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VILNIUS UNIVERSITY

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The problem of preventive ileostomy in colorectal surgery

DOCTORAL DISSERTATION

Medicine and Health Sciences,
Medicine M 001

VILNIUS 2022

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Marius Kryžauskas

Laikinosios ileostomos prevencija kolorektinėje chirurgijoje

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CONTENT

1. ABBREVIATIONS

AL – anastomotic leakage
ASA – American Society of Anaesthesiology
CCI – Charlson comorbidity index
CI – confidence interval
CRC – colorectal cancer
E – elderly
DFS – disease-free survival
ICG-FA – indocyanine green fluorescence angiography
MIS – minimally invasive surgery
NE – non-elderly
OR – odds ratio
OS – overall survival
TPN – total parenteral nutrition

2. PREAMBLE

The Ph.D. theses are submitted for defence as a set of research articles and some parts have been quoted verbatim from the previously published articles listed at the end of the book.

The dissertation consists of several parts, which are all connected.

First, we performed a retrospective analysis to identify the risk factors and the rate of anastomotic leakage and long-term outcomes. Moreover, anastomotic leakage rate and outcomes were compared between the elderly and non-elderly patients with left-sided colorectal cancer who underwent resection with primary anastomosis. After that, a meta-analysis was performed to analyse the impact of various intraoperative mechanical integrity and bowel perfusion tests. Also, we designed the experimental study focused on mechanical integrity testing and compared air-leak and methylene blue leak tests. Parallelly, the prospective study was performed for patients undergoing left-sided colorectal surgery with primary anastomosis. The bowel blood perfusion, tension, and mechanical integrity were checked by various tests which helped us to identify high-risk colorectal anastomosis. Preventive ileostomy was created for the majority of these patients. A novel idea has been born, how to replace ileostomy creation in high-risk anastomoses. Total parenteral nutrition was suggested as an alternative method for preventive ileostomy creation.

3. INTRODUCTION

3.1. Scientific background

Colorectal cancer (CRC) is the third most commonly diagnosed malignancy and the fourth leading cause of cancer-related deaths in the world [1, 2]. The treatment is multimodal, including chemotherapy, radiotherapy, and surgery [3–7]. A radical surgery remains the main curative option in majority cases [8, 9].

Anastomotic leakage (AL) is the most dreadful complication of colorectal surgery [10]. The incidence of AL after colorectal surgery varies widely and can be as high as 25% in high-risk anastomoses [11]. AL is defined as "a defect of the intestinal wall at the anastomotic site leading to a communication between intra- and extra- luminal compartments" which is based on clinical symptoms and proved with endoscopy, radiology, or reoperation [12]. AL may be a life-threating complication, although, even if it is managed it results in poor oncologic outcomes, prolonged hospital stay, and increased health care costs [13–15].

The aetiology of AL is still not fully clear, although, some risk factors have been suggested, including patient and disease related factors as well as surgical technique failure [16, 17]. Male sex, elderly age, obesity, severe comorbidities (higher American Society of Anaesthesiology (ASA) score), prolonged surgery time, perioperative blood transfusions, low anastomosis, and neoadjuvant chemoradiotherapy are proposed risk factors for AL [18, 19]. Nevertheless, AL may occur in patients without any risk factors as well, and therefore, it remains a challenging issue in CRC surgery. Insufficient blood supply at the proximal or distal ends of anastomosis, tension on anastomosis and insufficient integrity of anastomosis are the main causes of technical failure and they may be modified intraoperatively if detected [20, 21].

Various tests to investigate mechanical integrity of anastomosis have been proposed. The most common test for colorectal anastomosis is an air-leak test [22]. Some studies suggest saline or methylene blue leak tests alone or in combination with air-leak test as well [23, 24]. Although, these liquid-based tests are much more common in gastrointestinal anastomoses and there is a lack of data for colorectal surgery [25–27]. Intraoperative colonoscopy is another available method for mechanical integrity testing [28–30]. Tension testing has no specific measure and is evaluated subjectively by the surgeon. As shown previously, all of these tests for mechanical integrity reduce the rate of postoperative AL [23, 28, 29]. However, it remains unclear whether some of them may be more accurate than others and which tests should be used.

Moreover, negative results of integrity testing do not guarantee uneventful postoperative course.

Insufficient blood supply is another well-known factor which is responsible for a postoperative leak of intraoperatively non-leaking anastomosis. Historically, the bowel viability and blood supply were evaluated by the surgeon through visual inspection. The colour of the bowel wall, peristalsis of the bowel, pulsation of the marginal artery, or bleeding of the resected bowel margin is considered as clinical indicators of good vascularization [20]. However, this is very subjective, and it does not always properly evaluate the micro-perfusion of the bowel wall. Intraoperative indocyanine green fluorescence angiography (ICG-FA) was proposed as more objective alternative which also accurately evaluates the micro-perfusion [31, 32]. Recently published studies demonstrated very promising results for this technique, since AL rate was reduced when ICG-FA was used [33, 34]. The results are encouraging, but as with isolated mechanical integrity testing, the isolated blood supply testing does not prevent all postoperative AL.

Therefore, a significant proportion of the patients with high-risk pelvic anastomoses receive a proximal diversion to prevent AL or to reduce the consequences of AL damage. Nevertheless, preventive ileostomy has stoma-related complications, such as dehydration, peristomal skin irritation, parastomal hernia, stoma caused obstruction, high output stoma, which cause readmission [35–38]. Moreover, ileostomy requires additional operation with high postoperative morbidity rate reported up to 27.9% of the patients [39].

This study was designed to identify safe colorectal anastomosis and to reduce the number of postoperative ileostomy rate after left-sided colorectal surgery.

3.2. Study hypothesis

Systematic colorectal anastomosis quality check predicts the risk of colorectal AL and reduces the rate of preventive ileostomy for low-risk patients.

3.3. The aim of the study

The goal of the study is to reduce the number of patients who have diverting ileostomy after left-sided colorectal resection by establishing objective selection criteria.

3.4. Tasks of the study

1. To determine the risk factors for anastomotic leakage and its impact on long-term survival in left-sided colorectal cancer surgery.
2. To evaluate short and long-term outcomes of elderly patients undergoing left-sided colorectal resection with primary anastomosis for cancer.
3. To demonstrate the usefulness of intraoperative testing of colorectal anastomosis and present the incidence of anastomotic leak.
4. To compare mechanical integrity tests – air-leak test and methylene blue leak test – in experimental study.
5. To standardise the testing of colorectal anastomosis in prospective cohort study.
6. To propose an alternative method to avoid a preventive ileostomy in high-risk patients after left-sided colorectal surgery.

3.5. The novelty of the study

This is the first feasibility study, which so comprehensively tests colorectal anastomosis.

4. METHODS

4.1. Ethics

The study was approved by Vilnius Regional Bioethics Committee (Approval number 2019/3-116-608) and conducted according to the Declaration of Helsinki of 1964, as revised in later versions.

4.2. Retrospective study

All patients who underwent left-sided colorectal resection with a primary anastomosis below 15 cm from anal verge between January 2014 and December 2018 at two major gastrointestinal cancer treatment centres in Lithuania – Vilnius University Hospital Santaros Klinikos and National Cancer Institute – were screened for eligibility. Patients who underwent emergency surgery or those with a benign pathology were excluded. Finally, all patients who underwent elective colorectal resection with primary anastomosis for left-sided CRC were included in the study [40].

Task 1 of the study: to determine the risk factors for anastomotic leakage and its impact on long-term survival in left-sided colorectal cancer surgery.

4.2.1. Risk factors for AL in sigmoid and rectal surgery

Patients were divided into sigmoid and rectal surgery sub-groups based on a tumour location. The AL rate was calculated.

AL was defined as a defect at the anastomotic area with a communication between the intra- and extra-luminal compartments. AL was confirmed by digital rectal examination, endoscopic evaluation, or radiologic tests with proven extravasation of rectal contrast or evidence of a peri-anastomotic fluid collection with pus or feculent aspirate [12].

Patients were grouped to those who developed AL and those who did not develop AL. All potential risk factors were included in univariate and multivariable logistic regression analyses to identify independent variables associated with AL.

4.2.2. AL impact on short- and long-term survival

30-day and 90-day mortality rate was analysed in patients with and without AL. It was defined as short-term survival.

Moreover, overall survival (OS) and disease-free survival (DFS) in patients with or without AL was analysed in sigmoid and rectal surgery sub-groups.

OS was defined as the time from surgery to death. DFS was defined as the time from surgery to disease progression including local or distant recurrence.

Task 2 of the study: to evaluate short and long-term outcomes of elderly patients undergoing left-sided colorectal resection with primary anastomosis for cancer.

4.2.3. Short and long-term outcomes of elderly patients

Patients were divided into non-elderly (NE; ≤75 years) and elderly groups (E; > 75 years) according to the age at the time of surgery. The AL rate in NE and E patients, overall postoperative morbidity rate, in-hospital, 30-day, and 90-day mortality rates, the rate of minimally invasive surgery (MIS), OS and DFS rates were evaluated in NE and E patients [41].

Task 3 of the study: to demonstrate the usefulness of intraoperative testing of colorectal anastomosis and present the incidence of anastomotic leak.

4.3. Meta-analysis of intraoperative testing

A meta-analysis was performed of the studies that compared the use of intraoperative tests evaluating the integrity and the perfusion of the anastomosis with the standard care for the assessment of AL following lower gastrointestinal resection.

The search was restricted to human studies published in the English language only without a time limitation. Patients of any age undergoing colon or rectal resection with anastomosis were included, regardless of the operative approach, resection technique, urgency of surgery, and surgical indications.

An outcome measure was the rate of postoperative AL in the control group (no intraoperative testing of anastomosis) versus the rate of postoperative AL in the experimental group (with intraoperative mechanical integrity or perfusion testing) [42].

Task 4 of the study: to compare mechanical integrity tests – air-leak test and methylene blue leak test – in experimental study.

4.4. Experimental study

The aim of the study was to compare the methylene blue and the air-leak test in the experimental setting of single-stapled and double-stapled porcine bowels.

Twenty-four distal colons were excised from slaughtered pigs without delay. The proximal bowel end was closed with a linear stapler using blue cartridges (ECHELON FLEX GST, Ethicon, 60 mm blue reload with gripping surface technology, closed –1.5 mm, open –3.6 mm, 60 mm staple line). Each bowel was compressed for 15 s using the stapler.

The bowels were randomly divided into single-stapled or double-stapled groups. The proximal end was closed with a single cartridge or with two cartridges, depending on the group. Therefore, single-stapled bowels and double-stapled bowels were created. The flowchart of the study is presented in Figure 1.

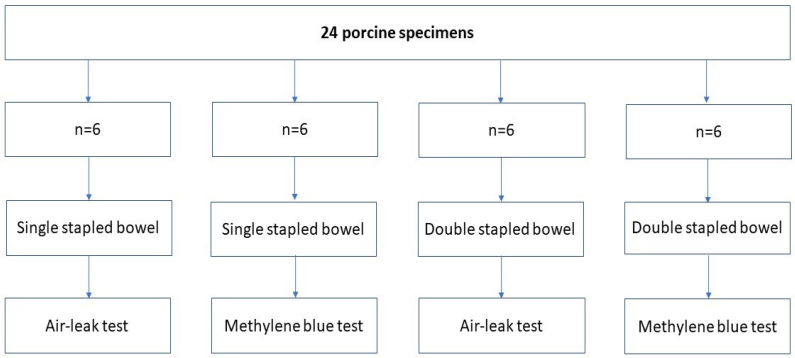

Figure 1. Experimental study flowchart

After that, air-leak and methylene blue leak tests were performed. The experimental model described by Schwab et al. for bursting strength measurement was used [43]. A digital pressure monitor with a gradual pressure increase function (BioTek® Instruments, Inc.) was used to both gradually increase pressure within the bowel and to determine the pressure at which the stapler line disintegrated.

A Foley catheter was introduced intraluminally from the distal end. After that, the distal end was occluded around the catheter to prevent the escape of air or methylene blue solution. The bowels were submerged in water to identify leaks. The Foley catheter was connected to the water-tight container.

A 0.9% sodium chloride solution, dyed with methylene blue, was used to test the bursting strength of half of the stapled bowels in the experiment. A watertight container filled with air was used for the other half of the stapled bowels in the experiment. The water-tight container was attached to the digital pressure monitor with the gradual pressure increase function. The pressure within the container was increased gradually by 4 mL with each stroke of airflow until leakage of air or of methylene blue dye was noted. The pressure at which the leak occurred was recorded [44].

Task 5 of the study: to standardise the testing of colorectal anastomosis in prospective cohort study.

4.5. Prospective study

4.5.1. Design

Multi-centre prospective cohort pilot study was conducted at two major colorectal surgery centres in Lithuania: Vilnius University hospital Santaros Klinikos and National Cancer Institute during the 2019–2020 period. The detailed study protocol was previously published [45].

4.5.2. Patients

Patients undergoing elective open or laparoscopic surgery for benign or malignant diseases of left-sided colon or rectum with the primary colorectal anastomosis below 15 cm from the anal verge by the rigid proctoscope were considered eligible in this study. All patients were over 18 years, willing to participate, and have signed the informed consent. The following exclusion criteria were as follows: (1) emergency surgery, (2) pregnancy, (3) allergy to indocyanine green dye, and (4) hand-sewn colorectal anastomosis.

4.5.3. Study outcomes

The primary outcome of the study was the AL during 60 days postoperatively. The secondary outcomes included the frequency of changed location of bowel resection after ICG testing; ileostomy rate; the rate of intraoperative AL; time, taken to perform trimodal anastomosis testing; post-operative morbidity and mortality; stoma rate after 1-year.

4.5.4. Intraoperative trimodal testing

Laparoscopic or open colorectal resection was performed according to standard techniques of the study institutions. The bowel was transected with green cartridges. Systolic blood pressure was > 100 mmHg during anastomosis formation. Trimodal anastomosis testing for blood supply, tension, and mechanical integrity was performed for all patients. Two doses of ICG dye were used and the perfusion of the bowel and newly formed anastomosis were evaluated. The main important time-points of intraoperative trimodal testing were as follows:

1. **Perfusion test before proximal bowel transection**

The first ICG dose was administered intravenously after the division of the mesentery just before bowel resection to evaluate blood supply at the planned point of resection. In case of insufficient blood perfusion at the planned point, the resection margin was changed to the area of good blood perfusion.

2. **Perfusion test before anastomosis formation**

The second ICG dose was injected just before anastomosis creation. The proximal and distal parts of the bowel were evaluated, and anastomosis was created.

3. **Trans-abdominal and trans-anal perfusion test after anastomosis formation**

Immediately after the formation of the anastomosis, the bowel perfusion was checked once again. The evaluation was not available in ultra-low colorectal anastomoses. When trans-abdominal perfusion evaluation was finished, trans-anal ICG testing was performed via proctoscope as described previously by our group [46]. The mucosa perfusion of the newly created anastomosis with proximal and distal bowel parts was checked by fluorescence circumferentially with camera via the proctoscope.

4. **Tension testing**

Tension on the anastomosis was tested visually. The aim was to create a floppy anastomosis where the proximal end of the bowel was freely falling into the pelvis. The straight anastomosis was considered in cases where the bowel was straight to the anastomosis but without obvious tension. Anastomosis under tension was corrected.

5. **Air-leak test**

A standard air-leak test was performed through a proctoscope at the same time as trans-anal perfusion testing. The anastomosis was placed under saline solution in the pelvic cavity during laparoscopy or laparotomy. The proximal colon was occluded by placing a soft bowel clamp across the bowel (without mesentery) in a comfortable distance above colorectal anastomosis. In the case

of a positive air-leak test, the leaking part of anastomosis was reinforced if it was identifiable and technically possible. Diverting ileostomy was created based on the surgeon's preference.

6. **Methylene blue leak test**

Methylene blue leak test was performed following the negative air-leak test. A 16 French Foley catheter was inserted into the anus and the balloon of the catheter was inflated up to 20–40ml, avoiding the stretching of the anastomosis. The catheter was gently withdrawn to the internal anal sphincter to avoid the spilling of the staining solution. The volume of injected staining solution depended on the height of colorectal anastomosis – the more anastomosis was distal to the anal verge; the less solution was injected. This step was performed under direct laparoscopic (or open) vision to avoid stretching of the anastomosis. In cases when low colorectal anastomosis was not visualized transabdominally, white gauze was introduced and positioned around anastomosis before dye injection. In case of a positive methylene blue leak test, the leaking part of the anastomosis was reinforced if it was technically possible. Diverting ileostomy was created based on the surgeon's preference [47].

Task 6 of the study: to propose an alternative method to avoid a preventive ileostomy in high-risk patients after left-sided colorectal surgery.

4.6. Bowel rest with total parenteral nutrition

Consecutive patients undergoing elective left-sided colorectal resection with high-risk primary anastomosis (anastomosis ≤ 10 cm from the anal verge and/or presence of severe, life-threatening comorbidity) who agreed to participate were included. The central venous line was placed during anaesthesia, and patients underwent bowel rest with total parenteral nutrition (TPN) for the first seven postoperative days.

TPN consisted of 1477 mL SmofKabiven, 10 mL of Addaven, 10 mL of Soluvit N, and 10 mL of Vitalipid N. The infusion starting speed was 30 mL/hour on the first postoperative day, 45 mL/hour on the second, and 62 mL/hour on the third until the seventh postoperative day.

Complete blood count, C-reactive protein, and electrolyte concentrations were monitored daily. After TPN, on the eighth postoperative day, patients were allowed to drink and eat liquid food.

The primary outcome of the study was the AL rate. Secondary outcomes included postoperative morbidity rate and tolerance of TPN. Postoperative complications were graded by the Clavien–Dindo classification [48].

5. RESULTS

5.1. Retrospective study

Task 1 of the study: to determine the risk factors for anastomotic leakage and its impact on long-term survival in left-sided colorectal cancer surgery.

5.1.1. Risk factors for AL in sigmoid and rectal surgery

5.1.1.1. Patients baseline characteristics

A total of 900 patients with a mean age of 65 ± 10 years were included in the study. The AL rate after sigmoid and rectal surgery was 5.1% (13 of 257) and 10.7% (69 of 643), respectively.

5.1.1.2. Risk factors for AL

According to the univariate analysis, higher ASA score (III–IV, $p = 0.002$) was associated with AL in patients undergoing sigmoid surgery, while male sex ($p = 0.002$), higher CCI score (> 5, $p = 0.004$), and advanced tumour stage (T3/T4, $p = 0.031$) was associated with AL in patients with rectal cancer.

Further, the multivariable analysis confirmed a higher ASA score (III–IV; OR = 10.539; $p = 0.007$) as an independent risk factor for AL after sigmoid surgery. The same analysis confirmed male sex (OR = 2.403, $p = 0.004$), higher CCI score (> 5, OR = 1.720, $p = 0.025$), and advanced tumour stage (T3/4, OR = 2.250; $p = 0.017$) as risk factors for AL after rectal surgery.

5.1.2. AL impact on short- and long-term survival

5.1.2.1. AL and 30- and 90-day mortality

The 30-day mortality rate was higher in patients with AL in the sigmoid (15.4% vs 0%, $p = 0.002$) and rectal (5.8% vs 1%, $p = 0.016$) surgery subgroups. Similarly, 90-day mortality rate remained higher in leaking patients (sigmoid 15.4% vs 1.6%, $p = 0.032$; rectal 8.7% vs 2.1%, $p = 0.008$).

5.1.2.2. AL and long-term outcomes

The median time of follow-up was 38 (Q1: 22; Q3: 53) months. The AL after sigmoid surgery impaired OS and DFS (Fig. 2a, b). Similarly, the AL impaired OS and DFS (Fig. 2c, d) after rectal surgery.

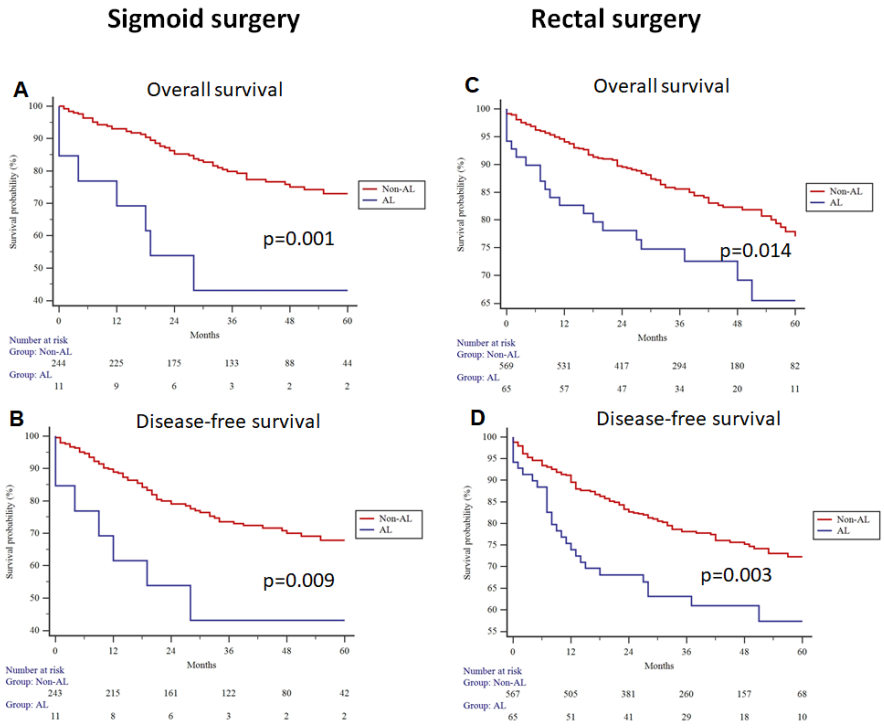

Figure 2. Overall and disease-free survival in sigmoid and rectal surgery

Further, AL was adjusted for the stage of the disease, gender, age, and comorbidities (CCI score) by COX regression analysis in the study cohort. After, the AL remained a significant factor for impaired OS (HR (95% CI) 1.53 (1.01–2.32), p = 0.041) and DFS (HR (95% CI) 1.51 (1.05–2.19), p = 0.026).

Task 2 of the study: to evaluate short and long-term outcomes of elderly patients undergoing left-sided colorectal resection with primary anastomosis for cancer.

5.1.3. Short and long-term outcomes of elderly patients

5.1.3.1. Patients baseline characteristics

A total of 900 patients were included in this study. Seven hundred thirty-eight (82%) patients were allocated to the NE group (≤75 years) and 162 (18%) patients were allocated to the E group (> 75 years). E patients had higher ASA and CCI scores, but a lower proportion of these was obese.

5.1.3.2. Intraoperative and postoperative outcomes

Lower proportion of E patients received MIS (52.7% vs 42.6%, p = 0.024). There was some tendency for a higher postoperative morbidity rate in the E (37.0%) group compared to NE (29.7%) group, however, the difference failed for significance (p = 0.066). Although, severe or lethal complications by Clavien-Dindo score III-V were more common in the E group (15.4% vs 9.8%, p = 0.040).

5.1.3.3. Anastomotic leakage in the study cohort

Eighty-two of 900 (9.1%) patients included in the study developed AL. Male gender, higher CCI score (> 5), advanced pT stage (pT3/T4), lower anastomoses, and open surgery were associated with AL in the univariate analysis.

The rate of AL was similar between NE (8.5%) and E (11.7%) groups, p = 0.201. Although, there was some tendency for increased 90-days mortality in E patients who developed AL, but without statistical significance (6.3% vs 21.1%, p = 0.079). Variables that showed significance in univariate analysis were included in subsequent multivariable analysis. Male gender (OR: 1.94; 95% CI: 1.15–3.29, p = 0.013), CCI score > 5 (OR: 1.90; 95% CI: 1.14–3.16, p = 0.013), and anastomoses at 6–12 cm from anal verge (OR: 2.29; 95% CI: 1.24–4.21, p = 0.008) were identified as a risk factor for AL.

5.1.3.4. Factors associated with postoperative morbidity in elderly patients

Since the E patients were at higher risk for postoperative morbidity and mortality, the univariate analysis was performed to identify the variables associated with postoperative complications in the subgroup of E patients. Open surgery was the only risk factor associated with postoperative complications in the univariate setting.

5.1.3.5. Survival

The median time to follow-up was 38 (Q1: 22; Q3: 53) months. OS and DFS was significantly lower in E patients (Figs. 3 and 4).

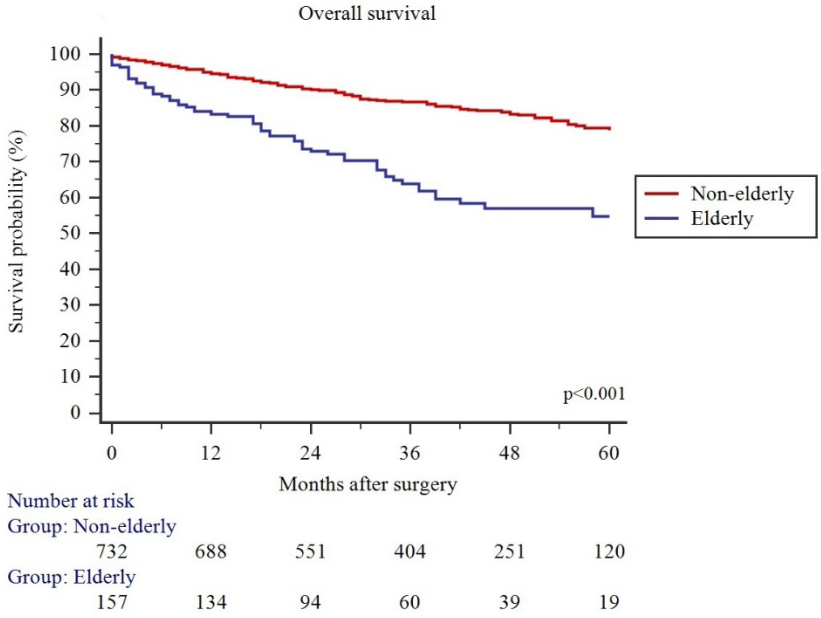

Figure 3. Overall survival in non-elderly and elderly patients who received colorectal resection with primary anastomosis for left-sided colorectal cancer

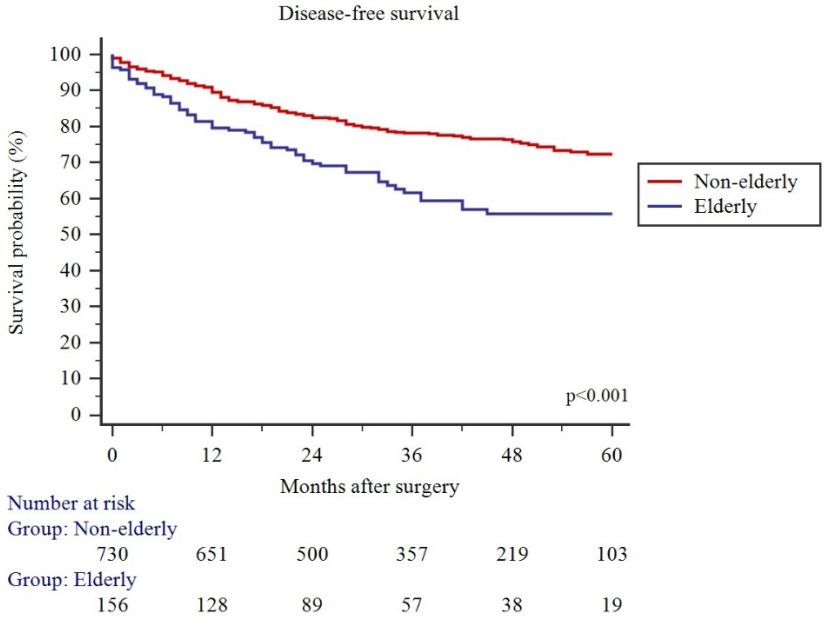

Figure 4. Disease-free survival in non-elderly and elderly patients who received colorectal resection with primary anastomosis for left-sided colorectal cancer

The multivariable Cox proportional hazards model was performed to identify the factors associated with OS and DFS in the E group. E patients who received MIS had higher probability for OS (HR: 0.47; 95% CI: (0.25–0.86), p = 0.015) and DFS (HR: 0.48; 95% CI: (0.27–0.86).

Task 3 of the study: to demonstrate the usefulness of intraoperative testing of colorectal anastomosis and present the incidence of anastomotic leak.

5.2. Meta-analysis of intraoperative testing

5.2.1. Intraoperative tests to evaluate the integrity

Twelve studies, involving 3787 patients, were included in the meta-analysis [28, 49–59]. Isolated air-leak test, intraoperative endoscopy with the air-leak test, and intraoperative endoscopy with both air-leak and blue-tinged saline tests were the methods of testing the integrity of anastomosis included in the study.

The pooled analysis with a total OR value – 0.52 (95% CI, 0.34–0.82) – revealed that intraoperative tests to evaluate the integrity of anastomosis (and anastomotic reinforcement, if applicable) were associated with a lower AL rate after lower gastrointestinal tract resection (Figure 5). The difference was statistically significant ($p < 0.001$), and there was no significant heterogeneity among the studies ($x^2=9.49$; degrees of freedom=11; P=.58; $I^2=0$).

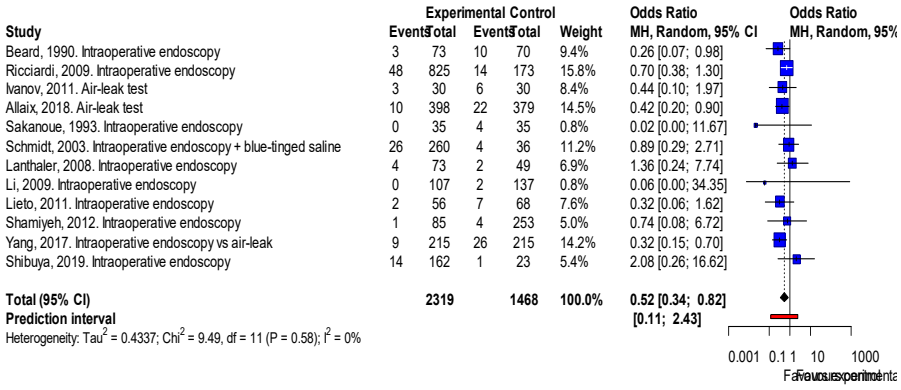

Figure 5. Forest plot showing odds ratios (OR) for AL following lower gastrointestinal surgery in experimental (intraoperative testing of anastomosis integrity and anastomosis reinforcement, if applicable) versus control (non-testing) group

5.2.2. Intraoperative tests to evaluate the perfusion

Eleven studies, involving 3328 patients, were included in the meta-analysis [31, 34, 60–68]. Included trials compared the rate of AL according to, whether intraoperative tests evaluating the perfusion of anastomosis (with anastomotic reinforcement or change in the resection margin, if applicable) were performed or not. The use of ICG-FA with or without an air-leak test and its impact on the rate of AL were investigated. In total, these studies included 1680 patients in the control and 1648 patients in the study group undergoing colorectal surgery.

Overall, the combined OR value was 0.40 (95% CI, 0.22–0.75), implying that the use of intraoperative ICG-FA was associated with a lower incidence of AL in the lower gastrointestinal tract anastomosis (Figure 6). The difference was statistically significant (P<.001). According to our set limits of considered heterogeneity, it could be described as low heterogeneity (x^2=13.53; degrees of freedom=10; P=.20; I^2=26).

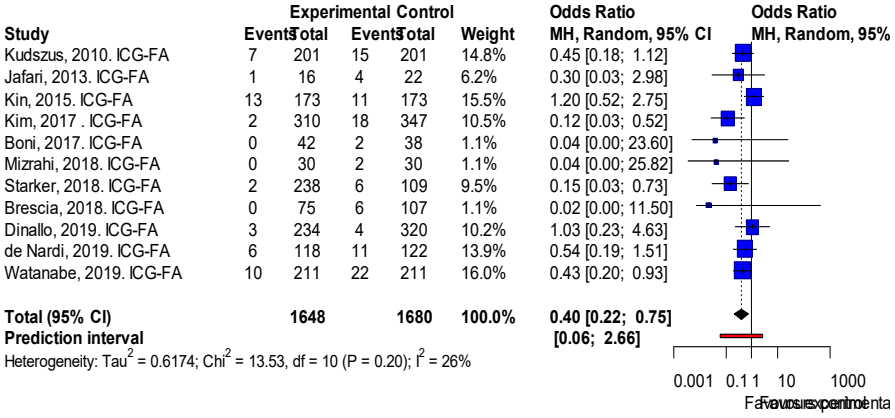

Figure 6. Forest plot showing odds ratios (OR) for AL following lower gastrointestinal surgery in experimental (intraoperative testing of anastomosis perfusion and anastomosis reinforcement or change in the resection margin, if applicable) versus control (non-testing) group

Task 4 of the study: to compare mechanical integrity tests – air-leak test and methylene blue leak test – in experimental study.

5.3. Experimental study

Thirty-six stapler cartridges were used to create 24 experiments: 12 in the single-stapled and 24 in the double-stapled groups. All 24 experiments were successful.

The differences between air-leak and methylene blue leak pressures are presented in Figure 7. The mean pressure in the air-leak test group was 51.62 ± 16.60 and 46.54 ± 16.78 in the methylene blue leak groups. The observed difference between the two methods in detecting stapled bowel leaks was not statistically significant (p = 0.312).

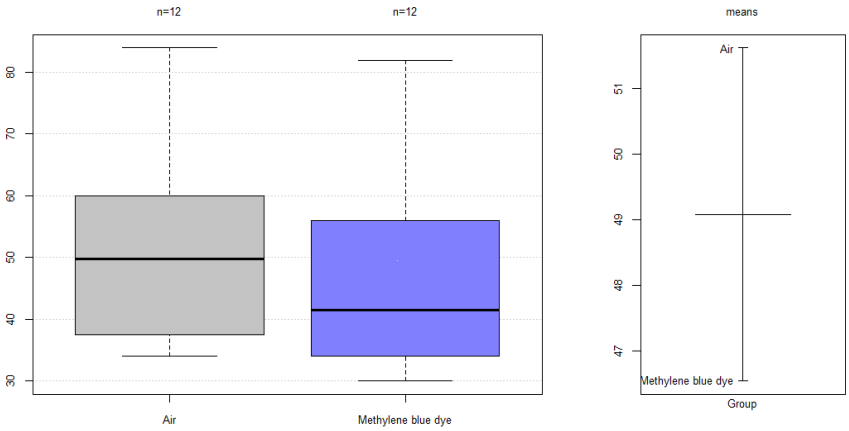

Figure 7. Box plots of bowel bursting pressure in air-leak and methylene blue leak test groups

The differences between air-leak and methylene blue leak pressures in single-stapled bowels are presented in Figure 8. The mean pressure in the air-leak test group was 48.58 ± 11.62 and 45.83 ± 17.13 in the methylene blue leak groups (p = 0.630).

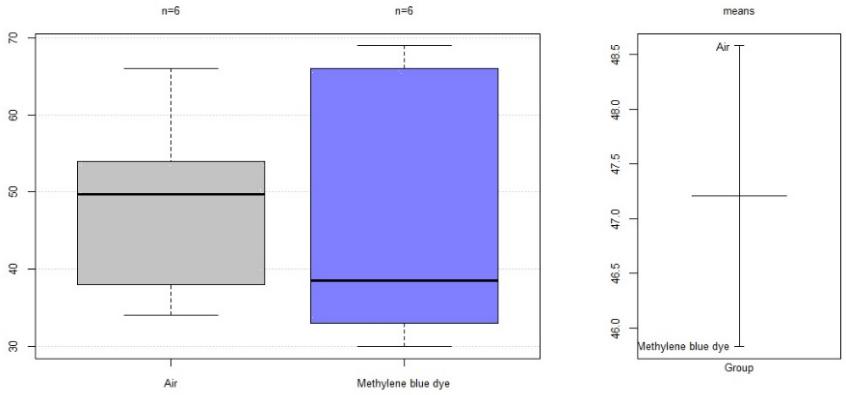

Figure 8. Box plots of air-leak and methylene blue pressure in single-stapled bowels

The differences between air-leak and methylene blue leak pressures in double-stapled bowels are presented in Figure 9. The mean pressure in the air-leak test group was 54.67 ± 21.19 and 47.25 ± 18.02 in the methylene blue leak groups (p = 0.575).

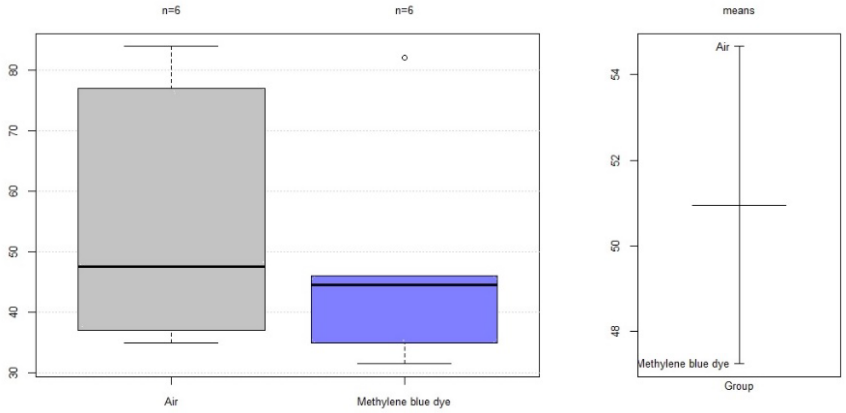

Figure 9. Box plots of air-leak and methylene blue leak pressure in double-stapled bowels

Overall, we found that the methylene blue leak test was not inferior to the air-leak test.

Task 5 of the study: to standardise the testing of colorectal anastomosis in prospective cohort study.

5.4. Prospective study

5.4.1. Baseline characteristics

A total of 60 patients with a median age of 64 years (Q1: 56.25; Q3: 76) were included in the study.

5.4.2. Trimodal testing of colorectal anastomoses

Trimodal anastomosis testing was feasible in all (100%) patients, and it identified 16 (26.7%) positive results. The median time for the trimodal testing was 8 min (Q1: 7; Q3: 9).

5.4.3. Blood supply by ICG-FA

Insufficient blood supply at the anticipated proximal bowel transection line by ICG-IF was detected in six (10.0%) patients. Transection point was changed in all these cases and the additionally resected segment varied between 1 and 8 cm. After these adjustments further ICG testing confirmed adequate vascularization at proximal and distal ends before and after anastomosis creation.

5.4.4. Tension testing by visual inspection

All anastomoses were confirmed as floppy, except one (1.7%), which was considered straight, but acceptable. No additional changes were performed after tension testing.

5.4.5. Mechanical integrity of anastomoses by air-leak test and methylene blue leak test

All patients were checked with the intraoperative air-leak test. Air-leakage occurred in four (6.7%) patients. All these anastomoses were reinforced where possible and diverted. Fifty-six patients with the negative air-leak tests were checked with the methylene blue leak test. Additional eight (14.3%) leaking anastomoses were identified. All anastomoses were reinforced where possible and diverted, except one. Together air-leak test and methylene blue test identified 12 (20.0%) intraoperative leakages.

5.4.6. Primary outcome: AL during 60 days postoperatively

The overall AL rate during 60 days postoperatively was 16.7% (10 patients). Three (30.0%) of 10 patients with postoperative AL had at least one positive intraoperative test, and the preventive ileostomy was created for all these patients at the initial operation. None of them developed grade C AL. Seven (70.0%) of 10 patients with postoperative AL had all negative tests at trimodal testing. Three of them developed grade C AL. One of them was readmitted due to late (day 18) grade C AL. Therefore, the reoperations were performed, and ileostomies were created.

5.4.7. Ileostomy creation

Preventive ileostomy was constructed in 33 patients (55.0%). Fourteen out of 16 patients (87.5%) with positive trimodal testing underwent preventive ileostomy compared to 19 out of 44 patients (43.2%) with negative trimodal testing (Fig. 10).

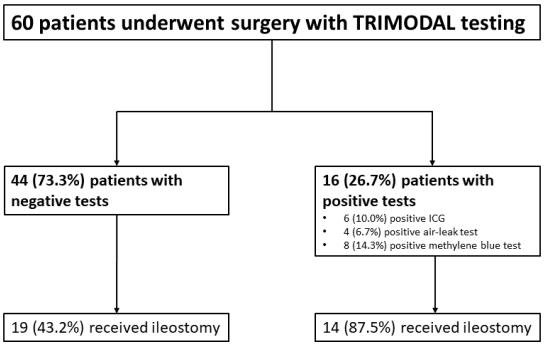

Figure 10. Flowchart of trimodal testing and ileostomy formation

5.4.8. Short-term morbidity and readmissions

The 30-day morbidity rate was 38.3% (23 patients). Mild complications (Clavien–Dindo I-IIIa) occurred in 15 patients (25.0%) and severe complications (Clavien–Dindo ≥ 3b) in 8 patients (13.3%). The reoperation rate was 8.3% for non-anastomotic complications. The median hospitalization time was 8 (Q1: 7.0; Q3: 11) days. There were no 30-day postoperative deaths. The 30-day readmission rate was 5.0%.

5.4.9. 1-year outcomes

Three patients died over the one-year period, with over-all 1-year mortality rate of 5.0%. One (1.7%) patient died because of suicide 2 months after surgery, one (1.7%) patient died because of cardiopulmonary failure during chemotherapy 3 months after surgery, and one (1.7%) patient died 10 months after surgery because of progressing Alzheimer's disease. Twenty-nine (87.9%) out of 33 patients had their ileostomy reversed during 1-year follow-up period. Two (6.0%) patients did not receive ileostomy closure because they died, one (3.0%) patient did not undergo ileostomy closure because of stricture of colorectal anastomosis and unsuccessful management with endoscopic balloon dilatation and one (3.0%) patient due to progression of the disease. All patients with diverted ileostomies after grade C AL were managed and closed.

5.4.10. Comparison of patients with positive and negative intraoperative trimodal testing

Based on trimodal testing results patients were grouped to positive (n = 16) and negative (n = 44) trimodal testing groups. Significantly higher proportion of patients in positive testing group received splenic flexure mobilization (75.0% vs 38.6%, p = 0.019), reinforcement of the anastomosis (31.2% vs 6.8%, p = 0.026), drain placement (100% vs 75.0%, p = 0.027), and preventive ileostomy (87.5% vs 43.2%, p = 0.003).

Task 6 of the study: to propose an alternative method to avoid a preventive ileostomy in high-risk patients after left-sided colorectal surgery.

5.5. Bowel rest with total parenteral nutrition

Six patients were included in the study. Patient details are described in Table 1. There was no clinical postoperative AL detected. Two patients had elevated C-reactive protein during the parenteral nutrition period. Chest, abdomen, and pelvic computed tomography scans with enteric contrast were performed, and AL was ruled out. These two patients developed grade II Clavien–Dindo complications: One patient developed postoperative fever, with negative blood and urine cultures, and the other developed wound seroma requiring drainage. Intravenous antibiotics were prescribed, and inflammatory markers normalised. All other four patients had an uneventful postoperative course. All six patients did not have any complications associated with TPN.

Table 1. Detailed patients, surgery and outcomes characteristics

Patient	Age	ASA	Gender (M/F)	BMI	Risk factors	Indication for surgery	Surgery (open/laparoscopic)	Indications for ileostomy	Highest CRP (mg/l)	Postoperative complications
1	55	II	F	25.6	Carcinoma of the fallopian tube	Carcinoma penetrating the rectal wall	Open	Low anastomosis (8 cm from anal verge) Positive methylene blue test	56.6	None
2	55	III	F	43.5	Morbid obesity	Carcinoma of the sigmoid colon	Laparoscopic converted to open	Low anastomosis (10 cm from anal verge) Obesity	219.8	Postoperative wound seroma
3	61	III	F	23.1	Acute renal failure Hypokalaemia Hyponatraemia Sepsis	Adenoma of the sigmoid colon (McKittrick–Wheelock syndrome)	Laparoscopic	Renal failure	181.9	Postoperative fever (second postoperative day)
4	77	III	F	33.2	Disseminated carcinoma of the uterus	Uterine carcinoma penetrating the rectal wall	Open	Low anastomosis (5 cm from anal verge)	71.7	None

5	50	IIIE	M	40.9	Chronic renal failure Haemodialysis Morbid obesity	Rectal carcinoma	Laparoscopic	Low anastomosis (7 cm from anal verge) Obesity Renal failure	43.3	None
6	43	II	M	22.6	Neoadjuvant chemoradiation	Rectal carcinoma	Laparoscopic	Low anastomosis (2 cm from anal verge)	21.3	None

M/F: Male/Female; BMI: Body mass index; CRP: C-reactive protein.

MAIN FINDINGS AND CONCLUSIONS

Task 1 of the study: to determine the risk factors for anastomotic leakage and its impact on long-term survival in left-sided colorectal cancer surgery.

- ASA score of III–IV is an independent risk factor for AL after sigmoid surgery, and male sex, higher CCI score, and advanced tumour stage are among risk factors for AL after rectal surgery.
- AL impairs the long-term survival in patients undergoing surgery for sigmoid and rectal cancer.

Task 2 of the study: to evaluate short and long-term outcomes of elderly patients undergoing left-sided colorectal resection with primary anastomosis for cancer.

- Short- and long-term outcomes of elderly patients who underwent resections with primary anastomosis for left-sided CRC are impaired.
- The risk of AL in the elderly and non-elderly patients is similar, but leakages in the elderly seem to be associated with a higher 90-day mortality rate.
- Minimally invasive surgery is associated with decreased morbidity in the elderly and better long-term outcomes.

Task 3 of the study: to demonstrate the usefulness of intraoperative testing of colorectal anastomosis and present the incidence of anastomotic leak.

- Intraoperative testing of both the integrity and the perfusion of anastomosis may reduce the rate of AL following lower gastrointestinal tract resections.

Task 4 of the study: to compare mechanical integrity tests – air-leak test and methylene blue leak test – in experimental study.

- The methylene blue solution leak test is not inferior to the air leak test in detecting leaks, even showing a tendency towards lower pressure; therefore, both methods are comparable.

Task 5 of the study: to standardise the testing of colorectal anastomosis in prospective cohort study.

- Comprehensive testing identifies anastomoses with initial technical failure where reinforcement of anastomosis or diversion can lead to an acceptable rate of AL.
- Identification of well-performed anastomosis could allow to a reduction of ileostomy rate by two-fold.
- However, the AL rate remains high in technically well-performed anastomoses.

Task 6 of the study: to propose an alternative method to avoid a preventive ileostomy in high-risk patients after left-sided colorectal surgery.

- Bowel rest with total parenteral nutrition may be a feasible option in high-risk left-sided colorectal anastomosis and a possible alternative to a preventive loop ileostomy.
- Further studies are necessary to evaluate it on a larger scale.

SANTRAUKA

Preambulė

Daktaro disertacijos tezės pateikiamos ginti kaip mokslinių straipsnių rinkinys, o kai kurios dalys pažodžiui cituojamos iš anksčiau publikuotų straipsnių, išvardytų knygos pabaigoje.

Disertaciją sudaro kelios dalys, kurios visos yra susijusios.

Pirmiausia atlikome retrospektyvią analizę, skirtą nustatyti rizikos veiksnius ir anastomozės nesandarumo dažnį bei ilgalaikius rezultatus. Be to, AN dažnis ir rezultatai buvo lyginami tarp vyresnio ir jaunesnio amžiaus pacientų, sergančių kairės pusės gaubtinės ir tiesiosios žarnos vėžiu, kuriems buvo atlikta rezekcija su pirmine anastomoze. Po to buvo atlikta meta-analizė, skirta išanalizuoti įvairių intraoperacinių mechaninio vientisumo ir žarnyno perfuzijos tyrimų įtaką. Taip pat, mes sukūrėme eksperimentinį tyrimą, skirtą mechaninio vientisumo bandymams, ir palyginome vandens-oro ir metileno mėlynojo sandarumo bandymus. Paraleliai buvo atliktas perspektyvinis tyrimas pacientams, kuriems atliekama kairės pusės kolorektinė operacija su pirmine anastomoze. Žarnyno kraujo perfuzija, tempimas ir mechaninis vientisumas buvo tikrinami įvairiais metodais, kurie padėjo mums nustatyti didelės rizikos gaubtinės ir tiesiosios žarnos anastomozę. Daugumai šių pacientų buvo suformuota prevencinė ileostoma. Tyrimų eigoje kilo nauja idėja, kaip pakeisti ileostomos suformavimą didelės rizikos jungtyse. Visiška parenterinė mityba buvo pasiūlyta kaip alternatyva profilaktinės ileostomos suformavimui.

Literatūros apžvalga

Kolorektalinis vėžys yra trečias dažniausiai diagnozuojamas piktybinis navikas ir ketvirta pagrindinė su vėžiu susijusių mirčių priežastis pasaulyje [1, 2]. Gydymas yra daugiarūšis, įskaitant chemoterapiją, radioterapiją ir chirurgiją [3–7]. Daugeliu atvejų radikali operacija išlieka pagrindiniu gydymo metodu [8, 9].

Anastomozės nesandarumas (AN) yra pavojingiausia kolorektinės chirurgijos komplikacija [10]. AN dažnis po gaubtinės ir tiesiosios žarnos operacijos labai skiriasi ir gali siekti 25 % didelės rizikos jungčių atveju [11]. AN apibrėžiamas kaip „žarnyno sienelės defektas jungties vietoje, dėl kurio atsiranda ryšys tarp vidinės ir išorinės dalies“, kuris pagrįstas klinikiniais simptomais ir yra įrodytas endoskopiniu ar radiologiniu tyrimu, arba pakartotine operacija [12]. AN turi neigiamos įtakos onkologinio gydymo ir

funkciniams rezultatams, prailgina paciento hospitalizacijos laiką ir padidina sveikatos priežiūros išlaidas. Be to, AN gali būti gyvybei pavojinga komplikacija [13–15].

AN etiologija vis dar nėra visiškai aiški, nors literatūroje yra aptariami rizikos veiksniai, susiję su pacientu ir liga, taip pat chirurginės technikos nesėkmė [16, 17]. Vyriška lytis, vyresnis amžius, nutukimas, sunkios gretutinės ligos (aukštesnis Amerikos anesteziologijos draugijos (ASA) balas), ilgesnė operacijos trukmė, perioperacinės kraujo transfuzijos, žema anastomozė ir neoadjuvantinė chemoradioterapija yra siūlomi AN rizikos veiksniai [18, 19]. Nepaisant to, AN gali pasireikšti ir pacientams, neturintiems jokių rizikos veiksnių, todėl AN išlieka sudėtinga kolorektinės chirurgijos problema. Nepakankama kraujotaka privedamajame ar nuvedamajame jungties galuose, suformuotos jungties tempimas ir nepakankamas anastomozės vientisumas yra pagrindinės techninės priežastys, kurios gali būti ištaisytos operacijos metu, jeigu yra nustatomos [20, 21].

Įvairūs bandymai buvo pasiūlyti anastomozės mechaniniam vientisumui ištirti. Dažniausiai taikomas kolorektalinės anastomozės tyrimas yra vandens-oro sandarumo testas [22]. Kai kurie tyrimai rodo, kad fiziologinio tirpalo arba metileno mėlynojo sandarumo bandymai atliekami atskirai arba kartu su vandens-oro sandarumo testu [23, 24]. Tačiau šie skysčių tyrimai daug dažniau atliekami viršutinio virškinimo trakto jungtims patikrinti, o duomenų apie apatinio virškinamojo trakto jungtis literatūroje trūksta [25–27]. Dar vienas prieinamas mechaninio vientisumo tyrimo metodas yra intraoperacinė kolonoskopija [28–30]. Tempimo vertinimas neturi specifinio mato ir yra subjektyviai vertinamas chirurgo. Visi šie mechaninio vientisumo testai sumažina pooperacinio AN dažnį [23, 28, 29]. Tačiau lieka neaišku, ar kai kurie iš jų gali būti tikslesni už kitus ir kokius testus reikėtų naudoti. Be to, neigiami vientisumo tyrimo rezultatai negarantuoja sklandžios pooperacinės eigos.

Nepakankamas kraujo tiekimas yra dar vienas gerai žinomas veiksnys, turintis įtakos AN atsiradimui po operacijos. Žarnyno gyvybingumą ir kraujo tiekimą įvertina chirurgas. Žarnyno sienelės spalva, žarnyno peristaltika, kraštinės arterijos pulsavimas arba kraujavimas iš rezekuotos žarnos krašto laikomi klinikiniais geros vaskuliarizacijos rodikliais [20]. Tačiau tai labai subjektyvu ir ne visada tinkamai įvertinama žarnyno sienelės mikroperfuzija. Kaip alternatyva, galinti padėti tiksliau įvertinti mikroperfuziją, buvo pasiūlyta intraoperacinė indocianino žaliosios fluorescencijos angiografija (ICG-FA) [31, 32]. Neseniai paskelbti tyrimai parodė labai perspektyvius šios technikos rezultatus, nes naudojant ICG-FA sumažėjo pooperacinis AN dažnis [33, 34]. Rezultatai teikia vilčių, tačiau, kaip ir atliekant izoliuotą

mechaninio vientisumo tyrimą, izoliuotas kraujo tiekimo tyrimas neapsaugo nuo visų pooperacinių AN atvejų.

Todėl nemažai daliai pacientų, esant didelės rizikos kolorektinėms jungtims, yra suformuojama prevencinė ileostoma, kad būtų išvengta AN arba sumažintos AN pažeidimo pasekmės. Nepaisant to, prevencinė ileostoma turi su stoma susijusių komplikacijų, tokių kaip dehidratacija, peristominė odos dirginimas, parastominė išvarža, stomos sukelta obstrukcija, gausiai funkcionuojanti stoma, kurios sukelia pakartotiną hospitalizaciją [35–38]. Be to, ileostoma reikalauja papildomos operacijos, o pooperacinis sergamumas siekia net iki 27,9% [39].

Šis tyrimas buvo skirtas saugiai kolorektinei anastomozei nustatyti ir sumažinti pooperacinės ileostomos dažnį po kairės pusės storosios žarnos operacijos.

Tyrimo hipotezė

Sisteminis gaubtinės ir tiesiosios žarnos anastomozės kokybės patikrinimas prognozuoja kolorektalinės jungties anastomozės nesandarumo riziką ir sumažina profilaktinės ileostomos dažnį mažos rizikos pacientams.

Tyrimo tikslas

Nustačius objektyvius atrankos kriterijus, sumažinti pacientų skaičių, kuriems po tiesiosios žarnos rezekcijos buvo atlikta prevencinė ileostoma.

Tyrimo užduotys

1. Nustatyti anastomozės nesandarumo rizikos veiksnius ir jų įtaką ilgalaikiam išgyvenamumui atliekant kairės pusės kolorektines operacijas dėl storosios žarnos karcinomos.
2. Įvertinti trumpalaikes ir ilgalaikes baigtis vyresnio amžiaus pacientams, kuriems atliekama kairioji gaubtinės ir tiesiosios žarnos rezekcija su pirmine anastomoze dėl storosios žarnos karcinomos.
3. Įrodyti kolorektinės jungties intraoperacinio vertinimo naudą ir nustatyti anastomozės nesandarumo dažnį.
4. Palyginti mechaninio vientisumo bandymus eksperimentinio tyrimo metu – vandens-oro sandarumo testą ir metileno mėlynojo sandarumo testą.
5. Standartizuoti gaubtinės ir tiesiosios žarnos anastomozės patikrinimą perspektyviniame kohortiniame tyrime.

6. Pasiūlyti alternatyvų metodą, kuris padėtų išvengti prevencinės ileostomos didelės rizikos pacientams po kairės pusės storosios žarnos operacijos.

Tyrimo naujumas

Tai pirmasis galimybių tyrimas, kuriame taip išsamiai tikrinama gaubtinės ir tiesiosios žarnos anastomozė.

Išvados

Pirmas tyrimo uždavinys: nustatyti anastomozės nesandarumo rizikos veiksnius ir jų įtaką ilgalaikiam išgyvenamumui atliekant kairės pusės kolorektines operacijas dėl storosios žarnos karcinomos.

- ASA III–IV balas yra nepriklausomas AN rizikos veiksnys po riestinės žarnos operacijos, o vyriška lytis, didesnis *Charlson comorbidity index* balas ir pažengusi naviko stadija yra AN rizikos veiksniai po tiesiosios žarnos operacijų.
- AN mažina ilgalaikį pacientų išgyvenamumą, kuriems atliekamos operacijos dėl riestinės ir tiesiosios žarnos vėžio.

Antras tyrimo uždavinys: įvertinti trumpalaikes ir ilgalaikes baigtis vyresnio amžiaus pacientams, kuriems atliekama kairioji gaubtinės ir tiesiosios žarnos rezekcija su pirmine anastomoze dėl storosios žarnos karcinomos.

- Trumpalaikiai ir ilgalaikiai rezultatai vyresnio amžiaus pacientams yra blogesni, kuriems buvo atlikta rezekcija su pirmine anastomoze dėl kairės pusės karcinomos.
- AN rizika tarp vyresnių ir jaunesnių pacientų yra panaši, tačiau vyresnio amžiaus pacientams yra susijęs su didesniu 90 dienų mirtingumu.
- Minimaliai invazinė chirurgija yra susijusi su sumažėjusiu vyresnio amžiaus pacientų sergamumu ir geresniais ilgalaikiais rezultatais.

Trečias darbo uždavinys: įrodyti kolorektinės jungties intraoperacinio vertinimo naudą ir nustatyti anastomozės nesandarumo dažnį.

- Intraoperacinis anastomozės vientisumo ir perfuzijos tyrimas gali sumažinti AN dažnį po kolorektinės jungties suformavimo.

Ketvirtas darbo uždavinys: palyginti mechaninio vientisumo bandymus eksperimentinio tyrimo metu – vandens-oro sandarumo testą ir metileno mėlynojo sandarumo testą.

- Metileno mėlynojo mechaninio tikrinimo testas nėra prastesnis už vandens-oro testą nustatant sandarumą, netgi rodo tendenciją mažesniam slėgiui, todėl abu metodai yra palyginami.

Penktas tyrimo uždavinys: standartizuoti gaubtinės ir tiesiosios žarnos anastomozės patikrinimą perspektyviniame kohortiniame tyrime.

- Detalus anastomozės tikrinimas identifikuoja jungtis su techninėmis nesėkmėmis.
- Nustačius gerai atliktą anastomozę, prevencinės ileostomos dažnis gali sumažėti du kartus.
- AN dažnis išlieka didelis techniškai gerai suformuotose anastomozėse.

Šeštas tyrimo uždavinys: pasiūlyti alternatyvų metodą, kuris padėtų išvengti prevencinės ileostomos didelės rizikos pacientams po kairės pusės storosios žarnos operacijos.

- Žarnyno poilsis su visišku parenteriniu maitinimu gali būti tinkamas pasirinkimas esant didelės rizikos pacientui po kairės pusės kolorektinės operacijos ir galima alternatyva prevencinei ileostomai.
- Reikia atlikti tolimesnius tyrimus, siekiant įvertinti naudą platesniu mastu.

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7. **Kryzauskas M**, Jakubauskas M, Gendvilaite N, Rudaitis V, Poskus T. Bowel Rest with Total Parenteral Nutrition as an Alternative to Diverting Ileostomy in High-Risk Colorectal Anastomosis: A Pilot Study. *Medicina (Kaunas)*. 2022 Apr 2;58(4):510.

Oral presentations

1. Bowel rest with total parenteral nutrition as an alternative to diverting loop ileostomy in high-risk colorectal anastomosis: randomised

controlled non-inferiority trial. Imbrasaite U, Kryzauskas M, Jakubauskas M, Poskus T. European Society of Coloproctology (ESCP), 17th Scientific and Annual Meeting, Dublin, Ireland, 2022.

2. Early results from a prospective cohort study on comprehensive testing of colorectal anastomosis. Kryzauskas M, Poskus E, Bausys A, Dulskas A, Imbrasaite U, Bausys R, Danys D, Kuliavas J, Jotautas V, Stratilatovas E, Strupas K, Poskus T. Joint International Meeting: 22nd EAA Congress, 15th ISGA Congress, 5th International Conference of Evolutionary Medicine, Vilnius, Lithuania, 2022.
3. Simultaneous intraperitoneal and intraluminal ICG fluorescence testing for low colorectal anastomosis. Kryzauskas M, Poskus T, Jakubauskas M, Dulskas A, Poskus E. European Association for Endoscopic Surgery and other Interventional Techniques (EAES), 27th International EAES Congress, Seville, Spain, 2019.
4. Anastomotic leak after low anterior resection. Are all problems solved? Kryzauskas M, Poskus E, Poskus T, Kuliavas J. X Baltic and Belarusian Colorectal Surgeon Meeting, Kaunas, Lithuania, 2019.
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1. Comprehensive testing of colorectal anastomosis: initial results of prospective cohort study. Kryzauskas M, Poskus E, Bausys A, Dulskas A, Imbrasaite U, Bausys R, Danys D, Jotautas V, Stratilatovas E, Strupas K, Poskus T. European Society of Coloproctology (ESCP), 15th Scientific and Annual Meeting, Virtual Vilnius, September 2020.
2. Outcomes of left-sided colorectal surgery in elderly patients. Kryzauskas M, Bausys A, Bickaite K, Bausys B, Poskus E, Dulskas A, Kuliavas J, Bausys R, Strupas K, Poskus T. European Society of Coloproctology (ESCP), 15th Scientific and Annual Meeting, Virtual Vilnius, September 2020.

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Marius Kryzauskas, Augustinas Bausys, Austeja Elzbieta Degutyte, Vilius Abeciunas, Eligijus Poskus, Rimantas Bausys, Audrius Dulskas, Kestutis Strupas, Tomas Poskus

Risk factors for anastomotic leakage and its impact on long-term survival in left-sided colorectal cancer surgery

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Risk factors for anastomotic leakage and its impact on long-term survival in left-sided colorectal cancer surgery

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Abstract

Background: Anastomotic leakage (AL) significantly impairs short-term outcomes. The impact on the long-term outcomes remains unclear. This study aimed to identify the risk factors for AL and the impact on long-term survival in patients with left-sided colorectal cancer.

Methods: Nine-hundred patients with left-sided colorectal carcinoma who underwent sigmoid or rectal resection were enrolled in the study. Risk factors for AL after sigmoid or rectal resection were identified, and long-term outcomes of patients with and without AL were compared.

Results: AL rates following sigmoid and rectal resection were 5.1% and 10.7%, respectively. Higher ASA score (III–IV; OR = 10.54, $p = 0.007$) was associated with AL in patients undergoing sigmoid surgery on multivariable analysis. Male sex (OR = 2.40, $p = 0.004$), CCI score > 5 (OR = 1.72, $p = 0.025$), and T3/T4 stage tumors (OR = 2.25, $p = 0.017$) were risk factors for AL after rectal resection on multivariable analysis. AL impaired disease-free and overall survival in patients undergoing sigmoid ($p = 0.009$ and $p = 0.001$) and rectal ($p = 0.003$ and $p = 0.014$) surgery.

Conclusion: ASA score of III–IV is an independent risk factor for AL after sigmoid surgery, and male sex, higher CCI score, and advanced T stage are risk factors for AL after rectal surgery. AL impairs the long-term survival in patients undergoing left-sided colorectal surgery.

Keywords: Colorectal cancer, Anastomotic leakage, Risk factors, Oncological outcomes, Overall survival, Disease-free survival

Introduction

Anastomotic leakage (AL) is one of the most devastating complications following colorectal resection for left-sided colorectal cancer (CRC) [1]. It leads to increased morbidity, mortality, treatment costs, and prolonged hospitalization. The AL rate varies between 6 and 12% after rectal resection and between 2 and 4% after sigmoid resection [2]. Male sex, elderly age, obesity, severe comorbidities (higher American Society of Anesthesiology (ASA) score), prolonged surgery time, perioperative blood transfusions, low anastomosis, and neoadjuvant chemoradiotherapy are proposed risk factors for AL [3, 4]. AL may occur in patients without any risk factors as well, and therefore, it remains a challenging issue in CRC surgery.

While AL has a negative impact on short-term surgical outcomes, the impact on long-term outcomes remains controversial. The study led by Karim et al. concluded that AL impairs overall survival (OS) and disease-free survival (DFS) [5]. In contrast, Crippa et al. reported similar outcomes in patients with or without AL in

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terms of OS, DFS, and local recurrence rates [6]. Therefore, the present study aimed to determine the impact of AL on the long-term outcomes in patients undergoing surgery for left-sided CRC and to identify the risk factors for AL after sigmoid and rectal resection.

Materials and methods

Ethics

Vilnius regional research ethics committee approval (no. 2019/3-116-608) was obtained before the study. The study was conducted according to the Declaration of Helsinki.

Patients

All patients who underwent left-sided colorectal resection with a primary anastomosis below 15 cm from anal verge between January 2014 and December 2018 at two major gastrointestinal cancer treatment centers in Lithuania—Vilnius University Hospital Santaros Klinikos and National Cancer Institute—were screened for eligibility. Patients who underwent emergency surgery or those with a benign pathology were excluded. Finally, all patients who underwent elective colorectal resection with primary anastomosis for left-sided CRC were included in the study (Fig. 1).

Data collection

All participants' characteristics were obtained from the prospectively collected and maintained databases. They included age, gender, body mass index (BMI), American Society of Anesthesiologists (ASA) score, comorbidities, Charlson comorbidity index (CCI), history of neoadjuvant treatment, tumor localization, surgical approach (open surgery and minimally invasive surgery, laparoscopic surgery, hand-assisted laparoscopic surgery, natural orifice specimen extraction surgery, and transanal total mesorectal excision surgery (taTME)), the level of the anastomosis, diverting ileostomy, simultaneous operation, high or low ligation of the inferior mesenteric artery (IMA), results of the intraoperative air-leak test, postoperative complications including AL, and the data of follow-up including progression of the disease. Tumor stage was coded according to the TNM system as described in the Union Internationale Contre le Cancer/American Joint Committee on Cancer 8th edition.

Study outcomes

The primary outcome of the study was overall survival (OS) in patients with or without AL. The secondary outcomes included disease-free survival (DFS), 30-day mortality, and the risk factors for AL.

OS was defined as the time from surgery to death. Data on survival and date of death were collected from the National Lithuanian Cancer registry and the National Lithuanian death registry. Mortality registration rates, from both resources, were over 98%. DFS was defined as the time from surgery to disease progression including local or distant recurrence.

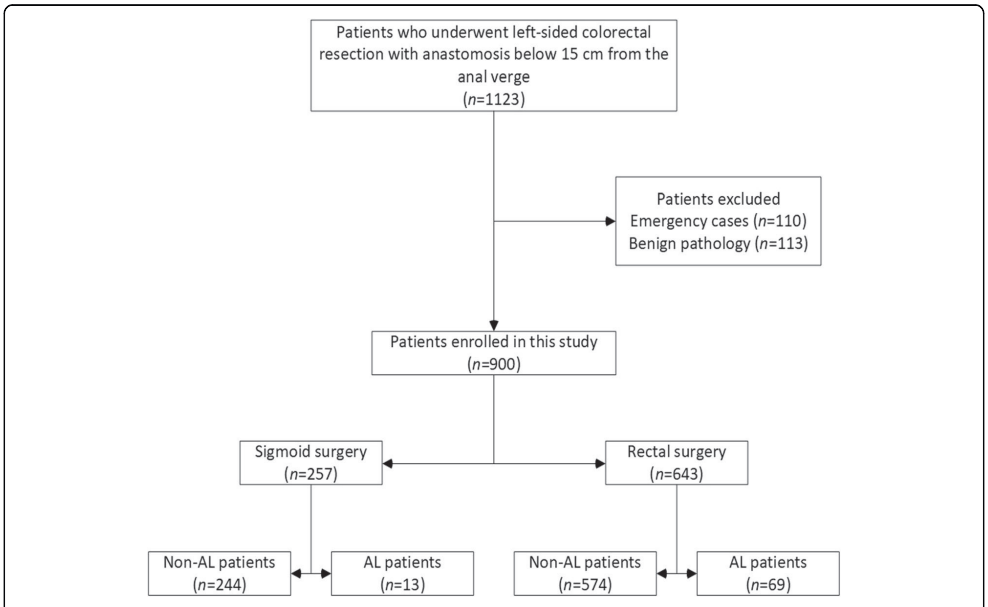

Fig. 1 Flowchart of the patients selection process

AL definition

AL was defined as a defect at the anastomotic area with a communication between the intra- and extra-luminal compartments. AL was confirmed by digital rectal examination, endoscopic evaluation, or radiologic tests with proven extravasation of rectal contrast or evidence of a peri-anastomotic fluid collection with pus or feculent aspirate [7].

Statistical analysis

All statistical analysis was performed by statistical package SPSS 25.0 (SPSS, Chicago, IL, USA). Patients were grouped to those who developed AL (AL) and those who did not develop AL (non-AL). All data were checked for normality. Continuous variables were compared by a two-tailed *t* test, one-way ANOVA, or non-parametric tests where appropriate and expressed as means ± standard deviation or median with first (Q1) and third (Q3) quartiles. Categorical data were expressed as proportions with percentages and compared by the chi-square test and Fisher exact test. To identify independent variables associated with anastomotic leakage, all potential risk factors were included in subsequent multivariable logistic regression analyses. Kaplan-Meier method was used for OS analysis, and survival curves were compared by the log-rank test. Multivariable survival analysis was performed using the Cox proportional hazards model (hazard ratio and 95% confidence intervals). A p value of < 0.05 was considered to be significant in all statistical analyses.

Results

Study participants

A total of 900 patients with a mean age of 65 ± 10 years were included in the study. For further analysis, patients were divided into sigmoid and rectal surgery sub-groups based on a tumor location. The AL rate after sigmoid and rectal surgery was 5.1% (13 of 257) and 10.7% (69 of 643), respectively. Baseline data of the patients are included in Table 1.

Risk factors for AL

Table 2 shows the univariate analysis of all potential risk factors for AL after sigmoid and rectal surgery. Higher ASA score (III–IV, p = 0.002) was associated with AL in patients undergoing sigmoid surgery, while male sex (p = 0.002), higher CCI score (> 5, p = 0.004), and advanced tumor stage (T3/T4, p = 0.031) was associated with AL in patients with rectal cancer.

Further, the multivariable analysis confirmed a higher ASA score (III–IV; OR = 10.539; p = 0.007) as an independent risk factor for AL after sigmoid surgery (Table 3). The same analysis confirmed male sex (OR = 2.403, p = 0.004), higher CCI score (> 5, OR = 1.720, p = 0.025), and advanced tumor stage (T3/4, OR = 2.250; p = 0.017) were among risk factors for AL after rectal surgery (Table 4).

AL and 30- and 90-day mortality

The 30-day mortality rate was higher in patients with AL in the sigmoid (15.4% vs 0%, p = 0.002) and rectal (5.8% vs 1%, p = 0.016) surgery sub-groups. Similarly, 90-day mortality rate remained higher in leaking patients (sigmoid 15.4% vs 1.6%, p = 0.032; rectal 8.7% vs 2.1%, p = 0.008).

AL and long-term outcomes

The median time of follow-up was 38 (Q1 22; Q3 53) months. The AL after sigmoid surgery impaired OS and DFS (Fig. 2a, b). Similarly, the AL impaired OS and DFS (Fig. 2c, d) after rectal surgery.

Further, AL was adjusted for the stage of the disease, gender, age, and comorbidities (CCI score) by COX regression analysis in the study cohort. After, the AL remained a significant factor for impaired OS (HR (95% CI) 1.53 (1.01–2.32), p = 0.041) and DFS (HR (95% CI) 1.51 (1.05–2.19), p = 0.026) (Table 5).

Discussion

Our study demonstrated that AL impairs long-term outcomes of the patients undergoing surgery for sigmoid and rectal cancer. Severe comorbidities, male sex, and advanced tumor stage are the risk factors for AL.

Several recent studies investigated the risk factors for AL because the identification of high-risk patients and avoidance of anastomosis in these patients could improve treatment outcomes [8–12]. Previously, studies demonstrated male gender as a risk factor for AL after rectal surgery, and our results were consistent with these findings [3, 8, 9, 13, 14]. Male gender is thought to increase the AL rate because of more technically demanding surgery in the narrow and deeper pelvis of men [13]. There is a possibility that hormonal functions may impact anastomotic healing as well [15, 16]. The advanced stage of tumor also makes surgery more technically challenging, and it was confirmed as another risk factor for AL by our study. Interestingly, we did not find a higher AL rate in patients receiving low anastomosis. These findings are conflicting with some previous reports indicating a higher risk for low anastomoses [3, 17]. Although, in our results, there was a strong tendency for higher AL rate in low anastomoses (≤ 5 cm (10.9%) vs 6–12 cm (13.6%) vs > 12 cm (5.8 %), p = 0.137), and it might be that our study was underpowered to detect significant differences because of the relatively small sample size.

Lower anastomoses may be secured by diverting ileostomy. However, the evidence on the impact of ileostomy on preventing the leak or reducing the symptoms is

Table 1 Basic characteristics of the sigmoid and rectal surgery groups

		Sigmoid surgery (n = 257)	Rectal surgery (n = 643)	p value
Age		65.4 ± 10.2	65.1 ± 10.9	0.172
BMI	< 30	152 (63.1%)	472 (77.6%)	0.001
	≥ 30	89 (36.9%)	136 (22.4%)	
Gender	Female	117 (45.5%)	300 (46.7%)	0.768
	Male	140 (54.5%)	343 (53.3%)	
ASA	I–II	160 (65.3%)	430 (70.1%)	0.167
	III–IV	85 (34.7%)	183 (29.9%)	
CCI	≤ 5	180 (70.0%)	470 (73.1%)	0.365
	> 5	77 (30.0%)	173 (26.9%)	
T stage	T0–T2	86 (33.5%)	215 (33.4%)	0.999
	T3–T4	171 (66.5%)	428 (66.6%)	
N stage	0	149 (59.4%)	392 (61.6%)	0.822
	1	72 (28.7%)	172 (27.0%)	
	2	30 (12.0%)	72 (11.3%)	
M stage	0	218 (84.8%)	592 (92.1%)	0.002
	1	39 (15.2%)	51 (7.9%)	
TNM stage	0	5 (1.9%)	7 (1.1%)	0.006
	1	66 (25.7%)	160 (24.9%)	
	2	71 (27.6%)	198 (30.8%)	
	3	75 (29.2%)	227 (35.3%)	
	4	40 (15.6%)	52 (7.9%)	
Approach of surgery	Open	78 (30.4%)	364 (56.6%)	0.001
	MI	179 (69.6%)	279 (43.4%)	
Postoperative complications	No	208 (80.9%)	413 (64.2%)	0.001
	Yes	49 (19.1%)	230 (35.8%)	
AL	No	244 (94.9%)	574 (89.3%)	0.007
	Yes	13 (5.1%)	69 (10.7%)	

ASA American Society of Anesthesiologists classification score, *CCI* Charlson comorbidity index score, *MI* minimally invasive, *AL* anastomotic leakage

conflicting. Two meta-analyses concluded that stoma reduces the rate of AL following low anterior resection [12, 18]. In contrast, our study did not confirm that ileostomy prevents AL. This finding is consistent with some previous studies [19, 20]. A temporary ileostomy may not prevent the AL but rather diminish its symptoms and consequences. Further, the true rate of AL in patients receiving ileostomy may be underestimated because usually asymptomatic patients do not undergo testing for anastomosis integrity at the early postoperative period [21, 22]. Similarly, in our study, asymptomatic patients underwent anastomosis integrity testing just before the ileostomy closure; thus, some cases of AL in patients who receive ileostomy might have been underestimated as well. Therefore, further studies are required to clarify the role of ileostomy in the prevention of the AL.

The existing data on AL impact on the long-term outcomes are conflicting as well. A recent study from the Mayo Clinic revealed similar OS, DFS, and local recurrence rates between patients with or without AL [6]. Propensity score-matched analysis by Sueda et al. also demonstrated a similar OS rate in AL and non-AL patients, except the higher rate of local recurrence in case of leakage [23]. In contrast, the previous meta-analysis by Bashir et al. concluded that patients with AL have a lower 5-year OS of 58% compared with 73% in non-leaking patients [24]. Moreover, the negative impact of AL on OS was indicated by Yang et al. and a large Scandinavian cohort study by Stormark et al. [25, 26]. Our study confirmed the impaired OS and DFS in patients suffering from AL, and there is a rationale for such findings. First, AL may lead to an increased rate of local recurrence because of cancer cell implantation and progression at the inflamed leaking anastomotic site [27, 28]. Despite AL occurs after surgical tumor removal, several viable tumor cells remain intraluminally,

Table 2 Univariate analysis of risk factors for postoperative AL in sigmoid and rectal surgery

		Sigmoid surgery			Rectal surgery		
		Non-AL (*n* = 244)	AL (*n* = 13)	*p* value	Non-AL (*n* = 574)	AL (*n* = 69)	*p* value
BMI	< 30	147 (96.7%)	5 (3.3%)	0.337	424 (89.8%)	48 (10.2%)	0.999
	≥ 30	83 (93.3%)	6 (6.7%)		122 (89.7%)	14 (10.3%)	
Gender	Female	111 (94.9%)	6 (5.1%)	0.999	280 (93.3%)	20 (6.7%)	0.002
	Male	133 (95.0%)	7 (5.0%)		294 (85.7%)	49 (14.3%)	
ASA	I–II	158 (98.8%)	2 (1.3%)	0.002	389 (90.5%)	41 (9.5%)	0.154
	III–IV	76 (89.4%)	9 (10.6%)		158 (86.3%)	25 (13.7%)	
CCI	≤ 5	172 (95.6%)	8 (4.4%)	0.538	430 (91.5%)	40 (8.5%)	0.004
	> 5	72 (93.5%)	5 (6.5%)		144 (83.2%)	29 (16.8%)	
Ischemic heart disease	Yes	13 (100%)	0 (0%)	0.999	26 (86.7%)	4 (13.3%)	0.551
	No	231 (94.7%)	13 (5.3%)		548 (89.4%)	65 (10.6%)	
Diabetes mellitus	Yes	28 (90.3%)	3 (9.7%)	0.197	54 (84.4%)	10 (15.6%)	0.200
	No	216 (95.6%)	10 (4.4%)		520 (89.8%)	59 (10.2%)	
History of CVD	Yes	8 (100%)	0 (0.0%)	0.999	17 (89.5%)	2 (10.5%)	0.999
	No	236 (94.8%)	13 (5.2%)		557 (89.3%)	67 (10.7%)	
Chronic renal failure	Yes	4 (100%)	0 (0.0%)	0.999	8 (88.9%)	1 (11.1%)	0.999
	No	240 (94.9%)	13 (5.1%)		566 (89.3%)	68 (10.7%)	
Neoadjuvant treatment	Yes	8 (88.9%)	1 (11.1%)	0.378	161 (88.0%)	22 (12.0%)	0.484
	No	236 (95.2%)	12 (4.8%)		413 (89.8%)	47 (10.2%)	
Approach of surgery	Open	71 (91.0%)	7 (9.0%)	0.069	320 (87.9%)	44 (12.1%)	0.247
	MI	173 (96.6%)	6 (3.4%)		254 (91.0%)	25 (9.0%)	
Anastomosis level from anal verge	≤ 5	20 (95.2%)	1 (4.8%)	0.999	155 (89.1%)	19 (10.9%)	0.137
	6–12				235 (86.4%)	37 (13.6%)	
	> 12	178 (93.7%)	12 (6.3%)		81 (94.2%)	5 (5.8%)	
Ileostomy	Yes	0 (0.0%)	1 (100%)	0.051	330 (88.5%)	43 (11.5%)	0.519
	No	244 (95.3%)	12 (4.7%)		244 (90.4%)	26 (9.6%)	
T stage	T0–T2	84 (97.7%)	2 (2.3%)	0.230	200 (93.0%)	15 (7%)	0.031
	T3–T4	160 (93.6%)	11 (6.4%)		374 (87.4%)	54 (12.6%)	
N stage	0	143 (96%)	6 (4.0%)	0.253	357 (91.1%)	35 (8.9%)	0.130
	1	70 (97.2%)	2 (2.8%)		149 (86.6%)	23 (13.4%)	
	2	27 (90.0%)	3 (10%)		61 (84.7%)	11 (15.3%)	
M stage	0	209 (95.9%)	9 (4.1%)	0.117	531 (89.7 %)	61 (10.3 %)	0.238
	1	35 (89.7%)	4 (10.3%)		43 (84.3 %)	8 (15.7 %)	
TNM stage	0	5 (100%)	0 (0.0%)	0.221	6 (85.7%)	1 (14.3%)	0.568
	1	64 (97.0%)	2 (3.0%)		147 (91.9%)	13 (8.1%)	
	2	68 (95.8%)	3 (4.2%)		178 (89.9%)	20 (10.1%)	
	3	72 (96.0%)	3 (4%)		200 (88.1%)	27 (11.9%)	
	4	35 (87.5%)	5 (12.5%)		43 (84.3%)	8 (15.7%)	
Ligation of IMA	High	189 (95.9%)	8 (4.1%)	0.165	442 (88.4%)	58 (11.6%)	0.265
	Low	50 (90.9%)	5 (9.1%)		117 (92.1%)	10 (7.9%)	
Simultaneous operation	Yes	20 (90.9%)	2 (9.1%)	0.308	53 (85.5%)	9 (14.5%)	0.286
	No	224 (95.3%)	11 (4.7%)		521 (89.7%)	60 (10.3%)	
Air-water test	Yes	121 (96.8%)	4 (3.2%)	0.255	454 (88.7%)	58 (11.3%)	0.429
	No	119 (93.0%)	9 (7.0%)		116 (91.3%)	11 (8.7%)	

BMI body mass index, *ASA* American Society of Anesthesiologists classification score, *CCI* Charlson comorbidity index score, *CVD* cardiovascular disease, *MI* minimally invasive, *IMA* inferior mesenteric artery, *AL* anastomotic leakage

Table 3 Multivariable analysis of risk factors for postoperative AL in sigmoid surgery

	Risk factor	Odds ratio	95% CI	*p* value
Age		0.962	0.878–1.054	0.632
Gender	Male	0.834	0.179–3.882	0.784
BMI	> 30	1.519	0.283–8.153	0.119
ASA	III–IV	10.539	1.292–85.976	0.007
CCI	> 5	0.348	0.029–4.199	0.928
Diabetes mellitus	Yes	2.150	0.285–16.233	0.095
Surgery type	Palliative	1.726	0.052–57.273	0.601
Neoadjuvant treatment	Yes	9.657	0.269–346.401	0.307
Anastomosis type	Stapled	0.901	0.092–8.821	0.316
Ligation of IMA	High	0.670	0.093–4.848	0.081
Air-water test	No	1.084	0.060–19.593	0.187
Simultaneous operation	Yes	1.318	0.088–19.748	0.904
T stage	T3–T4	0.887	0.122–6.470	0.408
Approach of surgery	Open	0.438	0.070–2.731	0.079

BMI body mass index, *ASA* American Society of Anesthesiologists classification score, *CCI* Charlson comorbidity index score, *IMA* inferior mesenteric artery, *AL* anastomotic leakage

proximally, and distally to cancer sites [29]. These cells were identified after the rectal wash-out or were washed-out from histologically tumor-free stapled doughnuts [30, 31]. The pre-clinical model confirms these intraluminal cancer cells can implant at the anastomotic site and initiate tumor growth in experimental animals [32]. Additionally, the leakage results in a local inflammation, which may further contribute to the increased risk of tumor cell implantation and proliferation at the anastomotic site [33]. Moreover, the AL is associated with an increased systemic inflammatory response as shown by increased levels of CRP, and such condition

Table 4 Multivariable analysis of risk factors for postoperative AL in rectal surgery

	Risk factor	Odds ratio	95% CI	*p* value
Gender	Male	2.403	1.204–4.797	0.004
Age		0.994	0.962–1.026	0.307
BMI	> 30	0.858	0.389–1.894	0.495
ASA	III–IV	1.346	0.635–2.854	0.156
CCI	> 5	1.720	0.759–3.898	0.025
Diabetes mellitus	Yes	1.297	0.478–3.522	0.155
Ischemic heart disease	Yes	0.933	0.250–3.487	0.303
Cerebrovascular disease	Yes	1.090	0.185–6.432	0.644
Surgery type	Palliative	0.606	0.059–6.273	0.980
Neoadjuvant treatment	Yes	1.430	0.645–3.170	0.260
Anastomosis type	Stapled	1.310	0.125–13.727	0.809
Ligation of IMA	High	2.345	0.939–5.856	0.167
Air-water test	No	1.339	0.529–3.392	0.350
Ileostomy	No	0.884	0.405–1.930	0.749
Simultaneous operation	Yes	1.188	0.436–3.237	0.450
T stage	T3–4	2.250	1.052–4.815	0.017
Approach of surgery	Open	0.633	0.316–1.269	0.186
Anastomosis level from anal verge	< 5	3.286	0.933–11.569	0.064
Anastomosis level from anal verge	5–12	2.629	0.636–10.868	0.182

BMI body mass index, *ASA* American Society of Anesthesiologists classification score, *CCI* Charlson comorbidity index score, *IMA* inferior mesenteric artery, *AL* anastomotic leakage

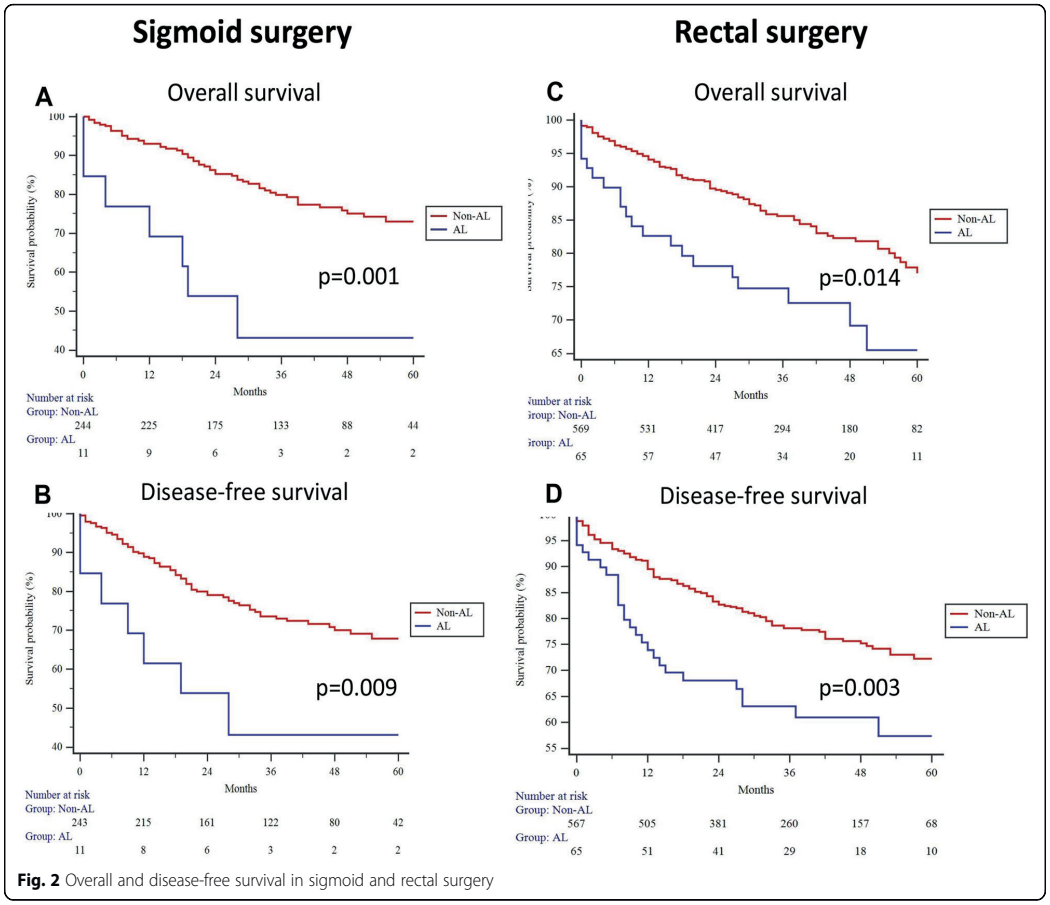

Fig. 2 Overall and disease-free survival in sigmoid and rectal surgery

Table 5 Cox regression (multivariable) analysis for overall and disease-free survival in the study cohort

		Overall survival		Disease-free survival	
		HR (95% CI)	*p*	HR (95% CI)	*p*
Anastomotic leakage	No	1 (reference)		1 (reference)	
	Yes	1.53 (1.01–2.32)	0.041	1.51 (1.05–2.19)	0.026
Stage of disease	I	1 (reference)		1 (reference)	
	II	1.26 (0.72–2.20)	0.403	1.52 (0.93–2.48)	0.090
	III	2.28 (1.38–3.78)	0.001	2.94 (1.88–4.59)	0.001
	IV	5.87 (3.26–10.56)	0.001	6.04 (3.51–10.38)	0.001
Gender	Male	1 (reference)		1 (reference)	
	Female	1.03 (0.76–1.39)	0.832	0.95 (0.73–1.23)	0.714
Age (years)	≤ 55	1 (reference)		1 (reference)	
	56–70	1.15 (0.71–1.85)	0.566	1.02 (0.70–1.49)	0.889
	≥ 71	1.90 (1.16–3.11)	0.010	1.15 (0.76-1.73)	0.498
Comorbidities by CCI	0–5	1 (reference)		1 (reference)	
	≥ 6	2.48 (1.64–3.74)	0.001	2.14 (1.48–3.10)	0.001

CCI Charlson comorbidity index score

may be related to the development and progression of the malignancy [34, 35]. AL is also associated with the delay or omission of the adjuvant chemotherapy. Therefore, AL may have a negative impact on long-term outcomes, especially in patients with the advanced stage of the disease, where adjuvant chemotherapy is necessary [36–39].

The present study has some limitations, including the retrospective design of the study. However, a considerable sample size, multicenter approach, and significant national registry-based long-term follow-ups increase the power of the study to demonstrate that AL is associated with impaired long-term outcomes in patients undergoing surgery for left-sided CRC. Future research is needed to find strategies to reduce or prevent the rate of AL in such patients [40].

Conclusion

ASA score of III–IV is an independent risk factor for AL after sigmoid surgery, and male sex, higher CCI score, and advanced tumor stage are among risk factors for AL after rectal surgery. AL impairs the long-term survival in patients undergoing left-sided colorectal surgery.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s12957-020-01968-8.

Additional file 1. STROBE Statement.

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Authors' contributions

Study conception design: Kryzauskas M., Bausys A., Poskus E., Dulskas A., Strupas K., Poskus T., Bausys R. Data acquisition: Degutyte A.E., Abeciunas V., Poskus T., Bausys R. Data analysis and interpretation: Kryzauskas M., Bausys A., Poskus T. Drafting the article: Kryzauskas M., Bausys A., Degutyte A.E., Abeciunas V., Poskus T., Bausys R. Critical revision for intellectual content: Poskus E., Dulskas A., Strupas K., Poskus T., Bausys R. Final approval of the manuscript: Kryzauskas M., Bausys A., Degutyte A.E., Abeciunas V., Poskus E., Dulskas A., Strupas K., Poskus T., Bausys R. Agree to be accountable for all aspects of work to ensure that questions regarding accuracy & integrity investigated and resolved: Kryzauskas M., Bausys A., Degutyte A.E., Abeciunas V., Poskus E., Dulskas A., Strupas K., Poskus T. The authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Vilnius regional research ethics committee approval (no. 2019/3-116-608) was obtained before the study. Individual patient consent is not required.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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RESEARCH

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Short and long-term outcomes of elderly patients undergoing left-sided colorectal resection with primary anastomosis for cancer

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Abstract

Background: The proportion of elderly colorectal cancer (CRC) patients requiring surgery is increasing. Colorectal resection for left-sided cancers is the most controversial as the primary anastomosis or end-colostomy and open or minimally invasive approaches are available. Therefore, this study was conducted to investigate the short- and long-term outcomes in elderly patients after resection with primary anastomosis for left-sided CRC.

Methods: The cohort study included left-sided colorectal cancer patients who underwent resection with primary anastomosis. The participants were divided into non-elderly (≤75 years) and elderly (>75 years) groups. Short- and long-term postoperative outcomes were investigated.

Results: In total 738 (82%) and 162 (18%) patients were allocated to non-elderly and elderly groups, respectively. Minimally invasive surgery (MIS) was less prevalent in the elderly (42.6% vs 52.7%, $p=0.024$) and a higher proportion of these suffered severe or lethal complications (15.4% vs 9.8%, $p=0.040$). MIS decreased the odds for postoperative complications (OR: 0.41; 95% CI: 0.19–0.89, $p=0.038$). The rate of anastomotic leakage was similar (8.5% vs 11.7%, $p=0.201$), although, in the case of leakage 21.1% of elderly patients died within 90-days after surgery. Overall- and disease-free survival was impaired in the elderly. MIS increased the odds for long-term survival.

Conclusions: Elderly patients suffer more severe complications after resection with primary anastomosis for left-sided CRC. The risk of anastomotic leakage in the elderly and non-elderly is similar, although, leakages in the elderly seem to be associated with a higher 90-day mortality rate. Minimally invasive surgery is associated with decreased morbidity in the elderly.

Keywords: Colorectal cancer, Elderly, Morbidity, Mortality, Anastomotic leakage

Introduction

Colorectal cancer (CRC) is a major health care issue as it is the third most deadly and fourth most commonly diagnosed cancer worldwide [1]. Surgery remains the only potentially curative treatment option for it [2]. As society is aging in many developed countries, the proportion of elderly patients requiring surgery for CRC is increasing as well [3, 4]. Despite improvements in perioperative care and surgical techniques, the treatment of elderly CRC patients remains challenging because of comorbidities, frailty,

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malnutrition, impaired functional, and cognitive status [5–8]. Such complex patients are at higher risk for various postoperative complications after major surgery, including a higher risk for infectious complications and anastomotic leakage (AL) [9–12]. Furthermore, elderly patients are at higher risk for death in case of postoperative complications because of the impaired functional reserve [13, 14]. These risks usually impact the surgeon's decision on the surgical plan, especially for elderly patients with left-sided CRC where Hartmann's procedure may be selected instead of primary anastomosis [15, 16]. Further, advanced age had initially been viewed as a relative contraindication to laparoscopic surgery [17], and minimally invasive surgery (MIS) is still underutilized in the elderly [18]. Since elderly patients are significantly underrepresented in the clinical studies due to careful participant selection by common age, performance status, or comorbidities restrictions [19, 20], there is a lack of evidence for the most appropriate surgical strategies in such patients. Therefore, this study was conducted to investigate the short- and long-term outcomes after resection with primary anastomosis for left-sided CRC in elderly patients, with a special focus on the rate of AL and utilization of MIS.

Materials and methods

Ethics

The study was approved by Vilnius Regional Bioethics Committee (Approval number 2019/3–116-608) and

Table 1 Baseline clinical characteristics of non-elderly and elderly patients

		NE group (≤75 years); *n* = 738	Missing data; n (%)	E group (> 75 years); *n* = 162	Missing data; n (%)	*p* value
BMI; n (%)	< 30	496 (71.2%)	41 (5.8%)	128 (84.2%)	10 (6.2%)	0.001
	≥30	201 (28.8%)		24 (15.8%)		
Gender; n (%)	Female	344 (46.6%)	0 (0%)	73 (45.1%)	0 (0%)	0.729
	Male	394 (53.4%)		89 (54.9%)		
ASA; n (%)	I-II	535 (76.0%)	34 (4.6%)	55 (35.7%)	8 (4.9%)	0.001
	III-IV	169 (24.0%)		99 (64.3%)		
CCI; n (%)	≤5	603 (81.7%)	0 (0%)	47 (29.0%)	0 (0%)	0.001
	> 5	135 (18.3%)		115 (71.0%)		
Ischemic heart disease; n (%)	Yes	26 (3.5%)	0 (0%)	17 (10.5%)	0 (0%)	0.001
	No	712 (96.5%)		145 (89.5%)		
Diabetes mellitus; n (%)	Yes	71 (9.6%)	0 (0%)	24 (14.8%)	0 (0%)	0.065
	No	667 (90.4%)		138 (85.2%)		
Cerebrovascular disease; n (%)	Yes	18 (2.4%)	0 (0%)	9 (5.6%)	0 (0%)	0.043
	No	720 (97.6%)		153 (94.4%)		
Chronic kidney failure; n (%)	Yes	9 (1.2%)	0 (0%)	4 (2.5%)	0 (0%)	0.267
	No	729 (98.8%)		158 (97.5%)		
Neoadjuvant treatment; n (%)	Yes	163 (22.1%)	0 (0%)	29 (17.9%)	0 (0%)	0.289
	No	575 (77.9%)		133 (82.1%)		
Specimen length, cm (Mean ± SD)		19 ± 8	22 (2.9%)	21 ± 6	4 (2.4%)	0.436
Proximal end, cm (Mean ± SD)		13 ± 7	27 (3.6%)	13 ± 6	5 (3.0%)	0.346
Distal end, cm (Mean ± SD)		4 ± 3	26 (3.5%)	4 ± 4	5 (3.0%)	0.109
T; n (%)	T0–2	271 (36.7%)	0 (0%)	30 (18.5%)	0 (0%)	0.001
	T3–4	467 (63.3%)		132 (81.5%)		
N; n (%)	N0	449 (61.8%)	12 (1.6%)	92 (57.1%)	1 (0.6%)	0.284
	N+	277 (38.2%)		69 (42.9%)		
M; n (%)	M0	666 (90.2%)	0 (0%)	144 (88.9%)	0 (0%)	0.566
	M1	72 (9.8%)		18 (11.1%)		
Stage; n (%)	0	11 (1.5%)	0 (0%)	1 (0.6%)	0 (0%)	0.002
	I	203 (27.5%)		23 (14.2%)		
	II	205 (27.8%)		64 (39.5%)		
	III	246 (33.3%)		56 (34.6%)		
	IV	73 (9.9%)		18 (1.1%)		

conducted according to the Declaration of Helsinki of 1964, as revised in later versions.

Patients and study design

This retrospective cohort study included all patients who underwent elective colorectal resection with primary anastomosis at two major gastrointestinal cancer treatment centers in Lithuania – National Cancer Institute and Vilnius University hospital Santaros Klinikos between January 2014 and December 2018. Patients were divided into non-elderly (NE; ≤75 years) and elderly groups (E; >75 years) according to the age at the time of surgery.

Data collection

The database used for the present study was used previously [12]. All patients' characteristics and clinical data were obtained from the medical records and prospectively collected databases. The preoperative data included: age, gender, body mass index (BMI), Charlson comorbidity index (CCI), comorbidities, American Society of Anesthesiology (ASA) score, type of neoadjuvant treatment, tumor localization. Chronic kidney failure was defined as a kidney damage or glomerular filtration rate (GFR) <60 mL/min/1.73 m^2 for 3 months or more, irrespective of cause as proposed by Kidney Disease: Improving Global Outcomes (KDIGO) [21]. Intraoperative details included: type of surgery, the approach of surgery (open or minimally invasive), operation time, blood loss, the height of anastomosis measured from the anal verge, presence of diverting ileostomy. Standard laparoscopic colorectal resection, hand-assisted laparoscopic surgery, natural orifice specimen extraction surgery, and transanal total mesorectal excision operations were defined as minimally invasive approaches. Postoperative data included histological report results, hospitalization time, postoperative complications graded by Clavien-Dindo classification, 30-day, and 90-day mortality rates. The tumor stage was set according to the TNM system as described at the American Joint Committee on Cancer 8th edition.

Study outcomes

The primary outcome of the study was the anastomotic leakage rate in NE and E patients. The secondary outcomes were overall postoperative morbidity rate; in-hospital, 30-day, and 90-day mortality rates; the rate of MIS; overall survival (OS), and disease-free survival (DFS) rates in NE and E patients. OS was defined as the time from surgery to death. DFS was defined as the time from surgery to disease progression including local or distant recurrence or death. Data on survival and date of death were collected from the National Lithuanian Cancer registry.

Table 2 Intraoperative and postoperative outcomes of non-elderly and elderly patients after resection with primary anastomosis for left-sided colorectal cancer

		NE group (≤75 years); *n* = 738	E group (>75 years); *n* = 162	*p* value
Type of surgery; n (%)	Sigmoid resection	214 (29.0%)	43 (26.5%)	0.565
	Rectal resection	524 (71.0%)	119 (73.5%)	
Approach of surgery; n (%)	Open	349 (47.3%)	93 (57.4%)	0.024
	Minimally invasive	389 (52.7%)	69 (42.6%)	
Operation time, minutes (mean ± SD)		147 ± 60	150 ± 67	0.190
Blood loss, ml (median; Q1, Q3)		50 (Q1: 50; Q3: 100)	100 (Q1: 50; Q3: 162)	0.522
Anastomosis level from anal verge; n (%)	≤5 cm	145 (23.7%)	29 (22.3%)	0.860
	6–12 cm	239 (39.0%)	54 (41.5%)	
	>12 cm	229 (37.3%)	47 (36.2%)	
Diverting ileostomy; n (%)	Yes	302 (40.9%)	72 (44.4%)	0.429
	No	436 (59.1%)	90 (55.6%)	
Postoperative hospitalization; days (mean ± SD)		10 ± 6	13 ± 11	0.001
Retrieved lymph nodes; n (%)	<12	130 (17.6%)	18 (11.1%)	0.046
	≥12	608 (82.4%)	144 (88.9%)	
Postoperative complications; n (%)	Yes	219 (29.7%)	60 (37.0%)	0.066
	No	519 (70.3%)	102 (63.0%)	
Severe complications by Clavien-Dindo score III-V; n (%)		73 (9.8%)	25 (15.4%)	0.040
30-day mortality; n (%)		7 (0.9%)	5 (3.1%)	0.048
90-day mortality; n (%)		12 (1.6%)	12 (7.4%)	0.001

Statistical analysis

All statistical analyses were performed using SPSS version 25.0 software (SPSS, Chicago, IL, USA). Continuous variables between groups were compared by Student's t-test or Mann– Whitney U-test depending on data distribution and expressed as mean ± standard deviation (±SD) or median with first (Q1) and third (Q3) quartiles. Categorical variables were compared by $\chi 2$ test or Fisher's exact test and expressed as proportion and percentages. Missing data was not handled at the statistical analysis and no imputation techniques were used. To determine the risk factors for anastomotic leakage, all potential risk factors were included in univariate analyses. These variables which showed significance were included in subsequent multivariable analysis. Kaplan-Meier method was used for OS and DFS analysis and curves were compared by the log-rank test. Multivariable survival analysis was performed using the Cox proportional hazards model

Table 3 Univariate analysis of risk factors for anastomotic leakage in patients after resection with primary anastomosis for left-sided colorectal cancer

		No anastomotic leakage	Anastomotic leakage	*p* value
Gender; n (%)	Female	391 (93.8%)	26 (6.2%)	0.005
	Male	427 (88.4%)	56 (11.6%)	
CCI; n (%)	≤5	602 (92.6%)	48 (7.4%)	0.004
	>5	216 (86.4%)	34 (13.6%)	
Ischemic heart disease; n (%)	Yes	39 (90.7%)	4 (9.3%)	0.999
	No	779 (90.9%)	78 (9.1%)	
Diabetes mellitus; n (%)	Yes	82 (86.3%)	13 (13.7%)	0.101
	No	736 (91.4%)	69 (8.6%)	
Cerebrovascular disease; n (%)	Yes	25 (92.6%)	2 (7.4%)	0.999
	No	793 (90.8%)	80 (9.2%)	
Chronic kidney failure; n (%)	Yes	12 (92.3%)	1 (7.7%)	0.999
	No	806 (90.9%)	81 (9.1%)	
Neoadjuvant treatment; n (%)	Yes	169 (88.0%)	23 (12.0%)	0.119
	No	649 (91.7%)	59 (8.3%)	
Tumor localization; n (%)	Rectum	458 (89.3%)	55 (10.7%)	0.132
	Rectosigmoid	112 (91.8%)	10 (8.2%)	
	Sigmoid	248 (93.6%)	17 (6.4%)	
T; n (%)	T0–2	284 (94.4%)	17 (5.6%)	0.010
	T3–4	534 (89.1%)	65 (10.9%)	
M; n (%)	M0	740 (91.4%)	70 (8.6%)	0.142
	M1	78 (86.7%)	12 (13.3%)	
Stage; n (%)	0	11 (91.7%)	1 (8.3%)	0.290
	I	221 (93.4%)	15 (6.6%)	
	II	246 (91.4%)	23 (8.6%)	
	III	272 (90.1%)	30 (9.9%)	
	IV	78 (85.7%)	13 (14.3%)	
Ligation of inferior mesenteric artery; n (%)	High	631 (90.5%)	66 (9.5%)	0.610
	Low	167 (91.8%)	15 (8.2%)	
Simultaneous operation; n (%)	Yes	73 (86.9%)	11 (13.1%)	0.183
	No	745 (91.3%)	71 (8.7%)	
Anastomosis level from anal verge; n (%)	≤5 cm	155 (89.1%)	19 (10.9%)	0.023
	6–12 cm	255 (87.0%)	38 (13.0%)	
	>12 cm	259 (93.8%)	17 (6.2%)	
Approach of surgery; n (%)	Open	391 (88.5%)	51 (11.5%)	0.013
	Minimally invasive	427 (93.2%)	31 (6.8%)	
Age; n (%)	NE group (≤75 years)	675 (91.5%)	63 (8.5%)	0.201
	E group (>75 years)	143 (88.3%)	19 (11.7%)	

(hazard ratio and 95% confidence intervals). Statistical significance was assumed for p values < 0.05.

Results

Patients baseline characteristics

A total of 900 patients were included in this study. Seven hundred thirty-eight (82%) patients were allocated to the NE group (≤75 years) and 162 (18%) patients were allocated to the E group (>75 years). Baseline clinical characteristics of the study patients are presented in Table 1. E patients had higher ASA and CCI scores, but a lower proportion of these was obese (Table 1).

Intraoperative and postoperative outcomes

Intraoperative and postoperative outcomes are shown in Table 2. Lower proportion of E patients received MIS (52.7% vs 42.6%, $p=0.024$). There was some tendency for a higher postoperative morbidity rate in the E (37.0%) group compared to NE (29.7%) group, however, the difference failed for significance ($p=0.066$). Although, severe or lethal complications by Clavien-Dindo score III-V were more common in the E group (15.4% vs 9.8%, $p=0.040$).

Anastomotic leakage in the study cohort

Eighty-two of 900 (9.1%) patients included in the study developed AL. Male gender, higher CCI score (>5), advanced pT stage (pT3–4), lower anastomoses, and open surgery were associated with AL in the univariate analysis (Table 3). The rate of AL was similar between NE (8.5%) and E (11.7%) groups, $p=0.201$. Although, there was some tendency for increased 90-days mortality in E patients who developed AL, but without statistical significance (6.3% vs 21.1%, $p=0.079$). Variables that showed significance in univariate analysis were included in subsequent multivariable analysis. Male gender (OR: 1.94; 95% CI: 1.15–3.29, $p=0.013$), CCI score > 5 (OR: 1.90; 95% CI: 1.14–3.16, p = 0.013), and anastomoses at 6–12 cm from anal verge (OR: 2.29; 95% CI: 1.24–4.21, $p=0.008$) were identified as a risk factor for AL (Table 4).

Table 4 Multivariable analysis of risk factors for anastomotic leakage in patients after resection with primary anastomosis for left-sided colorectal cancer

Risk factor		Odds ratio (95% CI)	*p* value
Gender	Female	1 (Reference)	
	Male	1.94 (1.15–3.29)	0.013
CCI	≤5	1 (Reference)	
	>5	1.90 (1.14–3.16)	0.013
pT stage	T0–2	1 (Reference)	
	T3–4	1.82 (0.97–3.42)	0.060
Anastomosis level from anal verge	>12 cm	1 (Reference)	
	6–12 cm	2.29 (1.24–4.21)	0.008
	≤5 cm	1.90 (0.93–3.87)	0.076
Approach of surgery	Open	1 (Reference)	
	Minimally invasive	0.65 (0.39–1.09)	0.109

Factors associated with postoperative morbidity in the subgroup of elderly patients

Since the E patients were at higher risk for postoperative morbidity and mortality, the univariate analysis was performed to identify the variables associated with postoperative complications in the subgroup of E patients. Open surgery was the only risk factor associated with postoperative complications in the univariate setting (Table 5).

Survival

The median time to follow-up was 38 (Q1: 22; Q3: 53) months. Overall and disease-free survival was significantly lower in E patients (Figs. 1 and 2). The multivariable Cox proportional hazards model was performed to identify the factors associated with OS and DFS in the E group. E patients who received MIS had higher probability for OS (HR: 0.47; 95% CI: (0.25–0.86), $p=0.015$) and DFS (HR: 0.48; 95% CI: (0.27–0.86) (Table 6).

Discussion

The present study demonstrated the trend of a slightly higher rate of postoperative morbidity in the elderly patients after colorectal resection with the primary anastomosis for left-sided cancer. However, the rate of severe or lethal complications was undoubtedly higher in the elderly patients group. Interestingly, the rate of AL was similar across the study groups, but in the case of leakage elderly patients were at much higher risk for death within 90-days after surgery. The MIS was associated with reduced postoperative morbidity in the elderly; however, this approach was underutilized in these patients.

The reported rate of postoperative complications in elderly colorectal cancer patients varies between 26 and 53.7% [22–24], as our study showed a comparable rate of 37%. The elderly patients often have a higher ASA score [25–27], which is the risk factor for postoperative complications as shown in the present study and some previous reports [22]. It is not surprising, that the frequent presence of comorbidities, frailty and impaired functional reserves in the elderly leads to the increased postoperative morbidity and mortality [23, 28–30]. However, it remains unclear if elderly patients are at a higher risk for all types of complications or only specific ones. The particularly important question is whether the elderly patients are at higher risk for the AL, especially after resection for left-sided cancer. This has special importance, because, the higher rate of AL

Table 5 Univariate analysis of risk factors for postoperative complications in elderly patients after resection with primary anastomosis for left-sided colorectal cancer

		No postoperative complications	Postoperative complications	*p* value
Gender; n (%)	Female	51 (50.0%)	22 (36.7%)	0.106
	Male	51 (50.0%)	38 (63.3%)	
ASA; n (%)	I-II	40 (40.8%)	15 (26.8%)	0.115
	III-IV	58 (59.2%)	41 (73.2%)	
CCI; n (%)	≤5	33 (32.4%)	14 (23.3%)	0.283
	>5	69 (67.6%)	46 (76.7%)	
Ischemic heart disease; n (%)	Yes	12 (11.8%)	5 (8.3%)	0.601
	No	90 (88.2%)	55 (91.7%)	
Diabetes mellitus; n (%)	Yes	16 (15.7%)	8 (13.3%)	0.820
	No	86 (84.3%)	52 (86.7%)	
Cerebrovascular disease; n (%)	Yes	7 (6.9%)	2 (3.3%)	0.487
	No	95 (93.1%)	58 (96.7%)	
Chronic kidney failure; n (%)	Yes	3 (2.9%)	1 (1.7%)	0.999
	No	99 (97.1%)	59 (98.3%)	
Neoadjuvant treatment; n (%)	Yes	19 (18.6%)	10 (16.7%)	0.834
	No	83 (81.4%)	50 (83.3%)	
Tumor localization; n (%)	Rectum	55 (53.9%)	33 (55.0%)	0.170
	Rectosigmoid	14 (13.7%)	14 (23.3%)	
	Sigmoid	33 (32.4%)	13 (21.7%)	
T; n (%)	T0–2	20 (19.6%)	10 (16.7%)	0.681
	T3–4	82 (80.4%)	50 (83.3%)	
M; n (%)	M0	92 (90.2%)	52 (86.7%)	0.606
	M1	10 (9.8%)	8 (13.3%)	
Stage; n (%)	0	1 (1.0%)	0 (0.0%)	0.735
	I	13 (12.7%)	10 (16.7%)	
	II	40 (39.2%)	24 (40.0%)	
	III	38 (37.3%)	18 (30.0%)	
	IV	10 (9.8%)	8 (13.3%)	
Ligation of inferior mesenteric artery; n (%)	High	71 (70.3%)	42 (72.4%)	0.857
	Low	30 (29.7%)	16 (27.6%)	
Simultaneous operation; n (%)	Yes	6 (5.9%)	8 (13.3%)	0.146
	No	96 (94.1%)	52 (86.7%)	
Anastomosis level from anal verge; n (%)	≤5 cm	16 (19.8%)	13 (26.5%)	0.351
	6–12 cm	32 (39.5%)	22 (44.9%)	
	>12 cm	33 (40.7%)	14 (28.6%)	
Approach of surgery; n (%)	Open	52 (51.0%)	41 (68.3%)	0.034
	Minimally invasive	50 (49.0%)	19 (31.7%)	

compared to right-side surgery [31] is preventable by utilizing Hartmann's procedure. The current data on the risk of AL in elderly patients is inconclusive. Some studies suggest a higher risk because of co-existing medical conditions, which are known risk factors for AL, such as coronary heart disease and diabetes [27, 32, 33]. In contrast, the other series of previous studies identified a similar risk of AL in elderly and non-elderly patients [34–37]. The present study shows that the risk in elderly and non-elderly patients after resection for left-sided CRC is similar. However, it is necessary to note, that the consequences of leakage in the elderly were much more dramatic since the 90-day mortality rate exceeded 20%. Thus, we consider, that primary anastomosis after left-sided resection for CRC is feasible in the elderly, but these patients must be monitored closely, and in the case of AL the aggressive treatment of the complication is mandatory.

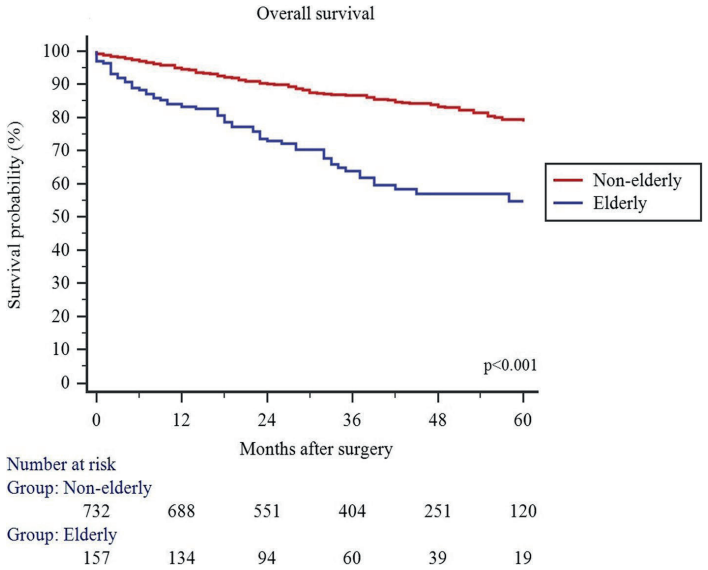

Fig. 1 Overall survival in non-elderly and elderly patients who received colorectal resection with primary anastomosis for left-sided colorectal cancer

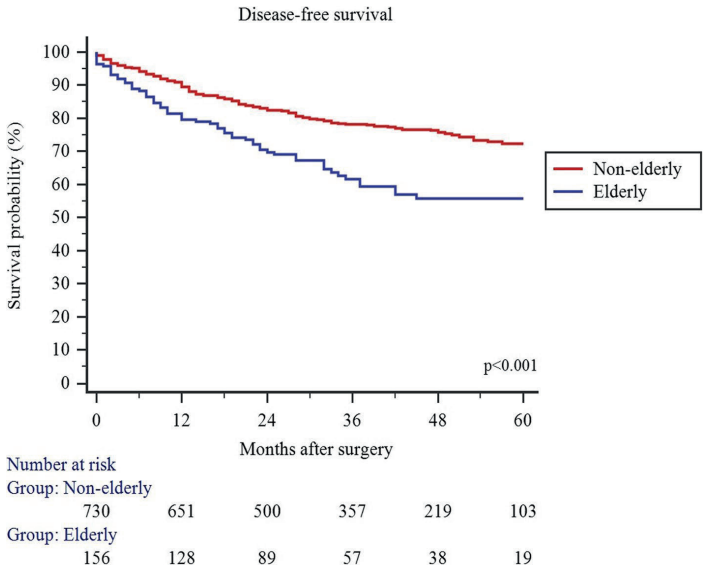

Fig. 2 Disease-free survival in non-elderly and elderly patients who received colorectal resection with primary anastomosis for left-sided colorectal cancer

Table 6 Cox regression (multivariable) analysis for overall and disease-free survival in the elderly patients after resection with primary anastomosis for left-sided CRC

		Overall survival		Disease-free survival	
		HR (95% CI)	*p*	HR (95% CI)	*p*
Gender	Female	1 (reference)		1 (reference)	
	Male	1.20 (0.68–2.13)	0.521	1.18 (0.67–2.07)	0.558
pT	T0–2	1 (reference)		1 (reference)	
	T3–4	0.89 (0.41–1.93)	0.783	0.87 (0.41–1.85)	0.723
pN	N0	1 (reference)		1 (reference)	
	N+	1.28 (0.69–2.36)	0.422	1.46 (0.80–2.66)	0.210
pM	M0	1 (reference)		1 (reference)	
	M1	2.00 (0.69–2.36)	0.422	1.94 (0.82–4.57)	0.128
ASA score	I-II	1 (reference)		1 (reference)	
	III-IV	1.91 (0.98–3.75)	0.057	2.12 (1.09–4.12)	0.026
Postoperative complications	No	1 (reference)		1 (reference)	
	Yes	0.82 (0.41–1.63)	0.580	0.92 (0.47–1.80)	0.816
Anastomotic leakage	No	1 (reference)		1 (reference)	
	Yes	1.69 (0.68–4.19)	0.256	1.85 (0.78–4.38)	0.160
Surgical approach	Open	1 (reference)		1 (reference)	
	Minimally invasive	0.47 (0.25–0.86)	0.015	0.48 (0.27–0.86)	0.015
LN retrieval	≥12	1 (reference)		1 (reference)	
	< 12	0.52 (0.26–1.02)	0.060	0.53 (0.27–1.02)	0.058
Tumor localization	Sigmoid	1 (reference)		1 (reference)	
	Rectum	1.64 (0.71–3.81)	0.242	1.45 (0.63–3.35)	0.375

MIS is currently considered an excellent alternative for open CRC surgery since large-scale RCTs demonstrated improved short-term and similar long-term outcomes [38–43]. Furthermore, large-scale population-based studies show that MIS is associated with decreased morbidity and mortality in CRC patients [44, 45]. Despite such evidence, MIS is underutilized in elderly patients as demonstrated by this study. A similar pattern of slow and even decreasing adoption of laparoscopic CRC surgery in the elderly is observed not only in our cohort but in other Western countries as well [18]. The reasons for such disparities in implementing MIS for younger and elderly CRC patients remain unclear. Although, some controversies exist on this topic and they may be responsible for the reluctance to perform MIS in the elderly. First, MIS is associated with significantly longer operative time, therefore there is a long time of the patient under anesthesia. Second, the potential cardiopulmonary changes induced by pneumoperitoneum and prolonged patient positioning remains a concern. Third, the studies which proved the benefit of MIS in CRC patients underrepresented the elderly population. Thus, there is a background for some scepticism regarding MIS adoption in elderly. Although, several previous studies showed the favourable outcomes of MIS in elderly CRC patients [46–50]. Further, our study confirmed, that MIS is associated with lower odds for postoperative complications in elderly patients who undergo resection with primary anastomosis for left-sided cancer. Hence, surgeons should not avoid MIS in the elderly, because this high-risk population seems to receive a significant benefit from this technique.

In contrast to some previous reports [51, 52], we found impaired long-term outcomes in elderly patients after resection for left-sided CRC. The first 3 months after surgery were suggested as the most critical for these patients [51] and the results of the present confirmed the importance of the early postoperative period as 90-days mortality reached 7.4% in elderly and only 1.6% in younger counterparts. Such findings indicate the need for remarkably close monitoring of late postoperative complications and life-threatening events during the early postoperative period in elderly population undergoing colorectal resection. To our surprise, we found impaired DFS in elderly patients as well. There is no clear explanation for such a finding since there is no evidence for a more aggressive biological behaviour of CRC in the elderly. However, few patients and treatment-related may be responsible. At first, the most frail elderly patients do not

receive adjuvant chemotherapy because of poor physical condition [53]. Second, elderly patients are at higher risk for postoperative complications, which are responsible for the delay of adjuvant chemotherapy [54], thus the impaired oncological outcomes [55]. Third, elderly patients, who receive adjuvant therapy, are at higher risk for dose de-escalation because of renal and liver dysfunctions [3]. For these reasons, successful surgical treatment with an uneventful postoperative course plays a key role in the management of CRC in this population. As the present study showed, the MIS is an excellent option for elderly patients since the lower odds for postoperative morbidity, recurrence of disease, and death.

Our study has several limitations. First, it is a retrospective cohort study, therefore it is subject to the biases and confounding factors linked to such methods of research. Moreover, missing data was not handled at the statistical analysis and no imputation techniques were used as missing rate of < 5% is considered inconsequential. Second, there was an unidentifiable bias in the decisions to perform open or MIS in elderly patients. It is possible that the choice was made in settings of surgeon experience and the patient's global health status, thus, lower morbidity after MIS may be the consequence of the selection bias, rather than the real advantage of the method. Third, this study did not include any patient-reported outcomes, such as quality of life or others.

A strength of the current multi-center study includes a large sample size of the left-sided CRC patients who receive resection with primary anastomosis with long-term survival data.

Conclusions

Short- and long-term outcomes of elderly patients who underwent resections with primary anastomosis for left-sided CRC are impaired. The risk of anastomotic leakage in the elderly and non-elderly patients is similar, but leakages in the elderly seem to be associated with a higher 90-day mortality rate. Minimally invasive surgery is associated with decreased morbidity in the elderly and better long-term outcomes.

Abbreviations

CRC: Colorectal cancer; AL: Anastomotic leakage; MIS: Minimally invasive surgery; NE: Non-elderly; E: Elderly; BMI: Body mass index; CCI: Charlson comorbidity index; ASA: American Society of Anesthesiology; OS: Overall survival; DFS: Disease-free survival.

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Authors' contributions

Study conception design: MK, AB, EP, RB, AD, KS, TP. Data acquisition: TP, KB, MK, AB. Data analysis and interpretation: MK, AB, TP. Drafting the article: MK, AB, KB, RB, JK, TP. Critical revision for intellectual content: EP, AD, KS, TP. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Vilnius Regional Research Ethics Committee approval (No. 2019/3–116-608) was obtained before the study. Because this study was retrospective and all included data were anonymous, the requirement that patients give informed consent was waived. Waiver of informed consent was approved by Vilnius Regional Research Ethics Committee.

Consent for publication

Not applicable.

Competing interests

The authors have no conflict of interest to declare.

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Intraoperative testing of colorectal anastomosis and the incidence of anastomotic leak

A meta-analysis

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Abstract

Background: AL remains one of the most threatening complications in colorectal surgery. Significant efforts are put to understand the pathophysiological mechanisms involved in the development of leakage and to create the strategies to prevent it. We aimed to determine whether intraoperative testing of mechanical integrity and perfusion of colorectal anastomosis could reduce the incidence of AL.

Methods: A systematic review and meta-analysis of papers published before November 2019 on PubMed, Scopus, Web of Science, and Cochrane Library databases and comparing intraoperative testing of the colorectal anastomosis with standard care were conducted. Odds ratios (ORs) and 95% confidence interval (CIs) were used to assess the association between intraoperative testing and AL.

Results: A total of 23 studies totaling 7115 patients were included. Pooled analysis revealed intraoperative tests, for integrity (OR 0.52, 95% CI 0.34–0.82, $P < .001$) and perfusion (OR 0.40, 95% CI 0.22–0.752, $P < .001$) of the lower gastrointestinal tract anastomoses are associated with significantly lower AL rate.

Conclusions: Intraoperative testing for either integrity or perfusion of anastomoses both reduce the AL rate. Studies looking at the combination of these two testing methods of anastomosis, especially intraoperative endoscopy, and indocyanine green fluorescence angiography may be very promising to further reduction of the AL.

Abbreviations: AL = anastomotic leakage, CI = confidence interval, ICG-FA = indocyanine green fluorescence angiography, IOE = intraoperative endoscopy, OR = odds ratio, RCT = randomized controlled trial.

Keywords: air-leak, anastomosis insufficiency, anastomotic leak, colorectal surgery, indocyanine green fluorescence, intraoperative endoscopy, intraoperative tests, methylene blue

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MK, AB, MJ, and JV have contributed equally and shares first authorship.

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Ethical approval and informed consent: This was a systematic review and meta-analysis of published studies, therefore no ethics approval and informed consent were required.

Mini-abstract: An anastomotic leak (AL) is one of the most devastating postoperative complications in colorectal surgery. A systematic review and meta-analysis were conducted with the aim to assess whether intraoperative testing of mechanical integrity and perfusion of colorectal anastomosis could reduce the incidence of AL.

The authors have no conflicts of interest to disclose.

Supplemental Digital Content is available for this article.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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1. Introduction

Anastomotic leak (AL) is one of the most serious postoperative complications in colorectal surgery because it prolongs the hospital stay, increases treatment costs, decreases the quality of life of the patient, impairs long-term outcomes in case of cancer surgery and increases postoperative morbidity and mortality.[1–3] The reported rate of AL in colorectal surgery varies from 1.8% to 19.2% with the highest risk for low rectal anastomoses.[4–6] Current evidence cannot fully clarify the reasons of AL in all cases, but some of the etiological factors are well known. These include poor technical construction of the stapled anastomosis when there are gaps between sutures, or anastomosis is formed under tension between the afferent and efferent loops. This may lead to an immediate or delayed AL.[7] Similarly, insufficient blood perfusion at the anastomotic site is another well-known reason for AL.[7,8] Therefore, some of the AL might be avoided if anastomoses were constructed in adequately perfused bowel ends and insufficiently integral anastomoses would be immediately reinforced or diverted. Historically surgeons relied on subjective parameters to avoid anastomosis formation in the poorly perfused area by judging the color of the bowel wall, bleeding from the edge of the resection margin and by the palpable pulsations of mesenteric arteries. Similarly, the integrity of the newly formed anastomosis can be evaluated by simple visual inspection. However, subjective judgment is unreliable and depends on the expertise and experience of an individual surgeon. Thus, many different tests to evaluate the anastomoses intraoperatively were created. Presently, it is still not clear whether and which tests should be used as the standard. We hypothesize that intraoperative anastomosis integrity and perfusion assessment may be associated with a reduced leak rate in patients undergoing colorectal anastomosis. We aimed to review the literature and to consolidate the current evidence on the use of various intraoperative tests to assess the colorectal anastomosis intraoperatively and to determine, whether above mentioned intraoperative tests reduce the rate of postoperative anastomotic leak.

2. Materials and methods

Our study was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and Meta-analysis Of Observational Studies in Epidemiology (MOOSE) checklist.[9,10] PRISMA and MOOSE checklists were filled according to mentioned recommendations (Supplemental digital content [Table, SDC1, http://links.lww.com/MD/F212 and 2, http://links.lww.com/MD/F213]).

2.1. Eligibility criteria

Studies that compared the use of intraoperative tests evaluating the integrity and the perfusion of the anastomosis with the standard care for the assessment of anastomotic leak following lower gastrointestinal resection were eligible for inclusion. The search was restricted to human studies published in the English language only without a time limitation. Patients of any age undergoing colon or rectal resection with anastomosis were included, regardless of the operative approach, resection technique, urgency of surgery, and surgical indications (Supplemental digital content [Table, SDC3, http://links.lww.com/MD/F214]). An outcome measure was the rate of postoperative AL in the control group (no intraoperative testing of anastomosis) versus the rate of postoperative AL in the experimental group (with intraoperative mechanical integrity or perfusion testing).

2.2. Information sources

Literature search was performed in PubMed, Scopus, Web of Science, and Cochrane Library online databases as suggested by Goossen et al[11] to identify randomized controlled trials (RCT) and comparative studies analyzing the impact of various intraoperative tests on the rate of AL. The most recent search was performed in November 2019.

2.3. Literature search strategy

We used the following combination of Medical Subject Headings (MeSH) and keywords with the employment of "AND" or "OR" Boolean operators:

"Indocyanine green" OR "ICG" OR "Coloring agents" OR "Fluorescence" OR "Fluorescein angiography" OR "Fluorescent dyes" OR "Narrow Band Imaging" OR "Methylene Blue" OR "Ultrasonography" OR "Doppler" OR "Duplex" OR "Colonoscopy" OR "Endoscopy" OR "Staple line bleed" OR "Staple line bleeding" OR "Leak Test" OR "Leak Testing" OR "Spectroscopy" OR "Near-Infrared imaging" OR "Spectrum analysis" AND "Anastomotic leak" OR "Anastomotic leakage" OR "Anastomotic perfusion" OR "Anastomosis, surgical" OR "Bowel perfusion" OR "Blood supply" OR "Perfusion assessment" OR "Anastomotic dehiscence" OR "Anastomosis dehiscence" AND "Gastrointestinal Tract" OR "Lower Gastrointestinal Tract" OR "Colorectal surgery" OR "Colon surgery" OR "Rectal surgery" OR "Colorectal resection" OR "Bowel resection" AND "Intraoperative Period" OR "Intraoperative" OR "Perioperative Period" OR "Perioperative" OR "Intraoperative care" OR "Perioperative care" OR "Intraoperative procedure" OR "Perioperative procedure."

2.4. Study selection

All titles and abstracts were independently screened for eligibility by 2 experienced reviewers using a piloted electronic database (Microsoft Excel). In the case of different opinions, the study was judged by the additional researcher. After relevant abstracts were identified, full-text articles were retrieved and re-reviewed. Letters, comments on articles, conference abstracts, short notes, meta-analyses, systematic reviews, review articles, and duplicates were manually excluded. An additional manual search of the reference lists of the included studies was performed to ensure the comprehensive search procedure. The authors of the included studies were not further contacted.

2.5. Data extraction

Finally, the following data were extracted from each study: date of publication, type of study design, study sample size, surgery-related data (access [open vs laparoscopic vs robotic], type of anastomosis [hand-sewn vs stapled], elective or emergency setting, anastomosis location), intraoperative tests used to evaluate the anastomosis and main findings of the study. Extracted data were only compared at the end of the reviewing process to reduce the selection bias.

2.6. Assessment of risk of bias

The risk of bias was assessed for each study using appropriate assessment tools. Two reviewers independently performed a duplicate outcome-specific assessment of the risk of bias for each study using the Cochrane Collaboration's tool for assessing the risk of bias.[12] For randomized controlled trials, we used Version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB 2), for nonrandomized studies the Newcastle-Ottawa scale (≥7) was utilized.

2.7. Statistical analysis

Statistical analysis was performed according to the recommendations of the Cochrane Collaboration Guidelines[10] using Review Manager Software (RevMan, version 5.3 for Windows, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Data from different studies were combined to obtain a pooled (summary) odds ratio (OR) and the 95% confidence interval (CI) using the Mantel–Haenszel (M–H) method for random effects model. Between-study heterogeneity was measured by Sidik-Jonkman I^2 test. $I^2 < 50\%$ was considered to indicate low between-study heterogeneity, while 50% to 75% and ≥75% indicated moderate and high heterogeneity, respectively. Small study effects were examined by funnel plots in order to distinguish publication bias from other causes. Sensitivity analyses were additionally performed. The sensitivity of ≥50% was considered to be high and sensitivity of <50% was considered low. Ninety-five percent confidence intervals for proportions were calculated according to the efficient-score method (corrected for continuity) described by Newcombe[13] and based on the procedure outlined by Wilson.[14]

3. Results

3.1. Search results and study characteristics

Three-thousand three-hundred and twenty-three studies were identified during the literature search. Seventy-six papers were reviewed as full-text articles. These were assessed for eligibility. Fifteen were excluded as not eligible for the inclusion: 1—review article, 3—editorial, 1—video vignette, 3—conference abstracts, 5—due to inadequate, and 1—due to overlapping data. Studies were grouped into those, which investigated the methods to test the mechanical integrity of the anastomosis (N=41), and those, which investigated the methods to test the perfusion of the anastomosis (N=20) and its' impact on AL after colonic resection with anastomosis. Twenty-three studies were selected for a meta-analysis, excluding those, lacking control group and necessary data[15–37] (Fig. 1).

3.2. Intraoperative tests to evaluate the integrity of anastomosis

Twelve studies, involving 3787 patients, were included in the meta-analysis.[15–26] Isolated air-leak test, intraoperative endoscopy with the air-leak test, and intraoperative endoscopy with both air-leak and blue-tinged saline tests were the methods of testing the integrity of anastomosis included in the study (Table 1). Two RCTs included showed the positive intraoperative endoscopy (IOE) test in 23% and 25% of the patients undergoing colorectal surgery.[15,17] Both trials revealed a clear benefit of testing, as the rates of AL in the study group of 4%[15] and 10%[17] were significantly lower compared with the control groups 14%[15] and 20%.[17] Observational studies included in the meta-analysis reported a slightly lower rate of intraoperative air-leakage ranging from 1.2% to 18.8%, although detection of leaking anastomosis did not prevent from AL in some cases.[16,18–26] The rate of AL in the study group was 0% to 10% compared with 1.5% to 12.1% in the control group. The biggest included study by Allaix et al[18] reports that 5% of included patients had a change in a surgery plan due to positive testing. Seventy percent of these patients received protective ostomy, while 30%—reinforcement of anastomosis, with great results as none of them developed AL. AL still occurred in 2.5% of the patients without intraoperative air-leakage but was notably higher in the controls (5.8%) without any testing at all.[18] Schmidt et al[20] tested the integrity of the anastomoses by IOE plus air-leak followed by blue stained saline test and reported an even higher rate (10%) of AL in rectal cancer patients with normal findings at testing. From those with positive tests, the stained saline compared with the air-leakage had a higher proportion of the AL (10.4% vs 6.9%).[20]

Lanthaler et al[21] and Shibuya et al[26] trials showed the most controversial results, with OR of 1.36 (95% CI, 0.24–7.74) and 2.08 (95% CI, 0.26–16.62), respectively, raising doubts about the efficacy and safety of intraoperative testing for the reduction of the AL (Fig. 2). However, these studies included fewer participants, providing only 6.9% and 5.4% of the weight on the total results of the meta-analysis. Contrarily, Yang et al[25] and Allaix et al[18] trials with considerable weights, (14.2% and 14.5%, respectively), showed a significant difference, 0.32 (95% CI, 0.15–0.70) and 0.42 (95% CI, 0.20–0.90), between the groups with the superiority of anastomosis integrity testing in reducing AL.[18,25] Similarly, Beard et al[15] and Ivanov et al[17]—both randomized controlled trials—confirmed a greater advantage of intraoperative endoscopy and air-leak testing.[25]

The pooled analysis with a total OR value—0.52 (95% CI, 0.34–0.82)—revealed that intraoperative tests to evaluate the integrity of anastomosis (and anastomotic reinforcement, if applicable) were associated with a lower AL rate after lower gastrointestinal tract resection. The difference was statistically significant ($P < .001$), and there was no significant heterogeneity among the studies ($\chi^2 = 9.49$; degrees of freedom = 11; $P = .58$; $I^2 = 0$). Additionally, we performed sensitivity analyses on the results of each trial and overall meta-analysis results (Supplemental Digital Content (Table, SDC 4, http://links.lww.com/MD/F215). Higher sensitivity was seen in RCTs compared with non-RCT trials with an exception of Lieto et al[23] observational prospective study with a relatively high sensitivity of 0.75. Shibuya et al[26] trial showed low sensitivity of 0.13, though the study was not excluded from the meta-analysis due to additional non-statistical input, presenting intraoperative colonoscopy as not only a method to reduce the AL, but also the one which is irreplaceable in certain cases, for example, bleeding.

3.3. Intraoperative tests to evaluate the perfusion of anastomosis

Eleven studies, involving 3328 patients, were included in the meta-analysis[27–37] (Table 2). Included trials compared the rate of AL according to, whether intraoperative tests evaluating the perfusion of anastomosis (with anastomotic reinforcement or change in the resection margin, if applicable) were performed or not (Fig. 3). The use of indocyanine green fluorescence angiography (ICG-FA) with or without an air-leak test and its

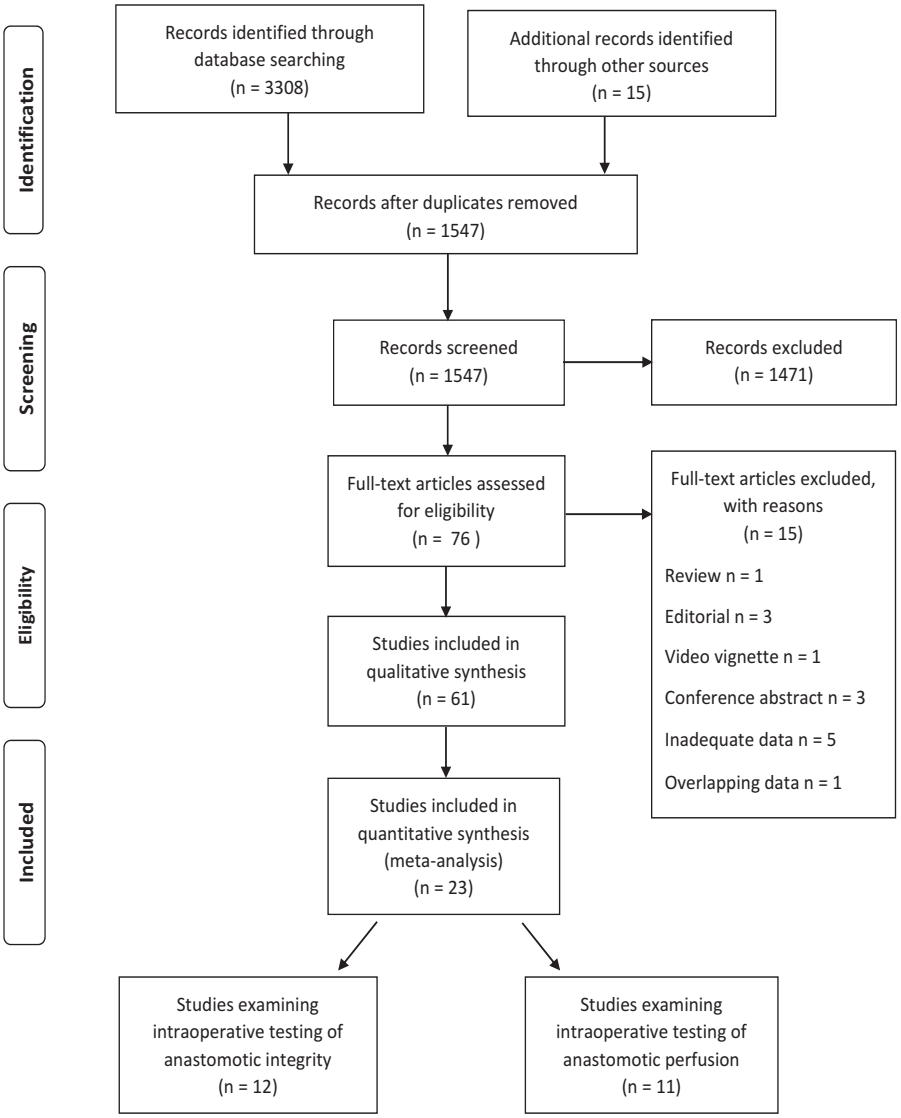

Figure 1. Flow diagram indicating selection of studies for the meta-analysis.

impact on the rate of AL were investigated. In total, these studies included 1680 patients in the control and 1648 patients in the study group undergoing colorectal surgery.

Among these trials, the rate of AL in the study group was 0% to 7.5% compared with 1.3% to 18% in the control group. 4.6% to 19% of patients had a change in the resection margin based on the results of the ICG-FA (Table 2).

The most significant input in this meta-analysis was provided by Watanabe et al.[37] This propensity score-matched cohort study created the largest statistical weight of 16% with OR value of 0.43 (95% CI, 0.20–0.93), favoring the intraoperative assessment of anastomosis perfusion in lowering the AL rates after lower gastrointestinal tract resections. Kin et al[29] and Dinallo et al[35] studies, though showing the equivocal effects of testing and non-testing in reducing the AL rates (1.20 [95% CI, 0.52–2.75] and 1.03 [95% CI, 0.23–4.63]), were included in the meta-analysis due to not statistical additional significance. Kin et al[29] trial was the first to explore the role of ICG-FA in improving outcomes in colorectal surgery. Similarly, Dinallo et al[35] trial presented the new North American experience.

By consolidating the available data, we could see a major decrease of the AL with the use of ICG fluorescence angiography from (6.0% (101/1680) in the control group to 2.7% (44/1648) in the study group.

Table 1

Studies investigating tests to evaluate the integrity of the anastomosis in the lower gastrointestinal tract.

Author; (publish date; study type)	Quality assessment (RoB 2.0 / Newcastle-Ottawa score)	Study group size (n)	Control group size (n)	Type of surgery (open/ laparoscopic/ robotic)	Anastomotic technique (stapled/hand-sewn/both)	Elective/ emergency surgery	Intraoperative test used	Positive test	AL rate study group	AL rate control group	*P* value
Beard et al[15] (1990; RCT)	Low risk	73	70	Open	CR; Both	Both	IOE + air-leak	25%	4%	14%	.043
Ricciardi et al[16] (2009)	8/9	825	173	Open/ laparoscopic	CR/ enterocolic/ enterorectal; Both	Both	IOE + air-leak	7.9%	3.8% (negative test) 7.7% (positive test)	8.1%	<.03
Ivanov et al[17] (2011; RCT)	Some concerns	30	30	Open/ laparoscopic	CR; Stapled	Elective	Air-leak	23%	10%	20%	n.s.
Allaix et al[18] (2018)	8/9	398	379	Laparoscopic	CR; Stapled	Elective	Air-leak	5%	2.5%	5.8%	.025
Sakanoue et al[19] (1993)	8/9	35	35	Open	CR; Stapled	Both	IOE + air-leak	5.7%	0%	11.4%	<.05
Schmidt et al[20] (2003)	8/9	260	36	Open	CR; Stapled	–	IOE + air-leak + blue-tinged saline	18.8%	10%	11.1%	–
Lanthaler et al[21] (2008)	8/9	73	49	Laparoscopic	CR; Stapled	Elective	IOE + air-leak	6.8%	5.4%	4.0%	n.s.
Li et al[22] (2009)	8/9	107	137	Laparoscopic	CR/enterorectal; Stapled	Elective	IOE + air-leak	2.8%	0%	1.5%	–
Lieto et al[23] (2011)	8/9	56	68	Open	CR; Stapled	Elective	IOE + air-leak	10.7%	3.6%	10.2%	–
Shamiyeh et al[24] (2012)	8/9	85	253	Laparoscopic	CR; Stapled	Elective	IOE + air-leak	2.4%	1.2%	1.6%	n.s.
Yang et al[25] (2017)	7/9	215	215	Open/ laparoscopic/ robotic	CR; Stapled	Elective	IOE + air-leak vs. air-leak	4.7%	4.2%	12.1%	.004
Shibuya et al[26] (2019)	7/9	162	23	Open/ laparoscopic	CR; Stapled	–	IOE + air-leak	1.2%	8.6%	4.3%	n.s.

AL = anastomotic leakage, CR = colorectal, IOE = intraoperative endoscopy, n.s. = non-significant.

Overall, the combined OR value was 0.40 (95% CI, 0.22–0.75), implying that the use of intraoperative ICG-FA was associated with a lower incidence of AL in the lower gastrointestinal tract anastomosis. The difference was statistically significant ($P < .001$). According to our set limits of considered heterogeneity, it could be described as low heterogeneity ($\chi^2 = 13.53$; degrees of freedom = 10; $P = .20$; $I^2 = 26$).

Similarly, we calculated sensitivities for experimental groups (Supplemental Digital Content [Table, SDC 5, http://links.lww.com/MD/F216]). Starker et al,[33] Kudszus et al,[27] and Dinallo et al[35] studies showed the highest, while Watanabe et al,[37] Kin et al,[29] and Kim et al[30]—the lowest (or not expressible) sensitivity values. Moreover, 1.00 sensitivity can be considered as false positive. Nevertheless, the latter studies were included in the meta-analysis due to the above mentioned non-statistical contribution. The overall sensitivity was 0.69.

3.4. Assessment of publication bias

We performed the funnel plot analysis for the outcomes and observed no obvious asymmetry (Fig. 4). We concluded that overall, there was no evidence of significant bias about these outcomes in the included trials and our results can be described as statistically reliable.

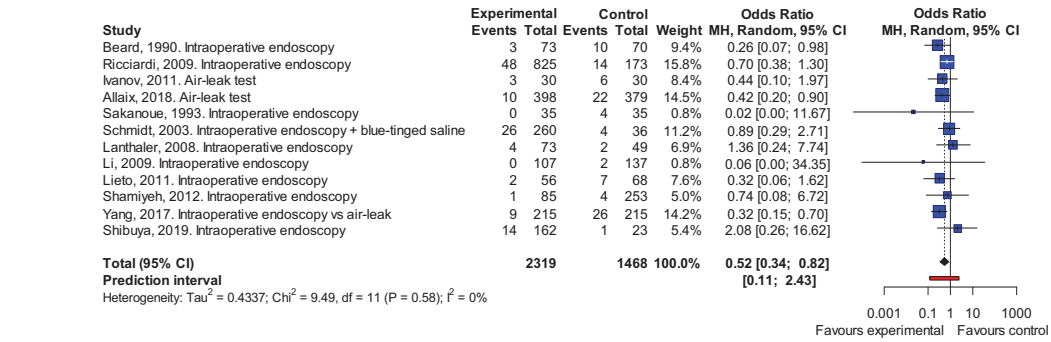

Figure 2. Forest plot showing odds ratios (OR) for AL following lower gastrointestinal surgery in experimental (intraoperative testing of anastomosis integrity and anastomosis reinforcement, if applicable) versus control (non-testing) group. AL = anastomotic leakage.

Table 2

Studies investigating tests to evaluate the perfusion of the anastomoses in the lower gastrointestinal tract.

Author; (publish date; study type)	Quality assessment (Rob 2.0 /Newcastle-Ottawa score)	Study group size (n)	Control group size (n)	Type of surgery (open/laparoscopic/ robotic)	Anastomotic technique (stapled/hand-sewn/both)	Elective/ emergency surgery	Intraoperative test used	Positive test	AL rate study group	AL rate control group	*P* value
Kudszus et al[27] (2010)	8/9	201	201	Both	Entero-colic/colo-colic/CR; Both	Both	ICG-FA	13.9%	3.5%	7.5%	-
Jafari et al[28] (2013)	8/9	16	22	Robotic	CR; Stapled	Elective	ICG-FA + air-leak	19%	6%	18%	-
Kin et al[29] (2015)	9/9	173	173	Open/ Laparoscopic	Colo-colic/CR/Colo-anal; stapled	Elective	ICG-FA	4.6%	7.5%	6.4%	n.s.
Kim et al[30] (2017)	7/9	310	347	Robotic	CR; Both	–	ICG-FA + air-leak	–	0.6%	5.2%	.006
Boni et al[31] (2017)	9/9	42	38	Laparoscopic	CR/ Colo-anal; Both	Elective	ICG-FA	4.7%	0%	5.3%	n.s.
Mizrahi et al[32] (2018)	8/9	30	30	Laparoscopic	CR/Colo-anal; Stapled	Elective	ICG-FA	13.3%	0%	6.7%	n.s.
Starker et al[33] (2018)	8/9	238	109	Open / Laparoscopic	Entero-colic/ Colo-colic/ CR; -	Elective	ICG-FA	4.6%	0.8%	5.5%	.004
Brescia et al[34] (2018)	9/9	75	107	Laparoscopic	Entero-colic/ Colo-colic/ CR; Stapled	Elective	ICG-FA	6.6%	0%	5.6%	.03
Dinallo et al[35] (2019)	7/9	234	320	Open/ Laparoscopic/ Robotic	Entero-colic/ Colo-colic/ CR; -	–	ICG-FA + air-leak	5.6%	1.3%	1.3%	n.s.
de Nardi et al[36] (2019; RCT)	Low risk	118	122	Laparoscopic	CR, colo-anal; Stapled/manual	–	ICG-FA + air-leak	11%	5%	9%	n.s.
Watanabe et al[37] (2019)	7/9	211	211	Laparoscopic	CR; Stapled	Elective	ICG-FA	5.7%	4.7%	10.4%	.042

AL = anastomotic leakage, CR = colorectal, IOE = intraoperative endoscopy, ICG-FA = indocyanine green fluorescence angiography, n.s. = non-significant.

4. Discussion

This systematic review and meta-analysis found that intraoperative testing of the mechanical integrity and the perfusion of anastomosis are significantly associated with a reduced rate of postoperative AL following colorectal surgery.

4.1. Tests to evaluate the mechanical integrity of the anastomosis

Overall, any of the above-mentioned methods can identify some leaking anastomosis intraoperatively. Unfortunately, some AL still occur even after reinforcement. This is especially true in cases of stapled leaking anastomoses, where reconstruction or diversion is the safer method of action. Negative intraoperative tests reduce the risk but do not completely prevent AL. There is also a lack of studies with properly selected controls to conclusively answer what is the real benefit of each test and which is the best. Air-leak and methylene blue tests through the Foley catheter are cheaper and easier to perform compared with IOE.[38] Moreover, some clinicians warn of the danger of powerful air insufflation using IOE, causing mechanical disruption of the staple lines, thus creating a high false-positive air-leak rate and even increasing the rate of AL itself.[19] However, the mean of the maximal pressure during IOE in humans is about only 42 mmHg, while at least 2-fold higher pressure is necessary to cause the leakage in experimental large animal studies.[39] Also, only IOE can identify some other—rare, but threatening intraoperative complications as intensive anastomotic suture-line bleeding or others.[34] Therefore, technically more challenging

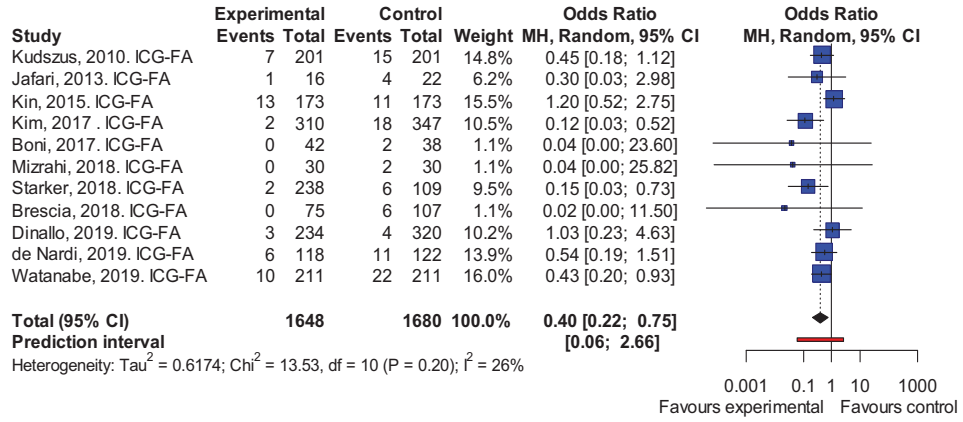

Figure 3. Forest plot showing odds ratios (OR) for AL following lower gastrointestinal surgery in experimental (intraoperative testing of anastomosis perfusion and anastomosis reinforcement or change in the resection margin, if applicable) versus control (non-testing) group. AL = anastomotic leakage.

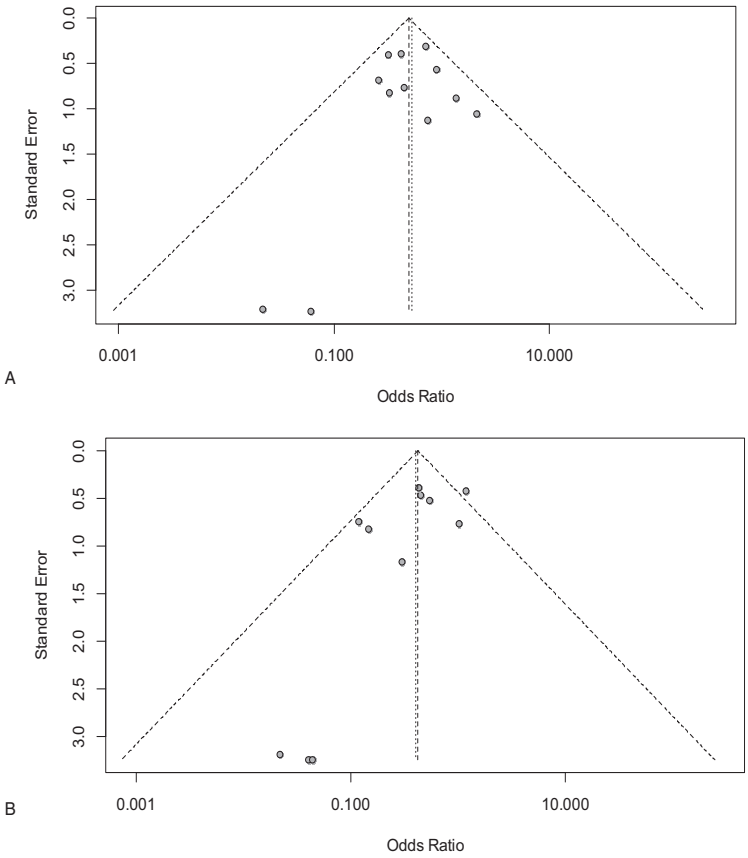

Figure 4. Funnel plots for visual inspection of publication bias. Each point represents a standardized comparison of a separate study, comparing the outcome effect (odds ratio) with the standard error. (A) Intraoperative testing of the anastomosis integrity compared with the control group; (B) intraoperative testing of the anastomosis perfusion compared with the control group.

and more expensive IOE may be a better alternative to air-leak and methylene blue tests.

4.2. Tests to evaluate the perfusion of the anastomosis

We identified 11 studies that have a control group and directly analyzed the impact of ICG-FA testing on the rate of AL.[27–37] This technique creates the possibility to identify high-risk patients who may benefit from a change in the surgical plan, where the anastomotic technique is tailored to the individual patient or even delayed by creating ostomies. However, the main drawback of application of ICG-FA in colorectal surgery is a lack of objective criteria to determine sufficient or insufficient perfusion. Some attempts to create an objective system exist. For instance, Protyniak et al[40] proposed a technique that measures the color intensity of the bowel during the ICG-FA, while Wada et al[41] suggested to measure how fast the color intensity reaches its maximum. Until these techniques are standardized, more and higher quality evidence from a larger scale studies is necessary. Further research to develop exact quantitative parameters, which would describe a threshold of adequate perfusion, below which most of the anastomoses will leak, has to be established to adopt ICG-FA in routine clinical practice.

4.3. Strengths of the study

We performed a comprehensive search of the topic and quality assessment of the trial methodology according to the recommendations of the Cochrane Collaboration. Only trials with a control group were included in the meta-analysis. The number of participants was comparatively large. All studies were looking at colonic or rectal resections with primary anastomosis. All results were statistically significant with not significant or low heterogeneity among the studies. There was no evidence of significant selection or outcome bias in the included trials.

4.4. Limitations

Most of the studies were retrospective, only a few were observational prospective, and only 2 RCTs in the anastomosis integrity testing group and 1 RCT in the anastomosis perfusion testing group were included. We did not include non-English

trials due to resource constraints and lack of policy relevance outside English-speaking countries. This could have hindered the efforts to avoid bias in review and meta-analysis. Moreover, due to low numbers of RCTs we mixed them together with other study types. Also, some of the studies showed relatively low sensitivity, though were not excluded due to additional non-statistical input. Trials looking both at resections due to colorectal cancer, and, at benign colorectal surgery were included. The studies examining both open and laparoscopic (or robotic) colorectal resections were included, which may affect the outcomes between the trials. The effect of the surgeon's experience and surgical methods (emergency vs elective, hand-sewn vs stapled anastomosis) on the procedure outcomes is also a concern. Intraoperative tests included different techniques for integrity testing (intraoperative endoscopy with the air-leak test, with or without blue-tinged saline, or air-leak test alone) and perfusion testing (ICG-FA with or without air-leak test), giving additional limitations to the meta-analysis. The study has not looked at the combination of mechanical integrity and perfusion tests. Therefore, prospective randomized controlled trials comparing combined use of intraoperative testing methods in colorectal anastomosis are necessary in the future. Our ongoing study investigates mechanical integrity testing by air-leak and methylene blue in combination with vascular perfusion evaluation by ICG-FA and its impact on AL.[42]

5. Conclusions

Intraoperative testing of both the integrity and the perfusion of anastomosis may reduce the rate of AL following lower gastrointestinal tract resections. Intraoperative endoscopy might be the best available test to check the integrity of anastomosis as it can also reveal other anastomosis-related complications, such as bleeding. ICG-FA seems to be the best method to evaluate perfusion of the anastomosis in the nearest future. Studies examining the combination of both mechanical integrity (intraoperative endoscopy) and perfusion (ICG-FA) tests, preventing the occurrence of the same complication through different pathways, may be very promising to further reduction of the postoperative anastomotic leaks.

Author contributions

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4th publication / 4 publikacija

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Experimental Study of Mechanical Integrity Testing in Stapled Large Bowel: Methylene Blue Leak Test Is Not Inferior to Air Leak Test

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Keywords
Colon · Anastomosis · Stapling · Anastomotic leak · Porcine colon · Air leak test · Methylene blue test

Abstract
Background/Objectives: Anastomotic leakage remains the most devastating postoperative complication in colorectal surgery. The mechanical integrity of the newly formed colorectal anastomosis can be evaluated by visual inspection intraoperatively; both air leak and liquid leak tests are also used to evaluate the integrity of stapled colorectal anastomoses. It is not clear whether double-stapled anastomoses are more prone to leaks than single-stapled anastomoses. The aim of our study was to compare the methylene blue and the air leak test in the experimental setting of single-stapled and double-stapled porcine bowels. ***Methods:*** Twenty-four distal colons were excised from slaughtered pigs without delay. The proximal bowel end was closed with a linear stapler using blue cartridges. The bowels were randomly divided into single-stapled or double-stapled groups. Air leak and methylene blue leak tests were performed. A digital pressure monitor with a gradual pressure increase function was used to both gradually increase pressure within the bowel and to determine the pressure at which the stapler line disintegrated. ***Results:*** Air leakage occurred at a mean pressure of 51.62 (±16.60) mm Hg and methylene blue leakage occurred at 46.54 (±16.78) mm Hg ($p = 0.31$). The air and methylene blue leaks occurred at comparable pressures in single-stapled bowels and in double-stapled bowels (47.21 [±14.02] mm Hg vs. 50.96 [±19.15] mm Hg, $p = 0.6$). ***Conclusions:*** The methylene blue solution leak test is not inferior to the air leak test. There is no significant difference in bursting pressure between single-stapled and double-stapled anastomoses.

Introduction

Anastomotic leakage (AL) remains the most devastating postoperative complication in colorectal surgery. It results in significant morbidity and mortality, prolonged hospital stay, and increased costs and demands on health services [1, 2]. There is an inevitable interplay between patient physiology and technical factors that predispose a patient to AL occurrence [3]. The AL rate after anterior resection varies considerably among published reports and ranges from 3 to 23% [4].

The anastomotic technique plays an important role in AL rates [5]. Most of the low colorectal anastomoses are stapled, as suturing in the low pelvis is difficult or even

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Fig. 1. Double-stapled colon.

impossible. Adequate blood supply of the bowel ends, as well as tension-free and mechanically impermeable (water-tight) anastomoses, are prerequisites for good anastomotic healing. The mechanical integrity of a newly formed colorectal anastomosis can be evaluated by visual inspection intraoperatively; however, this is impossible in most low colorectal anastomoses.

An air leak test of mechanical integrity was proposed immediately after the first description of stapled colorectal anastomosis [6]. It remains the test of choice for an overwhelming majority of surgeons who test anastomoses. Other tests, such as intraoperative sigmoidoscopy (which could also be described as a type of air leak test) and the methylene blue leak test, are occasionally being used [7–14]. We found 5 studies where the mechanical integrity of colorectal anastomosis was checked by methylene blue, Patent Blue dye, or intraluminal saline [11, 12, 15–17]. Our own recent experience suggested that the methylene blue leak test was positive in 20% of patients after a negative air leak test [18]. This was seen mostly in the area of intersection of two staple lines.

The aim of our study was to compare the methylene blue and the air leak test in the experimental setting of single-stapled and double-stapled porcine bowels.

Materials and Methods

Twenty-four distal colons were excised from slaughtered pigs without delay. All further manipulations were performed within 20 min from excision to prevent tissue degradation. All specimens were randomly divided into four groups. The proximal large bowel edge was separated from the mesentery at the stapler transection point. The proximal bowel end was closed with a linear stapler using blue cartridges (ECHELON FLEX GST, Ethicon, 60 mm blue reload with gripping surface technology, closed –1.5 mm, open –3.6 mm, 60 mm staple line). Each bowel was compressed for 15 s using the stapler.

The bowels were randomly divided into single-stapled or double-stapled groups. The proximal end was closed with a single cartridge or with two cartridges (Fig. 1), depending on the group. Therefore, single-stapled bowels and double-stapled bowels were created. The flowchart of the study is presented in Figure 2.

After that, air leak and methylene blue leak tests were performed. The experimental model described by Schwab et al. [19] for bursting strength measurement was used. A digital pressure monitor with a gradual pressure increase function (BioTek® Instruments, Inc.) was used to both gradually increase pressure within the bowel and to determine the pressure at which the stapler line disintegrated.

A Foley catheter was introduced intraluminally from the distal end. After that, the distal end was occluded around the catheter to prevent the escape of air or methylene blue solution. The bowels were submerged in water to identify leaks. The Foley catheter was connected to the water-tight container. A 0.9% sodium chloride solution, dyed with methylene blue, was used to test the bursting strength of half of the stapled bowels in the experiment. A water-tight container filled with air was used for the other half of the stapled bowels in the experiment. The water-tight container was attached to the digital pressure monitor with the gradual pressure increase function. The pressure within the container was increased gradually by 4 mL with each stroke of airflow until leakage of air or of methylene blue dye was noted. The pressure at which the leak occurred was recorded.

In order to ascertain whether different pressures are generated within the bowel by injecting the same quantity of methylene blue and air, the experimental system was modified by adding an additional Foley catheter at the free end of the bowel and connecting it to a syringe. A digital pressure manometer was used only to measure the pressure within the lumen of the bowel. The first round of testing included 400 mL of air injection into the bowel. The second round of measurement on the same bowel was performed using 400 mL of methylene blue solution. During both tests, the maximum pressure achieved was recorded.

Statistical Analysis

Statistical analyses were performed using the R statistical software package version 3.6.1 (© The R Foundation for Statistical Computing), RStudio version 1.2.1335 (© 2009–2019; RStudio, Inc.), IBM SPSS Statistics version 23, and G*Power version 3.1.9.4 (Universität Düsseldorf, Germany).

Interval and ratio variables are described by means and SD, medians, and median absolute deviations (MAD), as well as first (Q1) and third (Q3) quartiles. The Shapiro-Wilk test was used to check for data normality. The statistically significant relationship between two independent groups was tested using the Mann-Whitney U test. Once, statistically significant dependencies between groups were determined for rank variables, or when the normality assumption for our data was not satisfied. The Spearman correlation coefficient and Cliff's delta effect size were used to assess the strength of the relationships. The effect size of the Kruskal-Wallis, Mann-Whitney, or Wilcoxon test was calculated using the Rosenthal (1994) formula (Cohen's *d* alternative). Hedges' *g* is recommended rather than Cohen's *d* effect size for very small sample sizes (<20).

Boxplots (left sides of the figures) were used for graphical comparison of the data. In addition, the means in the groups and the overall mean (longer dash) are shown on the right side of the figures.

The relationship between groups was rated as statistically significant when the p value was <0.05 and the power of the statistical tests was $1 - \beta = 0.95$.

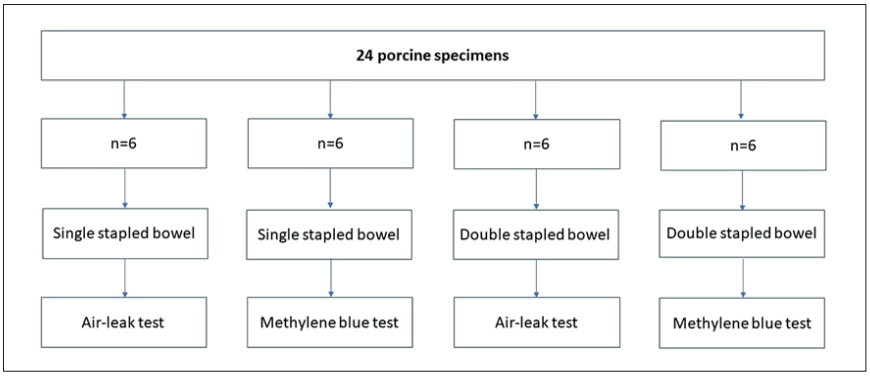

Fig. 2. Experimental study flowchart.

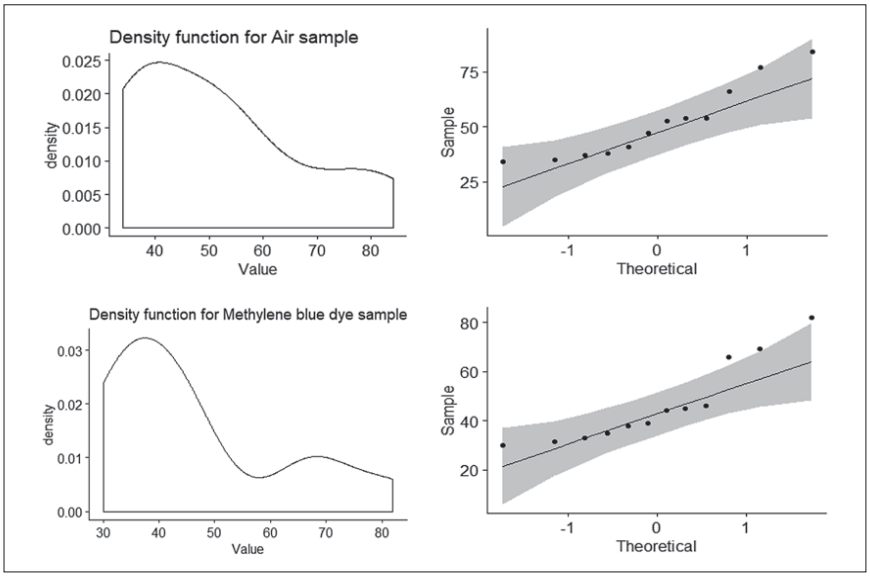

Fig. 3. Histograms (left) and Q-Q plots (right) for the air and methylene blue dye groups.

Results

Thirty-six stapler cartridges were used to create 24 experiments: 12 in the single-stapled and 24 in the double-stapled groups. All 24 experiments were successful. The differences between air leak and methylene blue leak pressures are presented in Figures 3 and 4 and in Table 1. The Shapiro-Wilk normality test result for air samples was W = 0.89, $p = 0.1$ (>0.05), and that for methylene blue dye samples was W = 0.85, $p = 0.03$ (<0.05).

A p value >0.05 implies that the distribution of the data is not significantly different from the normal distribution. In other words, we can assume normality. However, we can see from the graph (especially from the density graph; Fig. 3) that the condition of normality is not satisfied. The differences in stapled bowel bursting pressures between the methylene blue leak and the air leak test group are presented in Figure 4 and Table 1.

The observed difference between the two methods in detecting stapled bowel leaks was not statistically signifi-

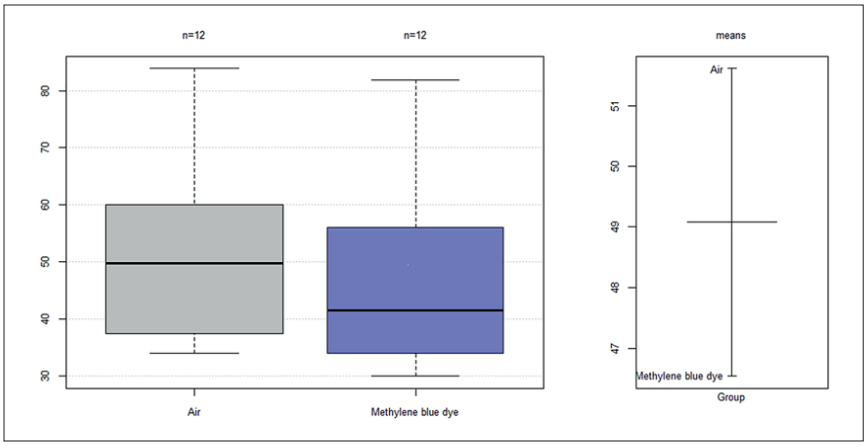

Fig. 4. Box plots of bowel bursting pressure (mm Hg) in the air leak and methylene blue leak test groups.

Table 1. Descriptive and quantitative statistics for stapled bowel bursting pressure (mm Hg) in the methylene blue leak and air leak test groups

	Air leak test group	Methylene blue leak test group
Mean (SD)	51.62 (16.60)	46.54 (16.78)
Median (MAD)	49.75 (18.16)	41.50 (11.12)
[Q1;Q3]	[37.00;54.00]	[33.00;46.00]
[Min.;max.]	[34.00;84.00]	[30.00;82.00]
p value (Mann-Whitney U test)	0.312 No statistically significant dependence was found	
Spearman's correlation coefficient/*p* value	0.653 No statistically significant correlation was found	
Cohen's *d* effect size	0.3044	
Hedges' *g* effect size	0.2941	
Cliff's delta effect size	0.2431	
Rosenthal effect size	0.2087	

cant. The effect size can make up for the weak point by providing information on the actual effect, which is independent of the sample size. In our case, we had a clinically significant – though small – dependency. The same can be said about the correlation coefficient. We calculated that if the same difference between the groups persisted, it would be significant with a sample size of 299, as calculated by the Rosenthal (1994) power size.

The differences between air leak and methylene blue leak pressures in single-stapled bowels are presented in Table 2 and Figure 5. The differences between air leak and methylene blue leak pressures in double-stapled bowels are presented in Table 3 and Figure 6. Overall, we found that the methylene blue leak test was not inferior to the air leak test.

Four additional bowels were used to test the pressure created by injection of air and methylene blue solution. There were no significant differences between created pressures after injecting 400 mL of air or methylene blue solution into the leak-proof system (Table 4; Fig. 7).

We found that there was no significant difference in burst pressure between single-stapled and double-stapled anastomoses (47.21 [±14.02] mm Hg vs. 50.96 [±19.15] mm Hg, $p = 0.6$). The comparison of bursting pressures between single-stapled and double-stapled bowels is presented in Figure 8.

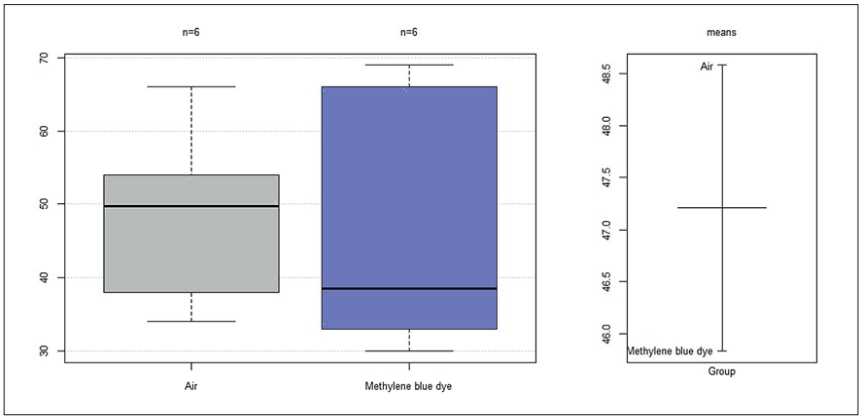

Fig. 5. Box plots of air leak and methylene blue pressure (mm Hg) in single-stapled bowels.

Table 2. Descriptive and quantitative statistics for bowel leak pressures (mm Hg) in single-stapled bowels

	Air leak test group	Methylene blue leak test group
Mean (SD)	48.58 (11.62)	45.83 (17.13)
Median (MAD)	49.75 (11.86)	38.50 (10.38)
[Q1;Q3]	[38.00;52.50]	[33.00;39.00]
[Min.;max.]	[34.00;66.00]	[30.00;69.00]
p value Mann-Whitney U test	0.630 No statistically significant dependence was found	
Spearman's correlation coefficient/*p* value	0.222 No statistically significant correlation was found	
Cohen's *d* effect size	0.1879	
Hedges' *g* effect size	0.1734	
Cliff's delta effect size	0.1667	
Rosenthal effect size	0.1391	

Based on our data, methylene blue solution leakage occurs at least at the same and possibly at a lower pressure than air leakage; thus, the methylene blue leak test is not inferior to the air leak test. Double-stapled bowels may be more resistant to pressure increases than single-stapled bowels.

Discussion

We compared the air leak and the methylene blue leak test in the experimental setting of single-stapled and double-stapled porcine bowels. We found that the methylene blue solution leak test is not inferior to the air leak test in detecting leaks, even showing a tendency towards lower pressure; therefore, both methods are comparable. We also discovered that bursting pressures do not differ statistically significantly between single-stapled and double-stapled anastomoses.

It is important to note that liquids and gases have different physical properties. The two most dominant factors contributing to the different leaking properties are viscosity and surface tension. The leakage of liquids is governed by the viscosity of the liquid. The higher the viscosity of the liquid, the more slowly will it leak through a particular hole. The viscosity of a gas is generally much lower than that of a liquid. The viscosity of air, for example, is roughly 50 times lower than that of water. This means that if we consider the influence of viscosity only, a particular leak that passes 20 mm^3 of air per second would only pass 0.4 mm^3 of water per second. The surface tension sets a limit to how small a leak can be and still pass

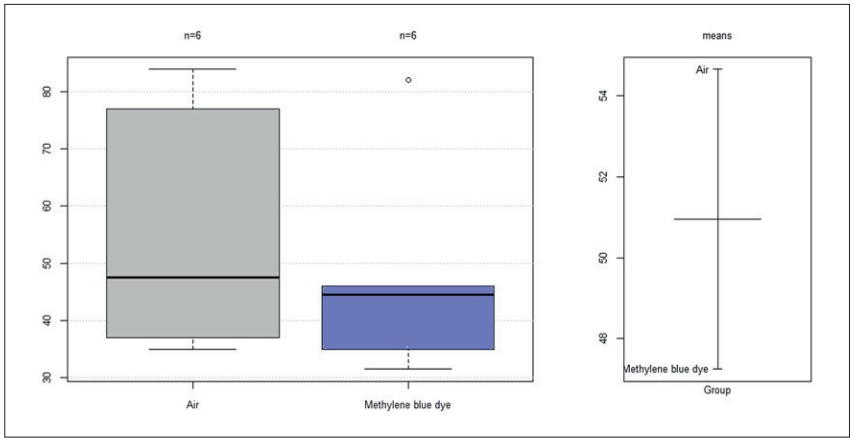

Fig. 6. Box plots of air leak and methylene blue leak pressure (mm Hg) in double-stapled bowels.

Table 3. Descriptive and quantitative statistics for bowel leak pressures (mm Hg) in double-stapled bowels

	Air leak test group	Methylene blue leak test group
Mean (SD)	54.67 (21.19)	47.25 (18.02)
Median (MAD)	47.50 (17.05)	44.50 (8.15)
[Q1;Q3]	[37.00;54.00]	[35.00;45.00]
[Min.;max.]	[35.00;84.00]	[31.50;82.00]
p value Mann-Whitney U test	0.575 No statistically significant dependence was found	
Spearman's correlation coefficient/*p* value	0.282 No statistically significant correlation was found	
Cohen's *d* effect size	0.3771	
Hedges' *g* effect size	0.3481	
Cliff's delta effect size	0.1944	
Rosenthal effect size	0.1619	

water (or another liquid). The actual size of the "limit" leak depends on a large number of properties such as pressure, temperature, material, and the shape of the leak and can therefore not be theoretically calculated [20, 21]. However, our study seems to show that methylene blue dye passes through small defects in the staple line with the same reliability as does air.

The main strength of this study is that porcine colons, which are very similar to human colons, were used [22]. Moreover, this experiment was conducted immediately after each colon had been removed to prevent ischemic tissue degradation. Another benefit was that we used a validated experimental model developed in previous studies [19]. The main difference from earlier experiments was that we compared air to methylene blue solution and included in the analysis single-stapled versus double-stapled bowels, but not circularly stapled anastomoses of two bowel ends.

Nevertheless, our study has some weaknesses. It must be taken into consideration that the ex vivo model that was used in this study may be less hydrated than an in vivo model with no blood circulation.

Current studies show that the degree of mucosal capture differs between staplers. Leaks in stapled bowels occur at a point where mucosal capture is poor [21]. Uncaptured mucosa may represent a source of intraluminal bleeding in live tissue. Poor mucosal capture may also expose the submucosa to more luminal contents including bacteria. Different studies have linked luminal bacteria to intestinal anastomotic failure [19]. In practice, we

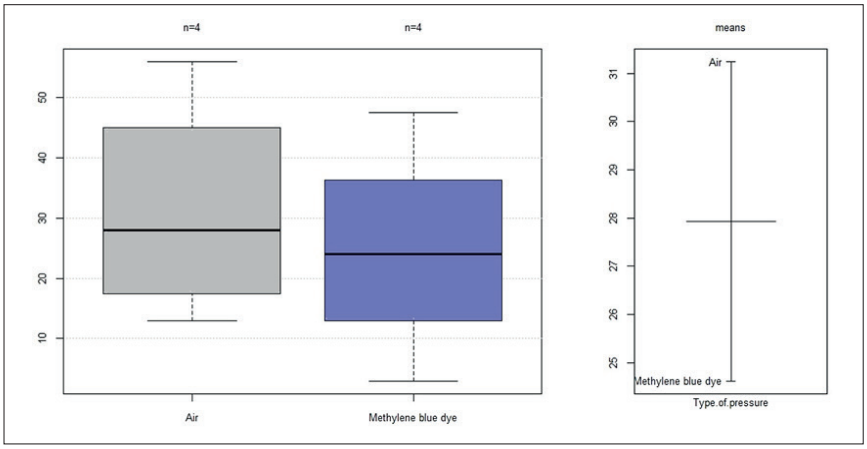

Fig. 7. Pressures (mm Hg) created by air and methylene blue solution.

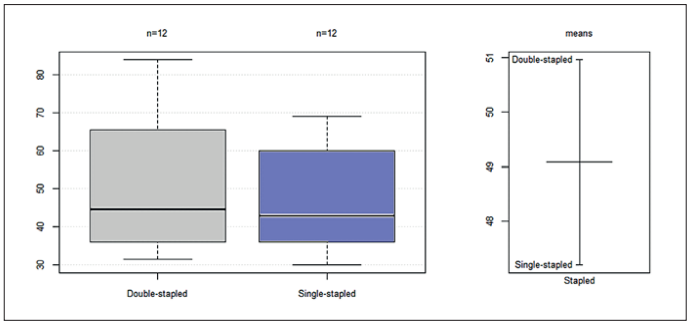

Fig. 8. Box plots of bursting pressures (mm Hg) of single- versus double-stapled bowels.

Table 4. Descriptive and quantitative statistics for pressures (mm Hg) created by air and methylene blue insufflation

	Air	Methylene blue solution
Mean (SD)	31.25 (18.61)	24.62 (18.20)
Median (MAD)	28.00 (15.57)	24.00 (16.31)
[Q1;Q3]	[13.00;34.00]	[3.00;25.00]
[Min.;max.]	[13.00;56.00]	[3.00;47.50]
p value Mann-Whitney U test	0.773 No statistically significant dependence was found	
Spearman's correlation coefficient/*p* value	0.137 No statistically significant correlation was found	
Cohen's *d* effect size	0.36	
Hedges' *g* effect size	0.313	
Cliff's delta effect size	0.125	
Rosenthal effect size	0.1022	

perform both air leak and methylene blue leak tests to check the mechanical integrity of colorectal anastomosis [18, 23]. First, we perform air leak testing of the newly formed anastomosis. Saline fluid is filled into the low pelvis and air is injected through the rectum in order to check the integrity of the anastomosis. After that, the saline is removed, and the solution, dyed with methylene blue, is injected through the anus to check the mechanical integrity of the anastomosis too. Our study differs from surgical practice in that the methylene blue test was done underwater, whereas in practice it is usually performed in atmospheric air (open surgery) or under CO_2 pressure (laparoscopic surgery).

It is current practice to check the mechanical integrity of a colorectal anastomosis by standard air leak test, insufflating air through a drain or Foley catheter. Also, some authors present intraoperative sigmoidoscopy as a method of checking the mechanical integrity of a colorectal anastomosis. We found two randomized controlled trials which presented a positive intraoperative endoscopy test for 23.2–25% of the patients. Postoperative AL occurred in 4–10% of the patients despite correction of insufficient colorectal anastomosis [7, 24]. Ricciardi et al. [25] found positive intraoperative air leak test results in 7.9% of the tested anastomoses. Postoperative AL occurred in 7.7% of the anastomoses with a positive air leak test result, compared to 3.8% of the anastomoses with a negative air leak test result. The postoperative AL rate was 8.1% for the untested anastomoses. Another study confirmed similar results. Allaix et al. [26] tested anastomoses by standard air leak test and found positive test results for 5% of the patients. The rate of postoperative AL was significantly lower in the study group than in the untested anastomoses (2.5 vs. 5.8%; $p = 0.025$). Moreover, no postoperative AL occurred in the patients with a positive air leak test result. Schmidt et al. [8] tested the mechanical integrity of anastomoses in combination with intraoperative endoscopy followed by a blue-stained saline test. The rate of postoperative AL after a negative test was 10.3%. These findings might be similar to those of our experimental study.

We found five studies where the mechanical integrity of colorectal anastomosis was checked by methylene blue, Patent Blue dye, or intraluminal saline [11, 12, 15–17]. Gilbert and Trapnell [15] presented positive intraluminal test results for 24% of their patients, whereas Wheeler and Gilbert [17] found 20.6% of their patients with a positive test result. The postoperative leakage rate was 9.5% in the study by Wheeler and Gilbert [17]. Smith et al. [11] tested colorectal anastomoses with methylene blue dye and found a positive test result for 7% of the anastomoses, with a 3.3% postoperative AL rate. Moreover, there was no detected postoperative AL in patients with positive methylene blue test results. Also Chen et al. [12] found similar results. A positive Patent Blue dye test result was noticed in 14.5% of their anastomoses. The postoperative AL rate was 1.3%. Similar to the Smith study, there was no confirmed postoperative AL in patients with positive intraoperative test results.

The air leak test and the methylene blue test can equally identify insufficient colorectal anastomosis. Nevertheless, there are not enough studies to answer which is the better mechanical integrity test, and they may possibly complement one another.

Conclusions

Our experiment showed that the methylene blue solution leak test is not inferior to the air leak test. Double-stapled bowels and single-stapled anastomoses were equally resistant to pressure increases in our experimental setting.

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Statement of Ethics

The research presented in the paper was conducted ethically in accordance with the World Medical Association Declaration of Helsinki as well as according to animal welfare regulations and was approved by the appropriate institutional review bodies.

Conflict of Interest Statement

The authors declare no conflicts of interest.

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Author Contributions

T.P., E.P., and M.K.: conceptualization; T.P., M.K., and E.J.: methodology; T.P., E.P., and K.S.: validation; E.J.: formal analysis; M.K., V.A., A.E.D., and B.L.: investigation; T.P. and E.P.: resources; T.P., V.A., and A.E.D.: data curation; V.A., A.E.D., M.K., and B.L.: writing – original draft preparation; M.K., T.P., and K.S.: writing – review and editing; V.A.: visualization; E.P., T.P., and K.S.: supervision; E.P., T.P., and K.S.: project administration.

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The problem of colorectal anastomosis safety

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Abstract

Introduction: Anastomotic leakage (AL) remains one of the most threatening complications in colorectal surgery with the incidence of up to 20%. The aim of the study is to evaluate the safety and feasibility of novel – trimodal intraoperative colorectal anastomosis testing technique.

Methods and analysis: This multi-center prospective cohort pilot study will include patients undergoing colorectal anastomosis formation below 15 cm from the anal verge. Trimodal anastomosis testing will include testing for blood supply by ICG fluorescence trans-abdominally and trans-anally, testing of mechanical integrity of anastomosis by air-leak and methylene blue leak tests and testing for tension. The primary outcome of the study will be AL rate at day 60. The secondary outcomes will include: the frequency of changed location of bowel resection; ileostomy rate; the rate of intraoperative AL; time, taken to perform trimodal anastomosis testing; postoperative morbidity and mortality; quality of life.

Discussion: Trimodal testing of colorectal anastomosis may be a novel and comprehensive way to investigate colorectal anastomosis and to reveal insufficient blood supply and integrity defects intraoperatively. Thus, prevention of these two most common causes of AL may lead to decreased rate of leakage.

Study registration: Clinicaltrials.gov (https://clinicaltrials.gov/): NCT03958500, May, 2019.

Abbreviations: AL = anastomotic leakage, EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30, ICG-FA = indocyanine green fluorescence angiography, LARS = low anterior resection syndrome.

Keywords: air-leak test, anastomosis testing, anastomotic leakage, colorectal anastomosis, indocyanine green test, methylene blue test

1. Introduction

Anastomotic leakage (AL) remains one of the most threatening complications in colorectal surgery with the incidence of up to 20%. AL may be a life-threating complication, although, even if it is managed it results in poor oncologic outcomes, prolonged hospital stay and increased health care costs.[1–3]

The etiology of AL is still not fully clear, although, some risk factors have been suggested, including patient and disease related factors as well as surgical technique failure.[4,5] Insufficient blood supply at the proximal or distal ends of anastomosis, tension on anastomosis and insufficient integrity of anastomosis are the main causes of technical failure and they may be modified intraoperatively if detected.[5,6] Various tests to investigate mechanical integrity of anastomosis have been proposed.[7–10] The most common test for colorectal anastomosis is an air-leak test. Some studies suggest saline or methylene blue leak tests alone or in combination with air-leak test as well.[7] Although, these liquid based tests are much more common in gastrointestinal anastomoses and there is a lack of data for colorectal surgery.[7,11–13] Intraoperative colonoscopy is another available method.[8,14] As shown previously all of these tests for mechanical integrity reduce the rate of postoperative AL.[7–10] However, it remains unclear whether some of them may be more accurate than others and which tests should be used. Moreover, negative results of integrity testing do not guarantee uneventful postoperative course.[15] Insufficient blood supply is another well-known factor which is responsible for a postoperative leak of intraoperatively non-leaking anastomosis. Historically, the bowel viability and blood supply were evaluated by the surgeon through visual inspection. The color of the bowel wall, peristalsis

We declare that this study is funded by Vilnius University. The individual data of the patients will remain confidential. The results of this study may be presented at national and international conferences and published.The study is a part of doctoral thesis of M.K. at the Faculty of Medicine Vilnius University. The proctoscope and an additional laparoscopic system with near-infrared fluorescence imaging camera were provided without pay by Karl Storz, Germany. No other financial support was received by any of the authors. All the authors declare that they have no additional conflict of interest.

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of the bowel, pulsation of the marginal artery, or bleeding of the resected bowel margin is considered as clinical indicators of good vascularization.[16] However, this is very subjective, and it does not always properly evaluate the micro-perfusion of the bowel wall. Intraoperative indocyanine green fluorescence angiography (ICG-FA) was proposed as more objective alternative which also accurately evaluates the micro-perfusion. Recently published study demonstrates very promising results for this technique, since AL rate was reduced twofold (3.5% vs 7.4%, respectively, $P = .002$) when ICG was used.[17] Moreover, the usage of ICG in the study lead to change of the bowel resection place in 10.8% of patients.[17] Similarly, De Nardi et al showed insufficient blood supply at the bowel requiring to extend the resection margin in 11% of patients, despite that this randomized controlled trial failed to show significantly reduced AL rate by using ICG.[18] These results are encouraging, but as with isolated mechanical integrity testing, the isolated blood supply testing does not prevent all postoperative AL.

Therefore, we hypothesize that by using trimodal testing for mechanical integrity, blood supply and tension of anastomosis we can comprehensively evaluate anastomosis intraoperatively and to reduce the level of AL to minimum.

2. Methods

2.1. Study setting

This multi-center prospective cohort pilot study will be conducted at the 2 major colorectal surgery centers in Lithuania: Vilnius University hospital Santaros Klinikos and National Cancer Institute. The volume of these centers together is more than 600 colorectal resections annually.

2.2. Eligibility criteria

The study will include patients undergoing elective open or laparoscopic surgery for benign or malignant diseases of left-sided colon or rectum when the colorectal anastomosis will be below 15 cm from the anal verge by the rigid proctoscope. Patients over 18 years willing to participate and signing the informed consent will be included. Exclusion criteria will include the pregnancy and allergy to indocyanine green dye.

2.3. Sample size

Thirty patients will be included in the study since Kieser and Wassmer calculated that a pilot trial sample size between 20 and 40 would minimize the overall sample size for a main study sample size of 80 to 250 participants corresponding to standardized effect sizes of 0.4 and 0.7 (for 90% power based on a standard sample size calculation).[19]

2.4. Preoperative care

Preoperative patients' preparation to surgery protocol will be standardized. Oral antibiotics (erythromycin 400 mg and metronidazole 500 mg) will be given 3 times on the day before surgery as well as oral mechanical bowel preparation. Low molecular weight heparin (nadroparin) will be administered 12 hours prior to surgery, according to patient's body weight. Standard preoperative antibacterial therapy (cefuroxime 1500 mg and metronidazole 500 mg) will be infused 30 minutes prior to incision.

2.5. Surgery and intraoperative testing of anastomosis

Laparoscopic or open colorectal resection will be performed according to standard techniques of the study institutions. Trimodal anastomosis testing for blood supply, tension and mechanical integrity will be performed as shown in Figure 1.

ICG-FA tests will evaluate the micro- and macro-perfusion of the anastomosis at several timepoints.

Two doses of ICG dye will be prepared by diluting 25 mg of VERDYE ICG dye (Diagnostic Green, Aschheim, Germay) in 10 ml of sterile water. The first ICG (12.5 mg/5 ml) dose will be administered intravenously after division of the mesentery just before bowel resection to evaluate blood supply at the planned point of resection. The illumination of clearly visible arterial branches and subsequent illumination of bowel wall tissues will be considered as good perfusion and the resection of the bowel will be performed. If blood supply at planned point will be considered as insufficient the resection margin will be changed to the area of enough perfusion. After second ICG (12.5 mg/5 ml) injection just before anastomosis creation second fluorescence test will be performed just before and immediately after the creation of anastomosis to evaluate the proximal and distal parts of anastomosis.

If any segments of anastomosis will show a poor blood supply, it will be recreated or reinforced. Sometimes anastomosis will be deep in the pelvis and evaluation of the perfusion of anastomosis trans-abdominally is not possible, then n/a will be marked. After the satisfactory results of trans-peritoneal evaluation of perfusion by ICG, the additional trans-anal ICG testing will be performed by the technique described previously.[20] Briefly, RECTOVISION proctoscope (Karl Storz, Tuttligen, Germany) for camera will be used, to ensure adequate trans-anal view air will be insufflated manually. The perfusion of the anastomosis from the mucosal side by fluorescence will be checked circumferentially. If any parts of anastomosis appear under perfused, corrections will be made.

Next, the tension on the anastomosis will be tested visually. We will aim at creating floppy anastomosis, whereby the bowel freely falls into the pelvis. The situation, where the bowel goes straight to the anastomosis but there is no obvious tension will be marked as straight anastomosis. If anastomosis appears to be under tension, corrections will be made.

Afterwards, mechanical integrity of the anastomosis will be tested by standard air-leak test through proctoscope. This will be performed simultaneously with the trans-anal perfusion testing under direct camera vision. The anastomosis should be under irrigation of saline solution in the pelvic cavity. The proximal colon is occluded by placing a soft bowel clamp across the bowel (without mesentery) comfortable distance above colorectal anastomosis. If air-leak test is positive, the leaking part of anastomosis will be reinforced. If leaking part is not identifiable temporary ileostomy will be created. Following air-leak test additional methylene blue leak test will be performed through a 16 French Foley catheter inserted in the anus. The catheter balloon will be inflated to 20 ml, avoiding the stretch of the anastomosis and gently withdrawn to the internal anal sphincter to avoid the spilling of staining solution. The volume of injected staining solution will depend on the height of colorectal anastomosis. This step is performed under direct laparoscopic (or open) vision to avoid stretching of anastomosis. In cases when low colorectal anastomosis will be impossible to visualize trans-abdominally, white gauze will be introduced and positioned

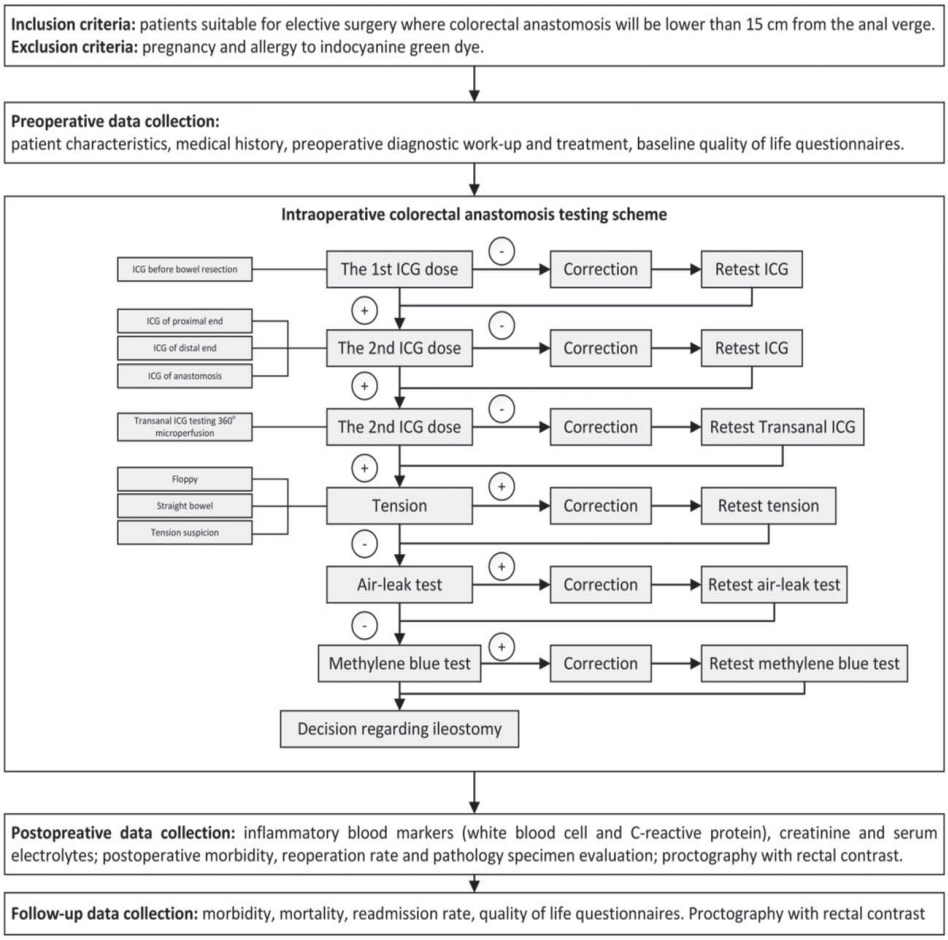

Figure 1. Detailed flowchart of the study.

around anastomosis before dye injection. If methylene blue leak test will be positive the defect in anastomosis will be repaired by reinforcing sutures; the decision to perform diverting ileostomy will be left to the surgeon.

2.6. Postoperative care

Postoperative care of the patients will be as per standard institutional protocol. The patients will be treated under the enhanced recovery after surgery (ERAS) protocol (early nutrition, early ambulation, early removal of catheter, prevention of nausea and vomiting, non-steroidal anti-inflammatory drug analgesia, no nasogastric tubes). The white blood cell count and C-reactive protein tests will be performed on the postoperative days 2, 4 and 6.[21] Creatinine level and serum electrolyte tests will be performed on postoperative days 2 and 6. Proctography with water-soluble rectal contrast enema will be performed to check the integrity of colorectal anastomosis on postoperative day 7 (±1). Digital rectal examination of very low anastomoses, endoscopy or computerized tomography with rectal contrast may be alternatives to evaluate the integrity of anastomosis when proctography will not be feasible.

2.7. Outcomes

The primary outcome of the study will be the AL at 60 days postoperatively. AL diagnosis will be made if clinical or radiological signs will be present. Proctography with water-soluble rectal contrast enema will be performed to check the integrity of anastomosis on postoperative day 7(±1) and 60(±7). In cases where proctography will not be feasible digital rectal examination, endoscopy or computerized tomography with rectal and/or oral contrast will be allowed as alternative methods. Fluid collection or abscess near the colorectal anastomosis will also be considered as AL.[22]

The secondary outcomes will include: the frequency of changed location of bowel resection after ICG testing; ileostomy rate; the rate of intraoperative AL; time, taken to perform trimodal

Table 1

Data collection plan.

	Baseline	Surgery	7 (±1) days postoperatively	60 (±7) days postoperatively
Informed consent	X			
Patient characteristics and medical history	X			
Quality of life questionnaires	X			X
Surgery details		X		
Inflammatory blood markers			X	
Proctography			X	X
Morbidity		X	X	X
Mortality		X	X	X

anastomosis testing; postoperative morbidity and mortality; quality of life.

Quality of life will be assessed using low anterior resection syndrome (LARS) score and European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 (EORTC QLQ-C30 (Version 3) before the operation and at day 60(±7).

3. Data collection and management

All the data will be recorded in a case report form. Data will be collected at preoperatively, intraoperatively, postoperatively during the intrahospital period and after discharge patients will be followed up until day 60. Data collected at various timepoints is shown in Table 1. Intraoperative anastomosis testing checklist used to evaluate the different aspects of the testing is shown in Table 2.

3.1. Trial registration and ethical considerations

The study was approved by Vilnius Regional Bioethics Committee (Approval number 2019/3-116-608) and registered on Clinicaltrials.gov database (NCT03958500) on May 2019. Written informed consent will be obtained from the patients before participation in the study. The trial will be performed guided by World Medical Association's Declaration of Helsinki, Guideline for Good Clinical Practice, and regulatory laws in Lithuania.

Table 2

Checklist of intraoperative colorectal anastomosis testing.

1. Test Before Proximal Bowel Transection	
Point of resection identified	1
2. Tests Before Anastomosis	
Good ICG-FA of proximal end	1
Insufficient blood supply	0
Good ICG-FA of distal end	1
Insufficient blood supply	0
Distal end not visible	N/A
3. Tests After Anastomosis	
Good ICG-FA of colorectal anastomosis	1
Insufficient blood supply	0
Anastomosis not visible	N/A
Good ICG-FA of colorectal anastomosis (trans-anal view)	1
Insufficient blood supply	0
No Tension – Floppy	1
No tension – Straight	0.5
Tension	0
No air-leak	1
Air-leak	0
No methylene blue leak	1
Methylene blue leak	0
Score	

4. Discussion

This pilot study will investigate the safety and feasibility of the comprehensive trimodal intraoperative testing of the blood supply, tension, and mechanical integrity of colorectal anastomosis.

The intraoperative blood supply, tension and mechanical integrity testing reduces the rate of postoperative AL when applied separately.[23] Although, even if anastomosis is tested intraoperatively the rate of AL remains high.[23,24] These 3 tests investigate different potential technical pitfals, therefore, there is a rationale to combine and perform all these tests together. Currently, there is a lack of studies investigating the potency of the multi-modal testing, therefore this study was designed. We hypothesize that trimodal testing will reduce the rate of postoperative AL to the minimal level by avoiding all the leakages due to technical failure and may identify the patients who can safely avoid preventive ileostomy.

Methylene blue leak test will be used for the mechanical integrity testing besides standard air-leak test. This test is cheap, safe and simple method to assess the integrity of anastomosis allowing the surgeon to identify leaking anastomosis at the time of surgery. There are no studies presenting methylene blue test as an additional technique for mechanical integrity testing in colorectal surgery to date and ours will be the first. Only few studies on methylene blue testing alone are published too. Smith et al reported the methylene blue leakage rate of 7% and 3.3% postoperative AL rate.[7] It is important to mention that all postoperative AL happened to patients with negative methylene blue test intraoperatively. The authors concluded that methylene blue is feasible and easier to pinpoint the leak compared to air-leak test. Chen et al also presented similar results with a 14.5% of intraoperative leakage in patients undergoing rectal surgery.[12] It seems, that methylene blue may have an advantage over other leak tests by easier identification of leakage site.[6,8] In addition, the methylene blue testing is very safe, since no untoward effects have been described.[7,11,25]

We do not expect this test to be perfect in preventing leaks completely, it might be associated with reduction of the risk.[7,12,26] The patients might have developed leaks after methylene blue test due to patient factors, insufficient blood supply, anastomotic tension and others.[7,12,27] ITCORA study (ClinicalTrials.gov registry identifier NCT03316677) is the only one which compares air-leak test and methylene blue test.[28]

Nevertheless, this trial is not yet recruiting patients. By testing systematically the mechanical integrity, blood supply and tension of anastomosis we could account for these factors in the development of the leak.

Recently, ICG-FA was shown to reduce the risk of postoperative AL. Nevertheless, the majority of the studies were cohort studies with insufficient level of evidence.[29–32] One of the first observational prospective study was PILLAR II trial by Jafari et al for colorectal anastomosis.[33] The surgical plan was changed in 8% of the patients. The postoperative AL rate was 1.4%, but there were none in the group of patients who had a change in surgical plan based on ICG-FA. After encouraging results, PILLAR III (ClinicalTrials.gov registry identifier NCT02205307) randomized controlled trial was initiated to compare AL rate after standard and ICG-FA based colorectal resection.[34] Unfortunately, PILLAR III study was terminated due to slow recruitment. There is only one published randomized controlled trial presented by De Nardi et al (ClinicalTrials.gov registry identifier NCT02662946).[18] The bowel resection was extended due to insufficient perfusion of the colon stump for 11% of the patients. The reported AL rate was 5% and 9% in the ICG and control groups, respectively.

There are three ongoing randomized controlled trials. ICG-COLORAL study (ClinicalTrials.gov registry identifier NCT03602677) has planned to enroll 1062 participants where anastomosis perfusion is evaluated using ICG-FA as an addition to standard clinical practice compared to surgical practice alone.[35] FLAG trial (ClinicalTrials.gov registry identifier NCT03390517) is similar to the one mentioned above.[36] The investigators have planned to involve 300 participants and to compare colon and rectal tissue perfusion with ICG-FA and without this method. The primary outcome of this study is AL rate. Besides, the radiological anastomosis integrity will be checked on 7 to 8 postoperative day.

IntAct trial (ISRCTN.com registry identifier ISRCTN13334746) is also ongoing randomized controlled trial comparing surgery with ICG-FA against standard surgical practice.[37] Moreover, there are 2 sub-studies which explore the role of the rectal microbiome in AL and the value of preoperative CT angiography and perfusion CT in predicting AL. Investigators consider it may help in understanding the mechanisms underlying AL.

None of these studies will systematically test the integrity and tension on the colorectal anastomosis, which, to our opinion, are important in the development of AL. We aim to develop an original, standardized, simple reproducible inspection method of colorectal anastomosis, which will systemically evaluate the colorectal anastomosis vascularity and mechanical integrity. We believe that combined evaluation should reduce the final AL risk.

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Comprehensive testing of colorectal anastomosis: results of prospective observational cohort study

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Comprehensive testing of colorectal anastomosis: results of prospective observational cohort study

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Abstract

Background Anastomotic leakage remains one of the most threatening complications in colorectal surgery. Intraoperative testing of anastomosis may reduce the postoperative anastomotic leakage rates. This study aimed to investigate a novel comprehensive intraoperative colorectal anastomosis testing technique to detect the failure of the anastomosis construction and to reduce the risk of postoperative leak.

Methods This multi-centre prospective cohort pilot study included 60 patients who underwent colorectal resection with an anastomosis at or below 15 cm from the anal verge. Comprehensive trimodal testing consisted of indocyanine green fluorescence angiography, tension testing, air-leak, and methylene blue leak tests to evaluate the perfusion, tension, and mechanical integrity of the anastomosis.

Results Ten (16.7%) patients developed an anastomotic leakage. Trimodal test was positive in 16 (26.6%) patients and the operative plan was changed for all of them. Diverting ileostomy was performed in 14 (87.5%) patients. However, two (12.5%) patients still developed clinically significant anastomotic leakage (Grade B). Forty-four (73.4%) patients had a negative trimodal test, preventive ileostomy was performed in 19 (43.2%), and five (11.4%) patients had clinically significant anastomotic leakage (Grade B and C).

Conclusion Trimodal testing identifies anastomoses with initial technical failure where reinforcement of anastomosis or diversion can lead to an acceptable rate of anastomotic leakage. Identification of well-performed anastomosis could allow a reduction of ileostomy rate by two-fold. However, anastomotic leakage rate remains high in technically well-performed anastomoses.

Keywords Air-leak test · Methylene blue test · Indocyanine green · Anastomosis testing · Anastomotic leakage · Colorectal anastomosis

Anastomotic leakage (AL) remains one of the most dreadful complications in colorectal surgery. The incidence of AL for colorectal anastomosis is reported up to 30% [1]. AL might be a lethal complication; it is associated with an increased morbidity, prolonged hospital stays, raised health care costs, or even reduced oncological outcomes and functional results. The aetiology of AL is not fully understood yet, although the risk factors are presented widely in the literature [1, 2]. Most risk factors are associated with patient and disease, but also the importance remains related to the surgical technique and quality of anastomosis formation. Insufficient blood perfusion of proximal and distal bowel ends plays an essential role in AL development [3]. Besides, tension and integrity of newly constructed anastomosis are also important. Routine mechanical integrity test after colorectal anastomosis is an

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air-leak test [4]. Also, intraoperative endoscopy and methylene blue test are the other diagnostic possibilities to evaluate mechanical integrity of colorectal anastomosis, though they are applied less frequently [5–8]. Tension testing has no specific measure and is evaluated subjectively by the surgeon. Traditionally, most surgeons evaluate bowel viability via visual and palpable inspection looking for the good colour of the bowel wall, pulsation of the marginal artery, or bleeding of the bowel wall after bowel transection is performed. Currently, technological advances suggest intraoperative indocyanine green fluorescence angiography (ICG-FA) as a more objective alternative for bowel perfusion evaluation [9, 10]. More than five meta-analyses concluded that ICG-FA reduces the rate of AL [11–15]. Unfortunately, only two randomized controlled trials (RCT) with different main findings are published yet [16, 17]. Though the presented results are encouraging, the AL was not avoided completely for study patients. Using the tests of bowel perfusion and anastomosis integrity in a combination might be beneficial to reduce the rate of postoperative AL.

Therefore, this study aimed to investigate a comprehensive intraoperative colorectal anastomosis testing technique to detect the failure of the anastomosis construction and to reduce the risk of AL.

Materials and methods

Design

This multi-centre prospective cohort pilot study was conducted at two major colorectal surgery centres in Lithuania: Vilnius University hospital Santaros Klinikos and National Cancer Institute during the 2019–2020 period. The detailed study protocol was previously published [18].

Ethics

The study was approved by Vilnius Regional Bioethics Committee (Approval number 2019/3-116-608) and registered on the Clinicaltrials.gov database (NCT03958500). All patients provided informed consent. The study was conducted according to the Declaration of Helsinki.

Patients

Patients undergoing elective open or laparoscopic surgery for benign or malignant diseases of left-sided colon or rectum with the primary colorectal anastomosis below 15 cm from the anal verge by the rigid proctoscope were considered eligible in this study. All patients were over 18 years, willing to participate, and have signed the informed consent. The following exclusion criteria were as follows: (1) emergency surgery, (2) pregnancy, (3) allergy to indocyanine green dye, and (4) hand-sewn colorectal anastomosis.

Data collection

All the data were recorded prospectively in a case report form. Data were collected during preoperative, intraoperative, and postoperative time periods. The follow-up period was 1 year following the surgery. The data included age, gender, body mass index (BMI), American Society of Anesthesiologists (ASA) score, Charlson comorbidity index (CCI), smoking, alcohol usage status, previous abdominal operation, history of neoadjuvant treatment, indication for surgery, tumour characteristics, tumour localization, surgical approach, the height of the anastomosis, presence of diverting ileostomy, simultaneous operation, splenic flexure mobilization, high or low ligation of the inferior mesenteric artery, results of the intraoperative air-leak test, methylene blue test, ICG test, time, taken to perform the trimodal testing, and other operative details, postoperative complications including AL, AL grade, hospitalization time. The tumour stage was coded according to the TNM system as described in the Union Internationale Contre le Cancer/American Joint Committee on Cancer 8th edition.

Study outcomes

The primary outcome of the study was the AL during 60 days postoperatively. The secondary outcomes included the frequency of changed location of bowel resection after ICG testing; ileostomy rate; the rate of intraoperative AL; time, taken to perform trimodal anastomosis testing; postoperative morbidity and mortality; stoma rate after 1-year. Quality of life will be analysed separately.

AL definition

AL was defined as a defect at the anastomotic area with a communication between the intra- and extra-luminal compartments. Most of the patients were tested by proctography with water-soluble rectal contrast enema on day 7($\pm$1) and 60($\pm$7). Computed tomography scan with water-soluble oral/rectal contrast enema or digital rectal examination was an additional test to evaluate the integrity of anastomosis, where proctography was not feasible. Proven extravasation of rectal contrast, evidence of a peri-anastomotic fluid collection or abscess, and pus or faecal drainage were considered as AL. AL was graded according to its impact on clinical management: grade A—radiologic leakage without clinical signs, grade B—a need of active therapeutic intervention, but controlled without re-operation, and grade C—AL requiring re-operation [19].

Preoperative care

All patients received oral antibiotics (erythromycin 400 mg and metronidazole 500 mg) three times on the day before surgery. Standard preoperative mechanical bowel preparation was started on the day before surgery. Low molecular weight heparin (nadroparin) was administered 12 h before the surgery, according to the patient's body weight. Standard preoperative antibacterial therapy (cefuroxime 1500 mg and metronidazole 500 mg) was administered 30 min before skin incision.

Intraoperative trimodal testing

Laparoscopic or open colorectal resection was performed according to standard techniques of the study institutions. The bowel was transected with green cartridges. Systolic blood pressure was > 100 mmHg during anastomosis formation. Trimodal anastomosis testing for blood supply, tension, and mechanical integrity was performed for all patients. Two doses of ICG dye were used and the perfusion of the bowel and newly formed anastomosis were evaluated. The main important time-points of intraoperative trimodal testing were as follows:

1. **Perfusion test before proximal bowel transection** The first ICG dose was administered intravenously after the division of the mesentery just before bowel resection to evaluate blood supply at the planned point of resection. In case of insufficient blood perfusion at the planned point, the resection margin was changed to the area of good blood perfusion.
2. **Perfusion test before anastomosis formation** The second ICG dose was injected just before anastomosis creation. The proximal and distal parts of the bowel were evaluated, and anastomosis was created.
3. **Transabdominal and transanal perfusion test after anastomosis formation** Immediately after the formation of the anastomosis, the bowel perfusion was checked once again. The evaluation was not available in ultra-low colorectal anastomoses. When trans-abdominal perfusion evaluation was finished, trans-anal ICG testing was performed via proctoscope as described previously by our group [20]. The mucosa perfusion of the newly created anastomosis with proximal and distal bowel parts was checked by fluorescence circumferentially with camera via the proctoscope.
4. **Tension testing** Tension on the anastomosis was tested visually. The aim was to create a floppy anastomosis where the proximal end of the bowel was freely falling into the pelvis. The straight anastomosis was considered in cases where the bowel was straight to the anastomosis but without obvious tension. Anastomosis under tension was corrected.
5. **Air-leak test** A standard air-leak test was performed through a proctoscope at the same time as trans-anal perfusion testing. The anastomosis was placed under saline solution in the pelvic cavity during laparoscopy or laparotomy. The proximal colon was occluded by placing a soft bowel clamp across the bowel (without mesentery) in a comfortable distance above colorectal anastomosis. In the case of a positive air-leak test, the leaking part of anastomosis was reinforced if it was identifiable and technically possible. Diverting ileostomy was created based on the surgeon's preference.
6. **Methylene blue leak test** Methylene blue leak test was performed following the negative air-leak test. A 16 French Foley catheter was inserted into the anus and the balloon of the catheter was inflated up to 20–40 ml, avoiding the stretching of the anastomosis. The catheter was gently withdrawn to the internal anal sphincter to avoid the spilling of the staining solution. The volume of injected staining solution depended on the height of colorectal anastomosis – the more anastomosis was distal to the anal verge; the less solution was injected. This step was performed under direct laparoscopic (or open) vision to avoid stretching of the anastomosis. In cases when low colorectal anastomosis was not visualized transabdominally, white gauze was introduced and positioned around anastomosis before dye injection. In case of a positive methylene blue leak test, the leaking part of the anastomosis was reinforced if it was technically possible. Diverting ileostomy was created based on the surgeon's preference.

Ileostomy

The decision to perform ileostomy was made according to subjective individual surgeon's preference including cases of negative trimodal testing.

Postoperative care

Standard postoperative care was ensured. The white blood cell count and C-reactive protein were examined on postoperative days 2, 4, and 6. Proctography with water-soluble rectal contrast enema was performed to check the integrity of colorectal anastomosis on postoperative day 7 (± 1). Ultra-low anastomoses were checked by digital rectal examination when proctography was not feasible. Computerized tomography with oral and rectal contrast was performed if clinical AL was suspected.

Statistical analysis

Statistical analysis was performed using the statistical package SPSS 25.0 (SPSS, Chicago, IL, USA). All data were checked for normality. Continuous variables were compared by a two-tailed *t*-test, Wilcoxon rank-sum test, or non-parametric tests where appropriate and expressed as median with first (Q1) and third (Q3) quartiles. Categorical data were expressed as proportions with percentages and compared by the chi-square test and Fisher exact test. A p value less than 0.05 was considered statistically significant.

Results

Baseline characteristics

A total of 60 patients with a median age of 64 years (Q1 56.25; Q3 76) were included in the study. Baseline characteristics are presented in Table 1.

Trimodal testing of colorectal anastomoses

Trimodal anastomosis testing was feasible in all (100%) patients, and it identified 16 (26.7%) positive results. The median time for the trimodal testing was 8 min (Q1: 7; Q3: 9).

Blood supply by ICG-IF

Insufficient blood supply at the anticipated proximal bowel transection line by ICG-IF was detected in six (10.0%) patients. Transection point was changed in all these cases and the additionally resected segment varied between 1 and 8 cm. After these adjustments further ICG testing confirmed adequate vascularization at proximal and distal ends before and after anastomosis creation.

Tension testing by visual inspection

All anastomoses were confirmed as floppy, except one (1.7%), which was considered straight, but acceptable. No additional changes were performed after tension testing.

Mechanical integrity of anastomoses by air-leak test and methylene blue leak test

All patients were checked with the intraoperative air-leak test. Air-leakage occurred in four (6.7%) patients. All these anastomoses were reinforced where possible and diverted.

Fifty-six patients with the negative air-leak tests were checked with the methylene blue leak test. Additional eight (14.3%) leaking anastomoses were identified (Fig. 1). All

Table 1 Basic characteristics of 60 patients undergoing colorectal anastomosis and included in trimodal testing study

Parameters	Patients (n = 60)
Age	64 (Q1 56.25; Q3 76.0)
BMI	
< 30	44 (74.6%)
≥ 30	15 (25.4%)
Smoking status	
Smoker	7 (11.7%)
Non-smoker	43 (71.7%)
Quit smoker	10 (16.7%)
Alcohol usage	
Yes	36 (60.0%)
No	24 (40.0%)
Gender	
Female	23 (38.3%)
Male	37 (61.7%)
Previous abdominal surgery	
Yes	29 (48.3%)
No	31 (51.7%)
ASA	
I–II	40 (66.7%)
III–IV	20 (33.3%)
CCI	
≤ 3	22 (36.7%)
4–6	30 (50.0%)
≥ 7	8 (13.3%)
Biological therapy	
Yes	3 (5.0%)
No	57 (95.0%)
Type of surgery	
Sigmoid resection	24 (40.0%)
Rectal resection	36 (60.0%)
Neoadjuvant therapy	
Yes	11 (18.3%)
No	49 (81.7%)
Rectum thirds	
Lower third	3 (8.3%)
Middle third	25 (69.5%)
Upper third	8 (22.2%)
Blood transfusion	
Yes	10 (16.7%)
No	50 (83.3%)
Approach of surgery	
Open	2 (3.3%)
MIS	58 (96.7%)
Conversion	
Yes	1 (1.7%)
No	57 (98.3%)
Adhesions	
Yes	11 (18.3%)
No	49 (81.7%)

Table 1 (continued)

Parameters	Patients (n = 60)
Splenic flexure mobilization	
Yes	29 (49.2%)
No	31 (50.8%)
Type of artery ligation	
High	56 (93.3%)
Low	4 (6.7%)
Anastomosis reinforcement	
Yes	8 (13.3%)
No	52 (86.7%)
Distal ring	
Full	58 (96.7%)
Defective	2 (3.3%)
Contamination	
Yes	2 (3.3%)
No	58 (96.7%)
Intraoperative complications	
Yes	4 (6.7%)
No	56 (93.3%)
Drainage	
Yes	49 (81.7%)
No	11 (18.3%)
Simultaneous operation	
Yes	1 (1.7%)
No	59 (98.3%)
Ileostomy	
Yes	33 (55.0%)
No	27 (45.0%)
Trimodal testing	
Positive	16 (26.7%)
Negative	44 (73.3%)
pT	
T0–T2	24 (43.6%)
T3–T4	31 (56.4%)
pN	
0	35 (63.6%)
1–2	20 (36.4%)
pM	
0	52 (94.5%)
1	3 (5.5%)
pTNM	
0	1 (1.8%)
1	19 (34.5%)
2	12 (21.8%)
3	20 (36.4%)
4	3 (5.5%)
R0	
Yes	58 (96.7%)
No	2 (3.3%)
Tumour size	4.5 (Q1 3.05; Q3 5.875)
Operation time	190 (Q1 170.0; Q3 235.0)
Blood loss	100 (Q1 50.0; Q3 100.0)

BMI body mass index, *ASA* American Society of Anesthesiologists classification score, *CCI* Charlson comorbidity index score, *MIS* minimally invasive surgery

anastomoses were reinforced where possible and diverted, except one. Together air-leak test and methylene blue test identified 12 (20.0%) intraoperative leakages.

Primary outcome: AL during 60 days postoperatively

The overall AL rate during 60 days postoperatively was 16.7% (10 patients). The detailed characteristics and trimodal testing results of patients with AL are presented in Table 2. Three (30.0%) of 10 patients with postoperative AL had at least one positive intraoperative test, and the preventive ileostomy was created for all these patients at the initial operation. None of them developed grade C AL.

Seven (70.0%) of 10 patients with postoperative AL had all negative tests at trimodal testing. Three of them developed grade C AL. One of them was readmitted due to late (day 18) grade C AL. Therefore, the reoperations were performed, and ileostomies were created.

Ileostomy creation

Preventive ileostomy was constructed in 33 patients (55.0%). Fourteen out of 16 patients (87.5%) with positive trimodal testing underwent preventive ileostomy compared to 19 out of 44 patients (43.2%) with negative trimodal testing (Fig. 1).

Short-term morbidity and readmissions

The 30-day morbidity rate was 38.3% (23 patients). Mild complications (Clavien–Dindo I-IIIa) occurred in 15 patients (25.0%) and severe complications (Clavien–Dindo ≥ 3b) in 8 patients (13.3%). Detailed description of severe complications is presented in Table 3. The reoperation rate was 8.3% for non-anastomotic complications. The median hospitalization time was 8 (Q1 7.0; Q3 11) days. There were no 30-day postoperative deaths. The 30-day readmission rate was 5.0%.

1-year outcomes

Three patients died over the one-year period, with overall 1-year mortality rate of 5.0%. One (1.7%) patient died because of suicide 2 months after surgery, one (1.7%) patient died because of cardiopulmonary failure during

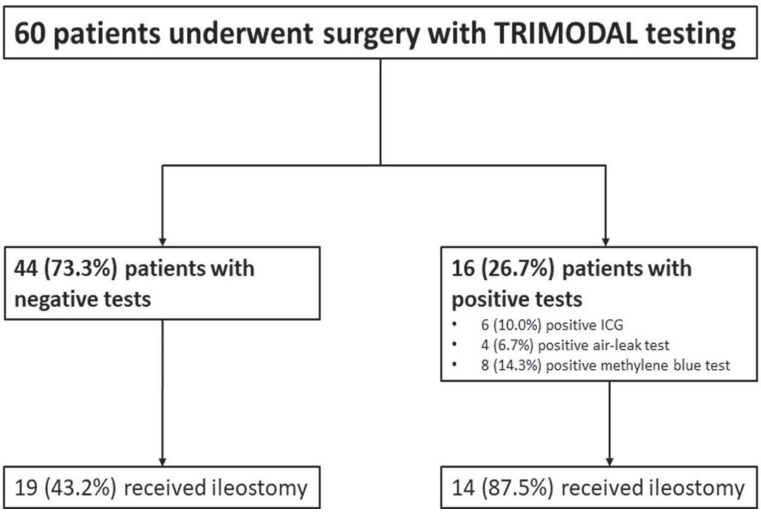

Fig. 1 Flowchart of trimodal testing and ileostomy formation

chemotherapy 3 months after surgery, and one (1.7%) patient died 10 months after surgery because of progressing Alzheimer's disease.

Twenty-nine (87.9%) out of 33 patients had their ileostomy reversed during 1-year follow-up period. Two (6.0%) patients did not receive ileostomy closure because they died, one (3.0%) patient did not undergo ileostomy closure because of stricture of colorectal anastomosis and unsuccessful management with endoscopic balloon dilatation and one (3.0%) patient due to progression of the disease. All patients with diverted ileostomies after grade C AL were managed and closed.

Comparison of patients with positive and negative intraoperative trimodal testing

Based on trimodal testing results patients were grouped to positive ($n=16$) and negative ($n=44$) trimodal testing groups. Significantly higher proportion of patients in positive testing group received splenic flexure mobilization (75.0% vs 38.6%, $p=0.019$), reinforcement of the anastomosis (31.2% vs 6.8%, $p=0.026$), drain placement (100% vs 75.0%, $p=0.027$), and preventive ileostomy (87.5% vs 43.2%, $p=0.003$) (Table 4).

Discussion

We present the results of a comprehensive technique to test the mechanical and vascular integrity of colorectal anastomosis. We unexpectedly found that the methylene blue leak test is frequently positive after a negative air-leak test in colorectal anastomosis. Our study demonstrated that the change of the operative plan occurs for a quarter of the patients after careful intraoperative anastomosis testing. In addition, patients with positive intraoperative anastomosis tests are diverted twice more frequently than patients with negative tests. Nevertheless, AL remains common even in mechanically integral anastomoses.

An air-leak test is the most popular mechanical integrity test amongst surgeons for colorectal anastomosis. Nevertheless, the mechanical integrity also might be tested by methylene blue or by intraoperative colonoscopy. Our study presented two mechanical integrity tests—air-leak and methylene blue leak. Several studies have been published using the methylene blue test alone. A previous study reported the positive methylene blue leak test in 7.0% of patients with a 3.3% postoperative AL. It is worth mentioning that all postoperative AL occurred in patients with negative intraoperative methylene blue test [7]. Similar results were presented using patent blue dye. A positive test was detected and treated intraoperatively in 14.5% of the patients. Moreover, the authors stated a low 1.3% postoperative AL rate in patients with negative intraoperative tests [8]. The triple mechanical integrity testing using intraoperative endoscopy, air-leak, and blue stained saline tests showed an 8.3% rate of postoperative AL. Abnormal anastomotic findings—anastomotic bleeding, the gap in the suture line, positive air-leak, or blue stained saline tests—were detected for 18.1% of the study patients. Unfortunately, intraoperative testing was not performed for all the cohort patients [21]. The recent study introduced a decalogue of ten intraoperative steps to reduce the need for preventive ileostomy for selected patients following anterior rectal resection. In a presented pilot trial, anastomosis integrity was checked by a methylene blue leak test. Nevertheless, the results about methylene blue test

Table 2 Detailed characteristics of patients with anastomotic leakage

No. patient	Age	Gender	BMI	Anastomosis level, cm	ICG test	Tension	Air-leak test	Methylene blue leak test	Ileostomy	Anastomotic leakage severity L grade	Anastomotic leakage detected during initial hospitalization occurred in hospital
1	67	M	26.30	10	Negative –	Straight	Negative –	Negative –	–No	B	Yes
2	80	M	33.51	15	Negative –	Floppy	Negative –	Negative –	No –	A	Yes
3	62	M	29.77	10	Negative –	Floppy	Negative –	Positive+	Yes+	B	Yes
4	64	M	19.94	6	Positive+	Floppy	Positive+	N/A	Yes+	A	No
5	57	F	30.45	15	Negative –	Floppy	Negative –	Negative –	No –	A	Yes
6	63	F	36.05	11	Negative –	Floppy	Negative –	Negative –	No –	C	No
7	75	F	28.52	5	Negative –	Floppy	Negative –	Negative –	Yes+	B	Yes
8	58	M	24.57	9	Negative –	Floppy	Negative –	Negative –	No –	C	Yes
9	50	F	23.80	15	Negative –	Floppy	Negative –	Negative –	No –	C	Yes
10	79	M	23.90	3	Negative –	Floppy	Positive+	N/A	Yes+	B	Yes

M male, *F* female, *BMI* body mass index, *ICG* indocyanine green, *N/A* not available, *AL* anastomotic leakage

Table 3 Severe complications of patients included in trimodal testing study

Patient	Readmission	Complication	Clavien–Dindo
1	No	Small bowel perforation	IVb
2	No	Small bowel perforation	IIIb
3	No	Bleeding from inferior epigastric artery (after ileostomy creation)	IIIb
4	No	Eventration of the greater omentum through laparoscopic wound	IIIb
5	No	Anastomotic leakage, grade C	IIIb
6	No	Anastomotic leakage, grade C	IIIb
7	No	Small bowel obstruction	IIIb
8	Yes	Anastomotic leakage, grade C	IIIb

positivity and its influence on further operative and postoperative outcomes were not reported [22]. In our experience, it was easier to pinpoint a leaking part of the colorectal anastomosis with the methylene blue leak test in comparison to the air-leak test. Moreover, a recent study presented that the methylene blue test is not inferior to the air-leak test in an experimental setting [23]. Therefore, the use of both mechanical tests is beneficial to ensure the integrity of the newly constructed anastomosis.

ICG-FA gained the popularity to test vascular perfusion of the bowel in the last decade. Reduction of postoperative AL is suggested with the use of ICG-FA in recent meta-analyses [13–15]. Unfortunately, most of the studies included in the meta-analyses were prospective observational or even retrospective in design, thus weakening the power of these meta-analyses. Until now, only two RCTs are published with contradictory results. As reported, inadequate perfusion of the colon stump was diagnosed for 11.0% of the patients with a need for additional bowel resection. Despite the fact, the trial demonstrated no statistical difference between the ICG and control groups with the postoperative AL rate 5.0% and 9.0%, respectively [16]. This might have not reached the statistical significance because the sample size was calculated on the premise, that the ICG-FA use would reduce the leak rate to 0%. Another RCT study revealed bad perfusion of the bowel for 19.0% of the patients and concluded that ICG-FA reduced the risk of postoperative AL only for low colorectal anastomoses comparing to control group patients (14.4% versus 25.7%, $p=0.04$) [17]. The most recent results of RCT—PILLAR III—were announced in ClinicalTrials.gov (NCT02205307) with a reported rate of postoperative AL 8.0% and 9.5% in ICG-FA and control groups, respectively. Interestingly, the study was stopped

Table 4 Basic characteristics of the study patients between the groups

	Positive trimodal testing ($n=16$)	Negative trimodal testing ($n=44$)	P value
Age	63 (Q1 56.75; Q3 77.50)	64.50 (Q1 55.50; Q3 75.75)	0.973
BMI			
<30	13 (81.3%)	31 (72.1%)	0.738
≥ 30	3 (18.8%)	12 (27.9%)	
Smoking status			
Smoker	3 (18.8%)	4 (9.1%)	0.535
Non-smoker	10 (62.5%)	33 (75.0%)	
Quit smoker	3 (18.8%)	7 (15.9%)	
Alcohol usage			
Yes	9 (56.3%)	27 (61.4%)	0.771
No	7 (43.8%)	17 (38.6%)	
Gender			
Female	4 (25.0%)	25 (56.8%)	0.242
Male	12 (75.0%)	19 (43.2%)	
Previous abdominal surgery			
Yes	9 (56.3%)	20 (45.5%)	0.563
No	7 (43.8%)	24 (54.5%)	
ASA			
I–II	9 (56.3%)	31 (70.5%)	0.360
III–IV	7 (43.8%)	13 (29.5%)	
CCI			
≤ 3	5 (31.3%)	17 (38.6%)	0.837
4–6	9 (56.3%)	21 (47.7%)	
≥ 7	2 (12.5%)	6 (13.6%)	
Biological therapy			
Yes	1 (6.3%)	2 (4.5%)	0.999
No	15 (93.8%)	42 (95.5%)	
Type of surgery			
Sigmoid resection	4 (25.0%)	20 (45.5%)	0.234
Rectal resection	12 (75.0%)	24 (54.5%)	
Neoadjuvant therapy			
Yes	5 (31.3%)	6 (13.6%)	0.143
No	11 (68.8%)	38 (86.4%)	
Blood transfusion			
Yes	3 (18.8%)	7 (15.9%)	0.999
No	13 (81.3%)	37 (84.1%)	
Approach of surgery			
Open	1 (6.3%)	1 (2.3%)	0.466
MIS	15 (93.8%)	43 (97.7%)	
Conversion			
Yes	1 (6.7%)	0 (0.0%)	0.259
No	14 (93.3%)	43 (100%)	
Adhesions			
Yes	3 (18.8%)	8 (18.2%)	0.999
No	13 (81.3%)	36 (81.8%)	
Splenic flexure mobilization			
Yes	12 (75.0%)	17 (38.6%)	0.019
No	4 (25.0%)	27 (61.4%)	
Type of artery ligation			
High	16 (100%)	40 (90.9%)	0.565
Low	0 (0.0%)	4 (9.1%)	

Table 4 (continued)

	Positive trimodal testing ($n=16$)	Negative trimodal testing ($n=44$)	P value
Reinforcement			
Yes	5 (31.2%)	3 (6.8%)	0.026
No	11 (68.8%)	41 (93.2%)	
Distal ring			
Full	14 (87.5%)	44 (100%)	0.068
Defective	2 (12.5%)	0 (0.0%)	
Contamination			
Yes	0 (0.0%)	2 (4.5%)	0.999
No	16 (100%)	42 (95.5%)	
Intraoperative complications			
Yes	1 (6.3%)	3 (6.8%)	0.999
No	15 (93.8%)	41 (93.2%)	
Drainage			
Yes	16 (100%)	33 (75.0%)	0.027
No	0 (0.0%)	11 (25.0%)	
Simultaneous operation			
Yes	0 (0.0%)	1 (2.3%)	0.999
No	16 (100%)	43 (97.7%)	
Ileostomy			
Yes	14 (87.5%)	19 (43.2%)	0.003
No	2 (12.5%)	25 (56.8%)	
pT			
T0–T2	8 (50.0%)	16 (41.0%)	0.565
T3–T4	8 (50.0%)	23 (59.0%)	
pN			
0	11 (68.8%)	24 (61.5%)	0.761
1–2	5 (31.3%)	15 (38.5%)	
pM			
0	16 (100%)	36 (92.3%)	0.548
1	0 (0.0%)	3 (7.7%)	
pTNM			
0	0 (0.0%)	1 (2.6%)	0.652
1	7 (43.8%)	12 (30.8%)	
2	4 (25.0%)	8 (20.5%)	
3	5 (31.3%)	15 (38.5%)	
4	0 (0.0%)	3 (7.7%)	
R0			
Yes	0 (0.0%)	2 (4.7%)	0.999
No	16 (100%)	41 (95.3%)	
Tumour size	4.6 (Q1 4.00; Q3 6.00)	4.5 (Q1 3.00; Q3 5.75)	0.403
Operation time	197.50 (Q1 171.25; Q3 262.50)	190 (Q1 162.50; Q3 233.75)	0.407
Blood loss	100 (Q1 100.00; Q3 175.00)	100 (Q1 50.00; Q3 100.00)	0.067

BMI body mass index, *ASA* American Society of Anesthesiologists classification score, *CCI* Charlson comorbidity index score, *MIS* minimally invasive surgery

prematurely and the final results with the conclusions are awaited. Moreover, there are several ongoing RCTs listed in the trial registry websites. The most interesting data are from an IntAct trial, where surgery with ICG-FA will be compared to standard surgery within the large sample size. Moreover, an interesting two sub-group analyses will be performed which investigate the role of the microbiome of the rectum and contrast-enhanced CT angiography and perfusion CT role in predicting AL before surgery [24]. To sum up, the results according to RCTs are controversial.

On the other hand, meta-analyses showed a significant decrease of postoperative AL with an ICG-FA usage. Our study demonstrated 10.0% of inadequate proximal bowel perfusion, thus additional resection was completed. Theoretically, this should reduce the risk of AL in some patients. However, anastomotic leaks still commonly occur in a visibly well-perfused anastomosis.

Diverting ileostomy might prevent postoperative AL or reduce the consequences of it, though this is still debatable. Unfortunately, ileostomy itself requires an operation for closure. Also, a proportion of patients will not be able to take down stoma due to poor clinical condition, progression of the disease, or other causes. Our study demonstrated that ileostomy was created twice more frequently after positive anastomosis testing. Moreover, two patients (6.1%) experienced 30-day readmission due to dehydration and acute kidney insufficiency and 6.5% of the patients were not able to close the stoma. Therefore, ileostomy should be created in carefully selected cases only when it is necessary. The results of real benefit for creating diverting ileostomy are controversial in the literature. A recent meta-analysis of five RCTs proved that diverting stoma reduces the postoperative AL rate (OR 0.292, 95% CI 0.177–0.481, $p < 0.001$). Moreover, the meta-analysis revealed a statistically significant lower reoperation rate for patients with diverting stoma [25]. Only one RCT included in the above mentioned meta-analysis did not achieve a statistically significant difference between the groups with diverting ileostomy and without diverting ileostomy and presented 6.0% and 11.0% AL rate, respectively [26]. Another study also did not show the clear advantage to prevent AL after rectal resection. The reported AL rate was 6.3% and 8.7% in patients with preventive ileostomy and without preventive ileostomy, respectively. Also, the authors found a 6.4% rate of permanent stoma in patients with diverting ileostomy [27]. One of the most common non-surgical complications of ileostomy requiring hospitalization is dehydration. The reported incidences of 30-day and 60-day readmission with dehydration were 5.0% and 10.3%, respectively, and this is similar to our study results (30-day readmission rate 6.1%) [28]. Moreover, a high rate of complications is associated with ileostomy closure and might be up to 32.0% [29, 30]. Ghost ileostomy might be a solution to avoid the real ileostomy creation and its related complications. Ghost ileostomy is diverted in cases when clinical signs of AL occurs, thus the number of diverting ileostomy is reduced [31]. A faecal diversion device is another option to avoid the diverting ileostomy with similar AL rates for patients with diverting ileostomy [32]. Therefore, ghost ileostomy or faecal diversion device could reduce the standard preventive ileostomy rates in high-risk patients, but with negative mechanical integrity tests of colorectal anastomosis. Thus, we suggest that diverting ileostomy is recommended only in selected cases with positive mechanical integrity tests to avoid grade C AL as observed in our study.

The present study has some limitations, including a small sample size and an absence of the control group. Moreover, the green cartridges with closed staple size of 2 mm were used to transect the rectum, and this might be the reason of high rate of positive intraoperative mechanical tests. In addition, there is a possibility that patients with positive intraoperative tests would not develop postoperative AL if the corrections have not been made. Moreover, not all known intraoperative risk factors such as elevation of perioperative blood glucose was evaluated [33, 34]. Another potential limitation of the present study is the subjective assessment of the ICG fluorescence intensity. Currently, there is a lack of objective criteria to evaluate if the fluorescence signal intensity is sufficient for anastomosis. Such quantification criteria are necessary for further development and adoption of the ICG-FA method.

The strength of the study is that the patients were carefully tested after the operation on day 7 and 60, thus asymptomatic AL were diagnosed, even for patients with preventive ileostomy. Therefore, the rate of postoperative AL is high. All patients were followed-up until one year after surgery. This is the first feasibility study, which so comprehensively tests colorectal anastomosis. Future RCT with an acceptable sample size of the patients is needed to show the possible benefits of this comprehensive testing of colorectal anastomosis.

Conclusion

Comprehensive testing identifies anastomoses with initial technical failure where reinforcement of anastomosis or diversion can lead to an acceptable rate of AL. Identification of well-performed anastomosis could allow to a reduction of ileostomy rate by two-fold. However, the AL rate remains high in technically well-performed anastomoses.

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Bowel Rest with Total Parenteral Nutrition as an Alternative to Diverting Ileostomy in High-Risk Colorectal Anastomosis: A Pilot Study

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Brief Report

Bowel Rest with Total Parenteral Nutrition as an Alternative to Diverting Ileostomy in High-Risk Colorectal Anastomosis: A Pilot Study

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Abstract: Anastomotic leakage remains the most feared complication in colorectal surgery. Various intraoperative tests evaluate bowel perfusion and mechanical integrity of the colorectal anastomosis. These tests reduce the risk of postoperative anastomotic leakage; however, the incidence remains high. Diverting loop ileostomy mitigates the damage if anastomotic leakage occurs. Nevertheless, ileostomy has a significant rate of complications, reducing patients' quality of life, and requiring an additional operation. We evaluated six consecutive cases where bowel rest with total parenteral nutrition was used instead of diverting loop ileostomy. All colorectal anastomoses were at high risk of postoperative anastomotic leakage. Total parenteral nutrition was administered for the first seven days postoperatively. There were no serious complications during the recovery period, and no clinical postoperative anastomotic leakage was detected. All patients tolerated total parenteral nutrition. Bowel rest with total parenteral nutrition may be a feasible option in high-risk left-sided colorectal anastomosis and a possible alternative to a preventive loop ileostomy. Further studies are necessary to evaluate it on a larger scale.

Keywords: anastomotic leakage; total parenteral nutrition; bowel rest; colorectal surgery

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1. Introduction

Anastomotic leakage (AL) remains one of the most feared complications in colorectal surgery. Despite immense research effort and practice changes, the percentage of AL remains high [1]. A diverting loop ileostomy is often used for damage control if AL occurs. However, ileostomies may cause complications, they significantly reduce patients' quality of life and require an additional operation to close [2,3]. Moreover, up to 20 percent of preventive ileostomies are never closed [4]. Total parenteral nutrition (TPN) was previously adopted for patients with confirmed AL after upper gastrointestinal tract surgery [5]. However, it was never widely adopted in colorectal surgery and was only described as a one-off case in the literature [6]. Therefore, we hypothesised that short-term bowel rest with TPN could replace diverting loop ileostomy in high-risk left-sided colorectal anastomoses.

2. Materials and Methods

Consecutive patients undergoing elective left-sided colorectal resection with high-risk primary anastomosis (anastomosis $\leq$ 10 cm from the anal verge and/or presence of severe, life-threatening comorbidity) who agreed to participate were included. The central venous line was placed during anaesthesia, and patients underwent bowel rest with TPN for the first seven postoperative days.

TPN consisted of 1477 mL SmofKabiven, 10 mL of Addaven, 10 mL of Soluvit N, and 10 mL of Vitalipid N. The infusion starting speed was 30 mL/hour on the first postoperative day, 45 mL/hour on the second, and 62 mL/hour on the third until the seventh postoperative day.

Complete blood count, C-reactive protein (CRP), and electrolyte concentrations were monitored daily. After TPN, on the eighth postoperative day, patients were allowed to drink and eat liquid food.

The primary outcome of the study was the AL rate. Secondary outcomes included postoperative morbidity rate and tolerance of TPN. Postoperative complications were graded by the Clavien–Dindo classification.

3. Results

Six patients were included in the study. Patient details are described in Table 1. There was no clinical postoperative AL detected. Two patients had elevated CRP during the parenteral nutrition period. Chest, abdomen, and pelvic computed tomography scans with enteric contrast were performed, and AL was ruled out. These two patients developed grade II Clavien–Dindo complications: One patient developed postoperative fever, with negative blood and urine cultures, and the other developed wound seroma requiring drainage. Intravenous antibiotics were prescribed and inflammatory markers normalised. All other four patients had an uneventful postoperative course. All six patients did not have any complications associated with TPN.

Table 1. Detailed patients, surgery, and outcomes characteristics.

Patient	Age	ASA	Gender (M/F)	BMI	Risk Factors	Indication for Surgery	Surgery (Open/Laparoscopic)	Indications for Ileostomy	Highest CRP (mg/L)	Postoperative Complications
1	55	II	F	25.6	Carcinoma of the fallopian tube	Carcinoma penetrating the rectal wall	Open	Low anastomosis (8 cm from anal verge) Positive methylene blue test	56.6	None
2	55	III	F	43.5	Morbid obesity	Carcinoma of the sigmoid colon	Laparoscopic converted to open	Low anastomosis (10 cm from anal verge) Obesity	219.8	Postoperative wound seroma
3	61	III	F	23.1	Acute renal failure Hypokalaemia Hyponatraemia Sepsis	Adenoma of the sigmoid colon (McKittrick–Wheelock syndrome)	Laparoscopic	Renal failure	181.9	Postoperative fever (second postoperative day)
4	77	III	F	33.2	Disseminated carcinoma of the uterus	Uterine carcinoma penetrating the rectal wall	Open	Low anastomosis (5 cm from anal verge)	71.7	None
5	50	IIIE	M	40.9	Chronic renal failure Haemodialysis Morbid obesity	Rectal carcinoma	Laparoscopic	Low anastomosis (7 cm from anal verge) Obesity Renal failure	43.3	None
6	43	II	M	22.6	Neoadjuvant chemoradiation	Rectal carcinoma	Laparoscopic	Low anastomosis (2 cm from anal verge)	21.3	None

ASA: American Society of Anesthesiology score; M/F: Male/Female; BMI: Body mass index; CRP: C-reactive protein.

4. Discussion

We present an alternative to diverting loop ileostomy by using bowel rest and TPN in high-risk left-sided colorectal anastomoses. There was no AL detected, and all patients tolerated bowel rest with TPN.

Colorectal surgeons aim to create safe anastomosis by ensuring adequate bowel perfusion and mechanical integrity of the anastomosis. Several studies showed the benefit of bowel perfusion (indocyanine green) and mechanical integrity (air-leak and methylene

blue) testing in reducing postoperative AL [1,7,8]. Unfortunately, the risk of postoperative AL remains quite high even though anastomosis mechanical integrity and bowel perfusion are ensured. Thus, preventive ileostomy remains relevant to reducing the risk and consequences of AL [9,10]. Bowel rest and TPN achieve the same goal—dysfunction colorectal anastomosis—but it avoids repeated operation, necessary for an ileostomy.

One of the recommendations for enhanced recovery after surgery (ERAS) is early postoperative oral nutrition [11]. Therefore, bowel rest with TPN is contradictory to current ERAS guidelines. However, an ileostomy is a significant burden for the patient, reducing the quality of life, and is one of the most undesirable effects of colorectal surgery Furthermore, in most cases, a diverting ileostomy needs additional hospitalisation to revert it. This type of surgery has its own complications, some of them even being life-threatening [12]. Some surgeons are even arguing against the routine use of diverting ileostomy due to the high long-term morbidity associated with it [13]. Taking all this into account, patients eagerly agreed to participate in the study when avoiding ileostomy was an option.

5. Conclusions

In conclusion, bowel rest with total parenteral nutrition may be a feasible option in high-risk left-sided colorectal anastomosis and a possible alternative to a preventive loop ileostomy. Further studies are necessary to evaluate it on a larger scale.

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Data Availability Statement: Data are available on reasonable request. All data relevant to the study are included in the article. Deidentified data that underlie the results reported in this article will be shared with third parties after a written request to the corresponding author describing the intention of data usage and full affiliation of the requesting organisation. To gain access to the data, a data access agreement needs to be signed.

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