version of SPSS (IBM, Armonk, New York, USA) will be used for statistical analysis. Categorical variables of the FGBA and CBA group will be compared by the Chi-Square test. Numerical variables will be compared by the independent sample T-test or the Mann-Whitney U test, depending on distribution. All p-values will be 2-sided. A p-value of less than 0.0492 will indicate a statistically significant difference. All data will be analysed on an intention-to-treat principle and, when applicable, on a per protocol analysis.

The primary outcome measure, clinically relevant AL within 90 days after surgery, will be compared using the Mantel-Haenszel test, stratified by centre.

An interim analysis will be conducted after 489 patients have been randomised and reached the last day of follow-up (day 90). This interim analysis will aim at stopping the study for futility, if the conditional power for the primary endpoint (clinically relevant AL within 90 days after surgery) with the planned sample size, based on the observed results at the interim analysis, using the original settings of null and alternative hypothesis, is less than 10%.

If this interim analysis shows efficacy based on the primary endpoint with a nominal alpha level of 0.0054, the study will be stopped as well. Already included

patients will be followed until the last follow-up moment. Sub-group analysis will be conducted by separately assessing patients with 1. colon and rectal resections, 2. left and right sided resections, 3. malignant and benign pathology, 4. laparoscopic and robotic-assisted surgery.

DATA MONITORING

The study will be monitored for quality and regulatory compliance, by study-independent LUMC staff. Monitoring frequency will be at least annually, but may be increased depending on findings.

ADVERSE EVENTS

All adverse events related to indocyanine green will be reported. Furthermore, all events that are serious adverse events will be registered in the online Dutch database, toetsingonline.nl, and in the ECRF of Castor EDC.

PATIENT AND PUBLIC INVOLVEMENT

Patients or public were neither involved in the development of the research questions and outcome measures nor the planning of the study design. Patients are not involved in the recruitment or conduct of the study. Results of the study will be published in peer-reviewed journals, no other information of the results of the study are provided to the patients. Patients will not take part in assessment regarding possible burden of the interventions of this study.

Expected limitations and difficulties

Intraoperative fluorescence assessment of bowel perfusion is currently a subjective tool. This will most likely influence our results as over 30 different surgeons will interpret the fluorescence output. Quantification of the NIR fluorescence signal would improve standardized assessment of tissue perfusion.

Using different NIR platforms (the Olympus Medical Imaging Video System and Laparoscope, and the Da Vinci Firefly) will have some influence on our results as well. Nevertheless, both systems are optimized for the detection of ICG, we therefore think its effect on our study results is minimal.

AL after colorectal surgery is a multifactorial complication. It is unclear which percentage of AL is solely based on compromised perfusion. It is especially questionable if compromised perfusion plays a role in late AL (> 7 days after surgery).

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