NEW CLINICAL PERSPECTIVES OF COLORECTAL ANASTOMOTIC LEAKAGE

Cloë L. Sparreboom

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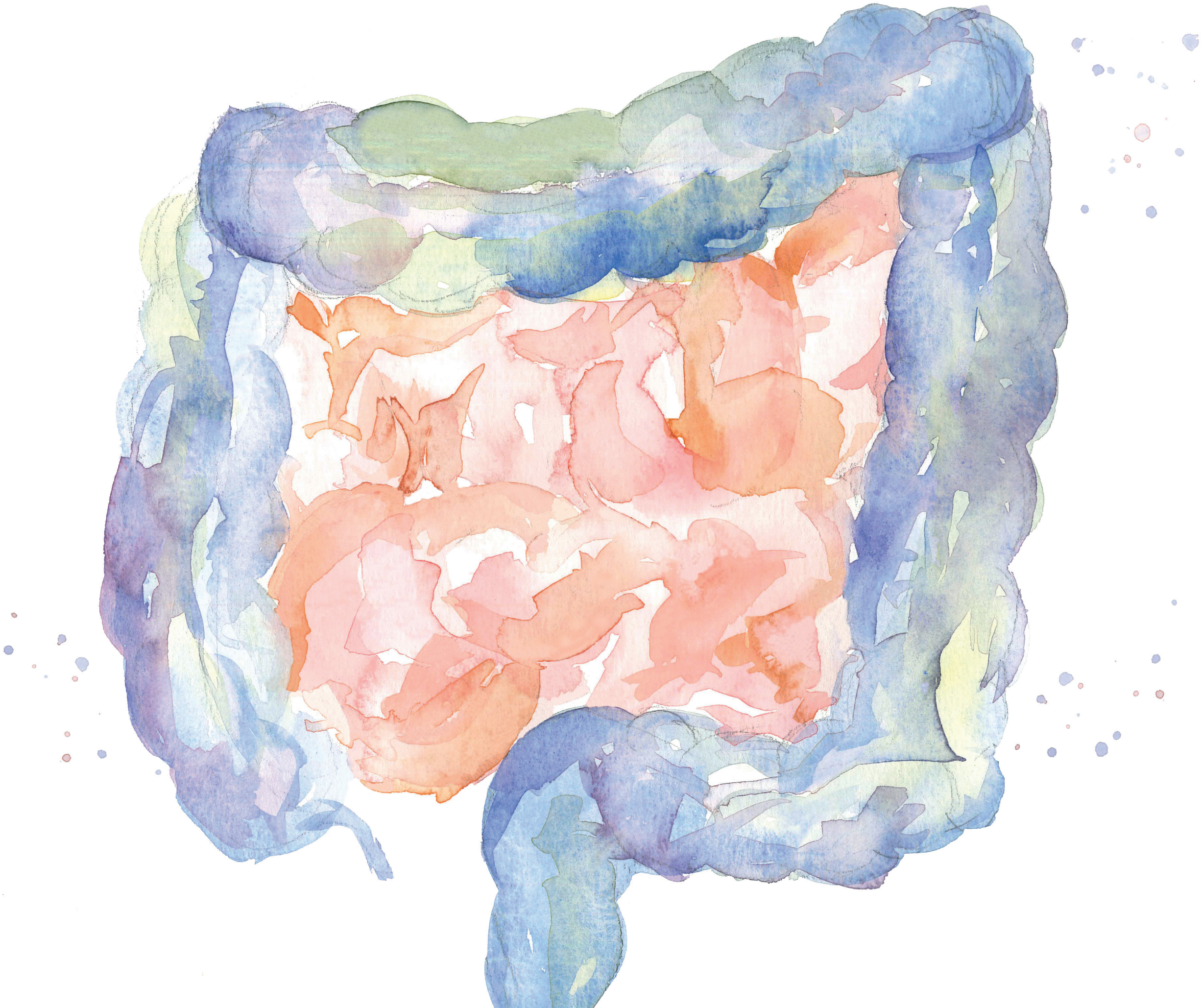

Chapter 1

INTRODUCTION

Integrated approach to colorectal anastomotic leakage: Communication, infection and healing disturbances*

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Z. Wu
J. Ji
J.F. Lange

Adapted from: World Journal of Gastroenterology 2016 Aug;22(32):7226-35

Introduction

Colorectal resection is a commonly performed procedure in surgery. The main indication is colorectal cancer, but inflammatory bowel disease also contributes. Restoring continuity of the bowel is essential, yet, unfortunate for both patients and surgeons, this includes the risk of anastomotic leakage (AL). AL is characterized by anastomotic dehiscence leading to leakage of intestinal content into the abdominal or pelvic cavity(1). AL can result in peritonitis, abscess formation and sepsis often requiring reoperation with a temporary or permanent stoma. This severe postoperative complication contributes to one-third of the postoperative mortality after colorectal surgery(2).

The incidence of AL varies from 4-33% with a higher incidence in the lower gastrointestinal tract, rectal anastomoses manifesting the highest rates(3). The incidence of AL has not been reduced over the last decades despite the introduction of minimally invasive techniques in colorectal surgery(4, 5). With 10.000 colorectal resections for colorectal cancer performed in The Netherlands yearly, a substantial number of patients is at risk for AL. In addition, AL substantially prolongs hospital stay and increases medical costs by as much as $24.000, thereby approximately tripling the expenditure relative to that of normal recovery after colorectal surgery(6, 7).

Although the exact pathophysiology is unknown, several risk factors for AL after colorectal surgery have been identified. Preoperative risk factors are male sex, American Society of Anesthesiologists fitness grade above II, renal disease, co-morbidity and history of radiotherapy. Tumor characteristics associated with AL are distal location, size, advanced stage and metastatic disease. Smoking, obesity, poor nutrition, alcohol abuse and immunosuppressants are considered adjustable risk factors(8).

Diagnosis

AL is usually diagnosed within 6 to 15 days after surgery(9, 10). However, it was recently demonstrated that 20% of leakages after low anterior resection were diagnosed even beyond 30 days(11). Clinical symptoms, laboratory results and radiological studies are part of the diagnostic strategy. Clinical manifestations of this postoperative complication include fever, abnormal vital signs and abdominal pain, however these symptoms are common after colorectal surgery and therefore not specific for AL(12). From laboratory tests, serum C-reactive protein (CRP) is the most used negative predictive marker(13). CRP is synthesized by the liver in response to inflammation(14). CRP levels also rise in response to trauma, ischemia, and other inflammatory complications, so CRP monitoring is also lacking specificity for AL(15). Radiological studies aim to show communication between intra- and extra-luminal compartments. In clinical practice, abdominal computed tomography (CT) scanning is most frequently used to diagnose AL(16, 17). The sensitivity is reported to be around 65% (18, 19). However, in comparison to the widespread use of CT scanning for AL, evidence on the diagnostic accuracy is scarce. Besides, the relatively poor diagnostic accuracy, radiation exposure and costs impede implementation of routine CT-scanning in clinical practice. In addition, this relatively low sensitivity is mostly due to high rates of false-negatives and must be taken into account in order to prevent delay in diagnosis(20). Delayed reintervention after false-negative CT scanning is associated with high mortality(21). Actually, delay in diagnosis of 2.5 days is associated with an increase in mortality from 24% to 39%(22). Hence, early detection of AL after colorectal surgery is crucial in order to minimize morbidity and mortality.

Reliable biomarkers might contribute to early detection of AL. Recent studies have focused on different biomarkers for AL in both serum and drain fluid. Several biomarkers representing different stages of ischemia, inflammation and necrosis have been identified and yielded promising results. Peritoneal cytokines, lactate and pH seem to have the potential to detect AL early after colorectal surgery(23, 24). In addition, measuring *Enterococcus faecalis* in drain fluid may be an affordable and fast screening method(25). A systematic review concluded that combining biomarkers yields improved predictive accuracy compared to separate analysis of biomarkers(26).

Intervention

The choice of intervention for suspected AL is quite complex with very limited evidence available. Treatment strategies consist of non-surgical and surgical treatment options. Antibiotics and radiological drainage are nonsurgical treatment options. Surgical drainage, removal or repair of the anastomosis and creation of a deviating ileostomy or permanent colostomy are surgical treatment options(27). The type of intervention strongly depends on the severity of AL and the general condition of the patient(28).

Preservation of the anastomosis, most often with diversion of the fecal stream by ostomy seems safe when both sepsis and fecal contamination are absent(29, 30). A questionnaire amongst members of the Dutch Society for Gastrointestinal Surgery showed that Dutch colorectal surgeons, in case of a left sided colonic or rectal anastomosis, prefer preserving the anastomosis in non-septic young patients whereas in older patients or in patients with abdominal sepsis, they prefer sacrificing the anastomosis with the construction of an end colostomy(28). Nevertheless, half of all patients who undergo stoma formation due to leakage are left with a permanent stoma(31).

Finally, also minimal invasive strategies for the management of AL after colorectal surgery are under scrutiny. Traditional management mandates laparotomy, however nowadays AL can safely be managed laparoscopically(32). Moreover, endoluminal vacuum therapy seems effective in treating extraperitoneal AL(33, 34).

Prevention

Prevention of AL and its clinical consequences after colorectal surgery is ideal, although most innovative prevention strategies are still in an experimental phase. The unknown pathophysiology of AL after colorectal resection impedes development of well-founded prevention strategies and emphasizes the need for an integrated approach.

Preoperative risk assessment and optimization of adjustable risk factors such as smoking and obesity might prevent AL(35). Moreover, pre-operative risk assessment also facilitates intra-operative decision-making whether to protect the anastomosis from passage of intraluminal content by constructing an ostomy. However, diversion seems not to reduce the incidence of AL, instead it only minimizes its consequences(8, 36).

The GRECCAR 5 trial has shown that pelvic drainage after rectal excision for rectal cancer does not prevent AL in an early postoperative phase, but it was not found to be detrimental either(37). Hence, the opportunity to detect AL with innovative drain fluid analysis might justify pelvic drainage after rectal resection.

Surgeons have attempted to detect leakage with intraoperative tests assessing anastomotic integrity and thereby leaving the possibility for immediate repair. These methods have emerged over the last decades. The air leak test (ALT) is one of these techniques and used most frequently, although convincing evidence is scarce(38). Endoscopic visualization of colorectal anastomoses is another intraoperative test and might be a useful tool visualizing the intraluminal anastomotic line(39). The next advancement involves measurement of microperfusion at the anastomotic site and holds great potential(40). In this field, indocyanine green (Icg)-enhanced fluorescence is one of the latest techniques yielding promising results(41). Future studies require proper study design and sufficient sample size in order to determine their effectiveness in preventing AL.

It was previously demonstrated that mechanical bowel preparation does not reduce the leakage rate and should therefore not be prescribed routinely(42). However, recent evidence showed that there may be a role for the combination of oral antibiotics and mechanical bowel preparation in the prevention of anastomotic leakage after colorectal resection(43, 44)

In addition, techniques that mechanically protect the anastomosis from leaking have been proposed. Tissue adhesives such as sealants used to reinforce the anastomosis showed promising results although translation to clinical research is lacking(45, 46). Intraluminal devices which mechanically shield intraluminal content from the anastomosis are under scrutiny, however results of recent studies were disappointing(47, 48).

Outline of this thesis

Even in 2019, colorectal AL remains the most serious complication after colorectal resection. Although the outcomes of colorectal surgery have been improved over the last decades, the incidence of AL has not been reduced. This emphasizes the need for an integrated approach of clinical perspectives for this postoperative complication. Improved risk assessment, surgical techniques and early detection offer opportunities to reduce the incidence as well as to minimize the consequences of this postoperative complication. Therefore, the aim of this thesis is to explore new clinical perspectives of colorectal AL in order to minimize the incidence and the consequences of this severe postoperative complication.

In *Part I* of this thesis, risk assessment of anastomotic leakage after colorectal resection is described.

In **Chapter 2** risk factors are identified for early and late AL separately. The hypothesis that early AL is related to technical failure and late AL to healing deficiencies is evaluated.

In **Chapter 3** it is investigated whether the interval between preoperative short-course radiotherapy and surgery for rectal cancer influences the incidence of AL.

In **Chapter 4** the association between age and AL after colorectal resection is explored.

In **Chapter 5**

In *Part II* of this thesis, surgical techniques are evaluated.

In **Chapter 6** postoperative morbidity between laparoscopic (LaTME) and transanal total mesorectal excision (TaTME) for rectal cancer is compared.

In **Chapter 7** it is assessed whether postoperative morbidity is influenced by the number of surgeons involved in the surgical procedure in a low-volume hospital.

In *Part III* of this thesis, prevention of AL after colorectal resection is addressed.

In **Chapter 8** a systematic review and meta-analysis are described exploring whether the intraoperative ALT prevents colorectal clinically manifest AL.

In *Part IV* of this thesis, innovative techniques for early detection of AL are evaluated.

In **Chapter 9** available literature on systemic and peritoneal inflammatory cytokines measurement for early detection of colorectal AL is evaluated in a systematic review and meta-analysis.

In **Chapter 10** an international multicenter prospective cohort study aims to assess a combination of biomarkers as a clinically useful tool for early detection of AL after rectal resection.

In **Chapter 11** the findings of this thesis will be discussed.

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PART I

RISK ASSESSMENT OF COLORECTAL ANASTOMOTIC LEAKAGE

Chapter 2

Different risk factors for early and late colorectal anastomotic leakage in a nation-wide audit*

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Abstract

Background

Anastomotic leakage remains a major complication after surgery for colorectal carcinoma, but its origin is still unknown. Our hypothesis was that early anastomotic leakage is mostly related to technical failure of the anastomosis, and that late anastomotic leakage to healing deficiencies.

Objective

The aim of this study was to assess differences in risk factors for early and late anastomotic leakage.

Design

This was a retrospective cohort study.

Settings

The Dutch ColoRectal Audit is a nationwide project that collects information on all Dutch patients undergoing surgery for colorectal cancer.

Patients

All patients undergoing surgical resection for colorectal cancer in the Netherlands between 2011-2015 were included.

Main Outcome Measures

Late anastomotic leakage was defined as anastomotic leakage leading to reintervention later than 6 days postoperatively.

Results

In total, 36 929 patients were included; early anastomotic leakage occurred in 863 (2.3%) patients, and late anastomotic leakage occurred in 674 (1.8%) patients. From a multivariable multinomial logistic regression model, independent predictors of early anastomotic leakage relative to no anastomotic leakage and late anastomotic leakage relative to no anastomotic leakage included male sex (OR 1.8 $p < 0.001$ and OR 1.2 $p = 0.013$) and rectal cancer (OR 2.1 $p < 0.001$ and OR 1.6 $p = 0.046$). Additional independent predictors of early anastomotic leakage relative to no anastomotic leakage included BMI (OR 1.1 $p = 0.001$), laparoscopy (OR 1.2 $p = 0.019$), emergency surgery (OR 1.8 $p < 0.001$) and no diverting ileostomy (OR 0.3 $p < 0.001$). Independent predictors of late anastomotic leakage relative to no anastomotic leakage were Charlson Comorbidity Index of ≥ II (OR 1.3 $p = 0.003$), ASA score

III to V (OR 1.2 p = 0.030), preoperative tumor complications (OR 1.1 p = 0.048), extensive additional resection because of tumor growth (OR 1.7 p = 0.003), and preoperative radiation (OR 2.0 p=0.010).

Limitations

This was an observational cohort study.

Conclusions

Most risk factors for early anastomotic leakage were surgery-related factors, representing surgical difficulty, which might lead to technical failure of the anastomosis. Most risk factors for late anastomotic leakage were patient related factors, representing the frailty of patients and tissues, which might imply healing deficiencies.

Introduction

Surgical resection is the standard for curative treatment of colorectal cancer. Unfortunately, anastomotic leakage (AL) remains a major complication after resection, but its origin is still mainly unknown. The incidence of AL in the literature varies from 3% to 28% and one-third of all postoperative mortality is related to AL(1). Delay in diagnosing AL results in increased postoperative mortality(2).

In general, AL is diagnosed within the first 2 weeks after surgery(3-5). In previous studies, late AL was defined as AL diagnosed 21 or 30 days after surgery or as AL diagnosed after hospital discharge(6-11). However, a recent study advocated that redefinition of early and late AL with a proper cutoff point of a specific day is necessary for precise discrimination and they determined the cutoff at postoperative day 6(12). This demonstrates that there is no consensus in the literature regarding the definition of late AL.

Most previous studies suggested that early and late AL are different entities, although these studies were based on relatively small sample sizes(6-11). These previous studies showed that the postoperative course differs for patients with early AL and late AL. Patients with early AL are more likely to undergo re-laparotomy as intervention(10, 12). However, the long-term stoma retention rate in patients with late AL is higher than in patients with early AL(11). These differences in postoperative course emphasize that, in clinical practice, more attention should be paid to the distinction between early AL and late AL. In addition, better insight in the nature of AL could also contribute to early detection of AL, especially of late AL, because one-third of AL is diagnosed after 30 days after surgery(13).

A technically not well-constructed anastomosis might result in immediate anastomotic dehiscence with subsequent clinical symptoms, whereas a well-constructed anastomosis will develop anastomotic dehiscence more slowly in case wound healing is impaired. The aim of this study was to assess differences in risk factors for early and late AL to demonstrate whether early AL is related to technical failure of the anastomosis and late AL to healing deficiencies.

Methods

Data were derived from the Dutch ColoRectal Audit (DCRA), a nationwide quality improvement project, that collects information on all Dutch patients undergoing surgical resection for primary colorectal cancer. Data registered were patients', tumor and treatment characteristics as well as patient outcomes. For this study no ethical approval or informed consent was required under Dutch law. Further details of this dataset regarding collection and methodology have been published previously(14).

Inclusion and exclusion criteria

All patients undergoing surgical resection for primary colorectal cancer in the Netherlands between January 2011 and December 2015 and registered in the DCRA before March 31th 2016 were included in this study. Patients without a primary anastomosis, and patients for whom the day of diagnosis of AL was unknown were excluded from analysis. Patients in whom AL occurred later than 90 days after surgery were excluded. Data are usually registered at 30 days after surgery unless the initial hospital stay takes longer. Therefore, we considered data registered about AL later than 90 days after surgery as unreliable. We excluded patients with multiple synchronous tumors due to differences in prognosis(15).

Early versus late AL

AL was defined as clinically relevant AL that requires radiological or surgical re-intervention(16). We defined early AL as AL leading to reintervention until day 6 postoperatively and late AL as AL leading to reintervention after day 6 postoperatively. In previous literature, there is no consensus on the definition of late AL. To test our hypothesis, it was not sufficient to base our definition on the day of discharge, which is highly sensitive to institutes and other postoperative complications. Although it might be a fluent transition for early to late AL, for precise discrimination we think it is important to use a definition based on a specific day. Besides, the transition in origin of AL from technical failure to healing deficiencies should be captured during the first postoperative days.

Outcomes

Early and late ALs were primary outcome measures. Potential risk factors for early and late AL were retrieved from the DCRA database including patients characteristics (sex, age, BMI, Charlson Comorbidity Index(17, 18), ASA score(19), and previous abdominal surgery), tumor characteristics (tumor location, tumor stage, metastasis, and preoperative tumor complication), and treatment characteristics (surgical technique, urgency of surgery, diverting ileostomy, additional resection of adjacent organs because of tumor growth or because of metastasis and preoperative radiotherapy). In the DCRA database, preoperative tumor characteristics were specified as anemia, ileus, abscess, and perforation.

Statistical analysis

Multiple imputation was performed to deal with missing values assuming data were missing at random(20). Five imputed datasets have been created based on AL, hospital, sex, Charlson Comorbidity Index, diverting ileostomy, metastasis and preoperative tumor complication. Multivariate multinominal logistic regression analyses were performed to test independent associations between patient, tumor and treatment characteristics and the occurrence of no, early and late AL. A multinominal logistic regression model is applicable when an outcome variable has more than 2 categories, but no ordering in these categories can be assumed. All clinically relevant variables were added to the model as independent variables (full model). Covariate selection was driven by available knowledge and biological plausibility of potential confounders. Tests for interactions between covariates were not implemented. More details concerning the relevant predictors of AL were described elsewhere(21, 22). Results were reported as ORs with 95% CI. Significance was considered as a p-value of <0.05. All statistical analyses were performed in SPSS version 22.

Results

A total of 49 941 patients underwent surgery for primary colorectal cancer in the Netherlands between 2011 and 2015. After exclusion of patients without a primary anastomosis (n = 11 246), 38 695 patients were eligible for inclusion. Patients in whom AL occurred later than 90 days after surgery, and patients for whom the day of diagnosis of AL was unknown (n = 558) were excluded from analysis. Because of differences in prognosis we excluded patients with multiple synchronous tumors (n = 1208). In total, 36 929 patients were included.

Of these 36 929 patients, 80.9% underwent surgery for a colon tumor and 63.1% underwent laparoscopic surgery (Table 1).

AL leading to re-intervention occurred in 1537 (4.2%) patients. Early AL occurred in 863 (2.3%) patients and late AL occurred in 674 (1.8%) patients. The median interval between colorectal resection and intervention for AL was 6 days. The median interval between colorectal resection and intervention for early AL was 4 days, and for late AL, the median interval between colorectal resection and intervention was 10 days. In 18%, AL was diagnosed after hospital discharge. In patients with early AL, 3.1% were diagnosed after hospital discharge, and in patients with late AL, 37.4% was diagnosed after hospital discharge. The incidence of early AL in patients with a colon tumor was 2.3% and, in patients with a rectum tumor, the incidence was 2.4%, whereas the incidence of late AL was 1.6% in patients with a colon tumor and 3.0% in patients with a rectum tumor.

Table 1. Patient, tumor and treatment characteristics. Values in parentheses are percentages unless identified otherwise

		No anastomotic leakage n = 35392	Early anastomotic leakage n = 863	Late anastomotic leakage n = 674
Patient characteristics				
Sex	Female	16373 (46.3%)	276 (32.0%)	273 (40.5%)
	Male	19008 (53.7%)	587 (68.0%)	401 (59.5%)
	Missing	11 (0.0%)	0	0
Age, mean ± SD, yr		69.3 (±10.67)	68.6 (±10.55)	69.0 (±9.83)
	Missing	16	0	0
BMI, mean ± SD, kg/m^3		26.3 (±4.71)	27.0 (±6.54)	26.4 (±4.81)
	Missing	1332	21	13
Charlson Comorbidity Index	0	18401 (52.0%)	428 (49.6%)	311 (46.1%)
	I	8025 (22.7%)	197 (22.8%)	159 (23.6%)
	≥ II	8966 (25.3%)	238 (27.6%)	204 (30.3%)
ASA score	I-II	27872 (78.8%)	650 (75.3%)	503 (74.6%)
	III-V	7471 (21.1%)	213 (24.7%)	171 (25.4%)
	missing	49 (0.1%)	0 (0.0%)	0 (0.0%)

Table 1. (Continued)

		No anastomotic leakage n = 35392	Early anastomotic leakage n = 863	Late anastomotic leakage n = 674
Previous abdominal surgery	No	23332 (65.9%)	603 (69.9%)	435 (64.5%)
	Yes	12006 (33.9%)	257 (29.8%)	238 (35.3%)
	missing	54 (0.2%)	3 (0.3%)	1 (0.1%)
Tumor characteristics				
Tumor location	Colon	28723 (81.2%)	697 (80.8%)	463 (68.7%)
	Rectum	6669 (18.8%)	166 (19.2%)	211 (31.3%)
Tumor stage	T1	3867 (11.0%)	84 (9.7%)	76 (11.3%)
	T2	7026 (20.0%)	140 (16.3%)	117 (17.4%)
	T3	19604 (55.4%)	524 (60.7%)	385 (57.1%)
	T4	4503 (12.8%)	112 (13.0%)	95 (14.1%)
	Missing	392 (0.8%)	3 (0.3%)	1 (0.1%)
Metastasis	No	32023 (90.5%)	770 (89.2%)	600 (89.0%)
	Yes	3369 (9.5%)	93 (10.8%)	74 (11.0%)
Preoperative tumor complication	No/missing	23378 (66.1%)	551 (63.8%)	423 (62.8%)
	Yes	12014 (33.9%)	312 (36.2%)	251 (37.2%)
	Perforation	253 (0.7%)	3 (0.3%)	5 (0.7%)
	Abscess	253 (0.7%)	3 (0.3%)	8 (1.2%)
	Anemia	6774 (19.1%)	147 (17.0%)	138 (20.5%)
	Ileus	3257 (9.2%)	116 (13.4%)	61 (9.1%)
Treatment characteristics				
Surgical technique	Open	12864 (36.3%)	292 (33.8%)	261 (38.7%)
	Laparoscopic	22343 (63.1%)	566 (65.7%)	410 (60.8%)
	Other/missing	185 (0.6%)	5 (0.5%)	3 (0.5%)
Urgency of surgery	Elective	31860 (90.0%)	738 (85.5%)	610 (90.5%)
	Urgent/ Emergency	3519 (9.9%)	125 (14.5%)	64 (9.5%)
	Missing	13 (0.0%)	0 (0.0%)	0 (0.0%)
Diverting ileostomy	No	29962 (84.7%)	796 (92.2%)	519 (77.0%)
	Yes	5430 (15.3%)	67 (7.8%)	155 (23.0%)
Additional resection because of tumor growth	No	31519 (89.1%)	797 (92.4%)	598 (88.7%)
	Limited	1727 (4.9%)	31 (3.6%)	38 (5.6%)
	Extensive	1121 (3.2%)	35 (4.1%)	38 (5.6%)
	Missing	1025(2.9%)	0 (0.0%)	0 (0.0%)
Additional resection because of metastasis	No	34140 (96.5%)	836 (96.9%)	642 (95.3%)
	Yes	1179 (3.3%)	26 (3.0%)	31 (4.6%)
	Missing	73 (0.2%)	1 (0.1%)	1 (0.1%)
Preoperative radiotherapy	No	28768 (81.3%)	694 (80.4%)	463 (68.7%)
	Radiation	2716 (7.7%)	52 (6.0%)	104 (15.4%)
	Chemo radiation	1994 (5.6%)	37 (4.3%)	56 (8.3%)
	Missing	1914 (5.4%)	37 (4.3%)	51 (7.6%)

From a multivariable multinomial logistic regression model, independent predictors of early AL relative to no AL and late AL relative to no AL included male sex (OR 1.8 95% CI 1.6 – 2.1 $p < 0.001$ and OR 1.2 95% CI 1.0 - 1.4 $p = 0.013$) and rectal cancer (OR 2.1 95% CI 1.6 -2.8 $p < 0.001$ and OR 1.6 95% CI 1.0 – 2.4 $p = 0.046$). Additional independent predictors of early AL relative to no AL included BMI (OR 1.1 95% CI 1.0 – 1.2 $p = 0.001$), laparoscopic surgery (OR 1.2 95% CI 1.0 - 1.4 $p = 0.019$), emergency surgery (OR 1.8 95%CI 1.4 - 2.2 $p < 0.001$) and no diverting ileostomy (OR 0.3 95% CI 0.2 – 0.4 $p < 0.001$). Independent predictors of late AL relative to no AL were Charlson Comorbidity Index of ≥II (OR 1.3 95% CI 1.1 – 1.6 $p = 0.003$), ASA score III to V (OR 1.2 95% CI 1.0 – 1.5 $p = 0.030$), preoperative tumor complications (OR 1.1 95% CI 1.0 – 1.4 $p = 0.048$), extensive additional resection because of tumor growth (OR 1.7 95%CI 1.2 – 2.5 $p = 0.003$), and preoperative radiation (OR 2.0 95%CI 1.2 - 3.4 $p = 0.010$) (Table 2).

Independent predictors for early AL relative to late AL were male sex (OR 1.5 95% CI 1.2 – 1.9 $p < 0.001$), laparoscopic surgery (OR 1.3 95% CI 1.0 – 1.6 $p = 0.048$), emergency surgery (OR 1.9 95% CI 1.3 – 2.7 p = < 0.001), no diverting ileostomy (OR 0.4 95% CI 0.2 – 0.6 $p < 0.001$), and no preoperative radiotherapy (OR 0.4 95% CI 0.2 – 0.8 $p = 0.005$). These variables had a different effect on the occurrence of early AL compared to late AL (Table 2).

In addition, stratification for colon and rectum showed that diverting ileostomy and preoperative radiotherapy were independent risk factors for late AL in rectum tumors but not for colon tumors. Furthermore, in the stratified analysis open surgery was an independent risk factor for early AL in colon tumors while laparoscopic surgery was an independent risk factor for early AL in rectum tumors.

Table 2. Multivariate multinomial logistic regression model representing independent risk factors for early and late anastomotic leakage**.**

		Early vs no anastomotic leakage		Late vs no anastomotic leakage		Early vs late anastomotic leakage	
		OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Patient characteristics							
Sex	Female	1.0		1.0		1.0	
	Male	**1.8 (1.6 - 2.1)**	**<0.001**	**1.2 (1.0 - 1.4)**	**0.013**	**1.5 (1.2 - 1.9)**	**<0.001**
Age, per 10-year increase		**0.9 (0.9 - 1.0)**	**0.015**	1.0 (0.9 - 1.1)	0.413	1.0 (0.9 - 1.0)	0.322
BMI, per 5 kg/m^2 increase		**1.1 (1.0 - 1.2)**	**<0.001**	1.0 (0.9 - 1.1)	0.881	1.0 (1.0 - 1.2)	0.079
Charlson Comorbidity Index	0	1.0		1.0		1.0	
	I	1.0 (0.9 - 1.2)	0.707	1.2 (1.0 - 1.5)	0.078	0.9 (0.7 - 1.1)	0.279
	≥ II	1.1 (0.9 - 1.3)	0.206	**1.3 (1.1 - 1.6)**	**0.003**	0.8 (0.6 - 1.1)	0.169
ASA score	I-II	1.0		1.0		1.0	
	III-V	1.2 (1.0 - 1.4)	0.091	**1.2 (1.0 - 1.5)**	**0.030**	0.9 (0.7 - 1.2)	0.618
Previous abdominal surgery	No	1.0		1.0		1.0	
	Yes	1.0 (0.8 - 1.1)	0.566	1.1 (0.9 - 1.3)	0.262	0.9 (0.7 - 1.0)	0.220
Tumor characteristics							
Tumor location	Colon	1.0		1.0		1.0	
	Rectum	**2.1 (1.6 - 2.8)**	**<0.001**	**1.6 (1.0 - 2.4)**	**0.046**	1.4 (0.8 - 2.3)	0.240
Tumor stage	T1	1.0		1.0		1.0	
	T2	1.0 (0.7 - 1.3)	0.721	0.8 (0.6 - 1.1)	0.119	1.2 (0.8 -1.8)	0.365
	T3	1.3 (1.0 - 1.6)	0.067	1.0 (0.8 - 1.3)	0.832	1.2 (0.9 - 1.7)	0.267
	T4	1.2 (0.9 - 1.6)	0.312	1.1 (0.8 - 1.5)	0.652	1.1 (0.7 - 1.7)	0.722
Metastasis	No	1.0		1.0		1.0	
	Yes	1.1 (0.8 - 1.4)	0.593	1.1 (0.8 - 1.4)	0.478	1.0 (0.7 - 1.4)	0.980
Preoperative tumor complication	No	1.0		1.0		1.0	
	Yes	1.0 (0.8 - 1.1)	0.816	**1.1 (1.0 - 1.4)**	**0.048**	0.8 (0.7 - 1.0)	0.220
Treatment characteristics							

Table 2. (Continued)

		Early vs no anastomotic leakage		Late vs no anastomotic leakage		Early vs late anastomotic leakage	
		OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Surgical technique	Open	1.0		1.0		1.0	
	Laparoscopic	**1.2 (1.0- 1.4)**	**0.019**	1.0 (0.8 - 1.1)	0.619	**1.3 (1.0 - 1.5)**	**0.048**
Urgency of surgery	Elective	1.0		1.0		1.0	
	Emergency	**1.8 (1.4 - 2.2)**	**<0.001**	0.9 (0.7 - 1.3)	0.711	**1.9 (1.3 - 2.7)**	**<0.001**
Diverting ileostomy	No	1.0		1.0		1.0	
	Yes	**0.3 (0.2 - 0.4)**	**<0.001**	0.8 (0.6 - 1.1)	0.207	**0.4 (0.2 - 0.6)**	**<0.001**
Additional resection because of tumor growth	No	1.0		1.0		1.0	
	Limited	0.8 (0.6 - 1.2)	0.364	1.2 (0.9 - 1.7)	0.259	0.7 (0.4 - 1.1)	0.146
	Extensive	1.3 (0.9 – 2.0)	0.136	**1.7 (1.2 - 2.5)**	**0.003**	0.8 (0.5 - 1.3)	0.330
Additional resection because of metastasis	No	1.0		1.0		1.0	
	Yes	0.9 (0.6 - 1.3)	0.544	1.2 (0.8 - 1.8)	0.478	0.8 (0.4 - 1.4)	0.347
Preoperative radiotherapy	No	1.0		1.0		1.0	
	Radiation	0.8 (0.6 - 1.2)	0.265	**2.0 (1.2 - 3.4)**	**0.010**	**0.4 (0.2 - 0.8)**	**0.005**
	Chemo radiation	0.9 (0.6 - 1.5)	0.684	1.4 (0.8 - 2.8)	0.256	0.6 (0.2 - 1.6)	0.310

Discussion

This study showed that male sex and rectal cancer were independent risk factors for both early and late AL. Younger age, increased BMI, laparoscopic surgery, emergency surgery, and no a diverting ileostomy were independent risk factors for early AL. In addition, high Charlson Comorbidity Index, high ASA score, preoperative complications, additional resection because of tumor growth, and preoperative radiotherapy were independent risk factors for late AL. Male sex, laparoscopic surgery, emergency surgery, construction of diverting ileostomy and preoperative radiotherapy had a different effect on the occurrence of early, compared with late AL. Our results demonstrated that most risk factors for early AL were surgery-related factors, representing surgical difficulty, which might lead to technical failure of the anastomosis. Most risk factors for late AL were patient-related factors, representing the frailty of patients and tissues that influences the healing capacity of bowel tissue.

The results of this study are in accordance to previous literature. A previous study has shown that prolonged duration of surgery and blood loss during surgery, both representing surgical difficulty, were related to early AL(6). Another study indicated that preoperative radiotherapy or chemoradiation was a risk factor for late AL(7, 10, 11). Although, it has been demonstrated that advanced tumor stage (American Joint Committee on Cancer stage III-IV) and a histological finding of poorly differentiated or mucinous adenocarcinoma were independent risk factors for early AL, this study did not find this(11). One study found a low incidence of late AL (0.04%) and the authors attributed this to the extended period of pelvic drainage, which may shortened the interval of diagnosis(8). On the contrary, another study reported an incidence of AL after 30 days postoperatively of 31.6%(23). It should be taken into account that these previous studies applied different definitions for late AL. Besides, these previous studies were based on relatively small sample sizes.

Male sex was an independent risk factor for both early AL and late AL, and thus for AL in general. However, male sex seemed to be a greater risk factor for early AL when compared to late AL. This could be attributable to the smaller pelvis and stronger muscular wall in males, which impedes surgery. Furthermore, rectal cancer was an independent risk factor for both early and late AL which can be explained by the fact the risk of AL in general is increased for anastomoses situated closer to the anal verge(24).

Younger age and increased BMI were independent risk factors for early AL, possibly because younger patients are less prone to healing deficiencies. Also, increased BMI is associated with AL in colorectal surgery(25). The increased mesocolon thickness and abdominal pressure in obese patients may complicate the construction of the anastomosis. However, increased BMI is related to impaired microcirculation, which is considered to decrease the healing capacity at the anastomotic site, which may also play a role for late AL, although this study did not demonstrate this.

Furthermore, we found that laparoscopic surgery was an independent risk factor only for early AL. The COLOR study indicated that the incidence of AL does not differ between laparoscopic and open surgery(26, 27). Nevertheless, it has been shown recently that risk factors for AL are different between laparoscopic and open surgery. Risk factors for AL after laparoscopic surgery were related to surgical difficulty(28). This is in accordance to our findings and hypothesis. Furthermore, in the early years of laparoscopic surgery some comorbidities were considered as contraindications for laparoscopic surgery. Therefore, in this observational study, we should take into consideration that selection bias might have affected our results even though we have adjusted for comorbidities in the multivariate analysis.

Emergency surgery was also identified as an independent risk factor for early AL. Emergency surgery is often performed during evening and night shifts because of acute indications. Surgery at these hours is associated with worse postoperative outcomes(29, 30). Colorectal surgery performed during evening and night shift is related to AL(31). Surgery at these times might be performed by less specialized surgeons implying surgical difficulty due to less experience highly suggestive for technical failure of the anastomosis.

Preoperative tumor complications were heterogeneous in influencing our hypothesis, because these not only represent surgical difficulty but also frailty of patients' tissue at the anastomotic site. Nevertheless, our results proposed that preoperative tumor complications were an independent risk factor for late AL. Table 1 showed that almost 20% of the preoperative tumor complications was anemia which may lead to reduced healing capacity at the anastomotic site. Furthermore, ileus could also strongly affect the quality of bowel tissue, but this also represents surgical difficulties constructing the anastomosis.

No diverting ileostomy was an independent risk factor for early AL. From DCRA it was previously shown that stoma construction in rectal surgery does not affect the incidence of AL or mortality rates(32). In addition, it was recently shown that, when AL occurred in patients with a diverting ileostomy that fewer reinterventions were required, which could be suggestive for less severe clinical presentation of AL(33). It might be possible that a diverting ileostomy delays the diagnosis of AL because of less severe presentation of AL.

Also, additional resection because of tumor growth was an independent risk factor for late AL. These major surgical procedures are demanding for patients, among others because of blood loss and hypotension during surgery. Hypotension compromises local tissue perfusion and leads to reduced tissue oxygenation, causing healing deficiencies. Surgery with additional resections because of tumor growth is also technically demanding but might not specifically complicate the construction of the anastomosis.

Preoperative radiotherapy is indicated in most cases of rectal cancer(34). Preoperative radiotherapy reduces the incidence of local recurrence but is also related to higher postoperative morbidity(35). Our results showed that preoperative radiotherapy was an independent risk factor for late AL. Preoperative radiotherapy not only affects tumor tissue but also the surrounding healthy tissue including the adjacent bowel wall and its vascularization. This could imply decreased healing capacity at the anastomotic site and therefore be related to late AL.

In addition, stratification for colon and rectum showed comparable results. As expected, diverting ileostomy and preoperative radiotherapy were not a risk factor for late AL in colon resections possibly due to the small numbers because these strategies are usually not applied in the treatment of colon tumors. Furthermore, in the stratified analysis open surgery was an independent risk factor for early AL in colon tumors while laparoscopic surgery was an independent risk factor for early AL in rectum tumors. However, laparoscopic approach reflects a technical challenging procedure, it is possible that, in colon surgery, open approach was used more often for difficult cases, resulting in selection bias.

In this study, the cutoff between early and late AL was set on 6 days based on the median. However, the transition from early AL, hypothesized to be related to surgical difficulty, to late AL, hypothesized to be related to frailty of tissue and patients, might not be captured at this exact day, and the transition might very well be a more fluent process. Therefore, we could not state that there are two separate populations of AL, but our findings indicate that, within the group of AL, there might be different entities.

This distinction in origin between early and late AL also has implications for fair comparison of quality of hospitals. In early AL, the technical skills of the surgeon have more of influence, and, hence the surgeon could be more accountable, whereas, for late AL, patient characteristics might be of more influence.

There were some limitations in our study. First, the definition of late AL was arbitrary. This study only evaluated clinically relevant AL that required re-intervention, and, therefore the definition of late AL was based on the day of reintervention. For this retrospective study, registration of day of intervention was more reliable than day of clinical symptoms. In previous studies, late AL was defined as AL diagnosed after hospital discharge, after 6, 21 or 30 days postoperatively. Most previous studies aimed to determine whether there are two entities of colorectal AL. However, we hypothesized that the time of occurrence of AL reflects the origin of leakage. Therefore, we defined late AL as AL leading to re-intervention after day 6 postoperatively, which was the median (postoperative day 6). Since data were available, we have also performed the analysis with the cutoff point of late AL at first quartile of discharge (day 5) and third quartile of discharge (day 10). These analyses did not fundamentally change the results presented in our study and the conclusion was similar.

Second, the DCRA data are usually registered until 30 days after surgery unless the initial hospital stay is longer. Therefore, extreme late AL is not included. Besides, the underregistration of AL in general might be a problem in nation-wide databases. Last, the analysis of observational data could be affected by confounding and this might lead to bias. Although we performed a multivariate analysis to adjust for patient, tumor and treatment characteristics, still unknown confounding factors could be present that were not registered in the DCRA, such as medication use, smoking, criteria for diverting ileostomy, mobilization of splenic flexure, blood loss, and operative time.

However, the strength of this study was that results were based on a nationwide cohort representing a large sample size that induces statistical power to detect differences between risk factors for early and late AL. Furthermore, previous studies only concerned AL of the sigmoid and rectum; we have now shown that our hypothesis may be applicable to AL of all colorectal cancers.

Conclusion

This study demonstrated that early and late AL have different risk factors. Our findings suggest that risk factors for early AL are related to surgical difficulty that may lead to technical failure of the anastomosis, resulting in immediate anastomotic dehiscence, whereas risk factors for late AL are related to frailty of patients and tissues, which may imply healing deficiencies at the anastomotic site leading to delayed anastomotic dehiscence in a possibly technically well-constructed anastomosis. In our opinion, especially in patients with high risk for late AL, it is important for surgeons to inform patients about possible occurrence of AL in the late postoperative period especially since 18% of AL occurred after hospital discharge. Furthermore, in early AL, quality of the surgery seems more of influence than in late AL, so hospital comparison should consider the different entities separately, with different case-mix adjustments.

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Chapter 3

Anastomotic leakage and interval between preoperative short-course radiotherapy and operation for rectal cancer*

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Abstract

Background

Short-course preoperative radiotherapy is indicated in patients with resectable rectal cancer to control local recurrence. Although no clear evidence is available, short-course radiotherapy with operation within one week is common practice. The aim of this study was to investigate the impact of timing of operation for rectal cancer after short-course radiotherapy on anastomotic leakage.

Study Design

Data from the Dutch ColoRectal Audit (DCRA) were used. All patients who received short-course preoperative radiotherapy and underwent elective operation within 14 days for rectal cancer between January 1st, 2011 and December 31th, 2016 were included. Interval between radiotherapy and operation was calculated by extracting date of start of radiotherapy from the date of operation. Patients were divided into short interval (<4 days) and long interval (>4 or more days). The interval and other patient or perioperative parameters were included in univariable and multivariable logistic regression analyses to identify independent associations with anastomotic leakage.

Results

In total, 2131 patients were eligible for analysis: 1055 (49.5%) patients had operations <4 days after radiotherapy and 1076 (50.5%) patients had operation after 4 or more days. One hundred and eighty-five (8.7%) patients experienced anastomotic leakage. The incidence of anastomotic leakage was significantly higher in patients who underwent operation within <4 days (10.1% vs 7.2% p = 0.018). In the multivariable analysis, an interval of <4 days was significantly associated with anastomotic leakage (OR 1.438, 95% CI 1.054 - 1.962 p = 0.022).

Conclusion

Elective surgery for rectal cancer <4 days after preoperative short-course radiotherapy resulted in an increase of anastomotic leakage.

Introduction

Short-course preoperative radiotherapy (RT) is indicated in patients with resectable rectal cancer to control local recurrence and to improve long-term cancer specific survival(1-3). Although acknowledged for its evident benefit for oncological outcomes, RT has also been challenged for its influence on postoperative morbidity and mortality. Mortality has been proven not to be increased with optimal strategies of radiation(4), and, with regard to post-operative morbidity, short-course preoperative RT seems to lead to slightly more complications after operation. Among these, anastomotic leakage (AL) is the most feared, and leads to increased postoperative morbidity and mortality(5).

In most countries, operations are scheduled within 1 week after the end of short-course RT. However, no clear evidence regarding the optimal timing of operation after short-course RT is currently available. Performing operation at the time of maximum radiation effect might complicate the construction of an anastomosis because of inflammation and irritation of the bowel tissue. This might also compromise anastomotic healing and could even result in AL. To this end, we aim to investigate the influence of the interval between short-course preoperative RT and operation for rectal cancer with regard to the incidence of AL.

Methods

Dutch ColoRectal Audit

Data were derived from the Dutch ColoRectal Audit (DCRA), which registers all colorectal cancer resections in The Netherlands. The DCRA is a nationwide web-based registry. Completeness and accuracy of the DCRA is validated by comparison to the Netherlands Cancer Registry. No ethical approval nor informed consent was required for this study under Dutch law. Detailed information regarding data collection and methodology of the DCRA was published previously(6).

Patient selection

All patients who received short-course preoperative RT and underwent operation for rectal cancer between January 1, 2011 and December 31, 2016 were selected. Patients without a primary anastomosis and patients with preoperative chemotherapy were excluded. In addition, patients with an unknown interval between RT and operation or with an interval <0 days or >14 days were excluded. Patients with an interval <0 days were operated before the end of RT because of an acute indication or incorrectly registered. Patient with an interval of >14 days did not comply to common clinical practice or were patients who were too frail to undergo chemoradiation including long-course radiation (25x5 Gy) or long-course radiation without chemotherapy and received short-course RT with delayed operation after 8 weeks, as this is indicated in the Dutch Guidelines. In this respect, patients with an interval >14 days were excluded to ensure homogeneity. In addition, patients undergoing urgent operations were excluded.

Interval

A conventional short-course preoperative RT scheme for rectal cancer consists of 5x5 Gy, which is delivered at consecutive days (www.oncoline.nl). Interval in days between RT and operation was calculated with the start date of RT and the date of operation. It was possible to calculate the interval between the end of RT and operation because RT was administered during weekdays only. Therefore, the interval between the end of RT and operation could be estimated by subtracting 4 days from the interval when the RT started on Monday or by subtracting 6 days from the interval when the RT started on another day of the week, taking into account the weekend. Based on the median of the interval (4 days), patients were divided into short interval (<4 days) and long interval (≥4 days).

Outcomes

Anastomotic leakage was the primary outcome measure. In the DCRA, AL was defined as clinically relevant AL that requires radiological or surgical re-intervention (i.e. Grade B/C)

(7). The circumferential resection margin (CRM) and mortality within 30 days after operation were also registered in the DCRA database. Potential confounding factors were retrieved from the DCRA database including patient, tumor and treatment characteristics (sex, age, BMI, Charlson Comorbidity Index, ASA score, pathological TNM stage, resection margin, surgical technique, urgency of operation, construction of a diverting ileostomy, additional resection because of tumor growth).

Statistical analysis

Continuous variables were represented as medians with interquartile range and the Mann Whitney U test was used to compare medians. The Chi-square test or Fisher's exact test was used to compare dichotomous variables. One-way ANOVA test was used to compare categorical variables. Multivariate logistic analysis was performed to identify the effect of time interval on AL, while adjusting for confounding. All clinically relevant variables were included in the multivariable model. We calculated the area under the receiver's operating characteristics curve and performed the Hosmer-Lemeshow test for the full multivariable model. Statistical significance was defined as 2-sided P value < 0.050. SPSS® software 21.0 was used for statistical analysis (IBM, Armonk, New York, USA)

Results

In total, 5888 patients with preoperative short-course RT for rectal cancer were registered in the DCRA database between January 1th, 2011 and December 31th, 2016. Of these patients, 2747 patients without a primary anastomosis were excluded and 387 patients with preoperative chemotherapy were excluded. In addition, 134 patients with an unknown interval between RT and operation were excluded and 484 patients with an interval <0 days or >14 days were excluded. In addition, 5 patients underwent urgent operation and were excluded. In total, 2131 patients were eligible for analysis (Figure 1).

Figure 1. Flowchart of patient selection. DCRA, Dutch ColoRectal Audit.

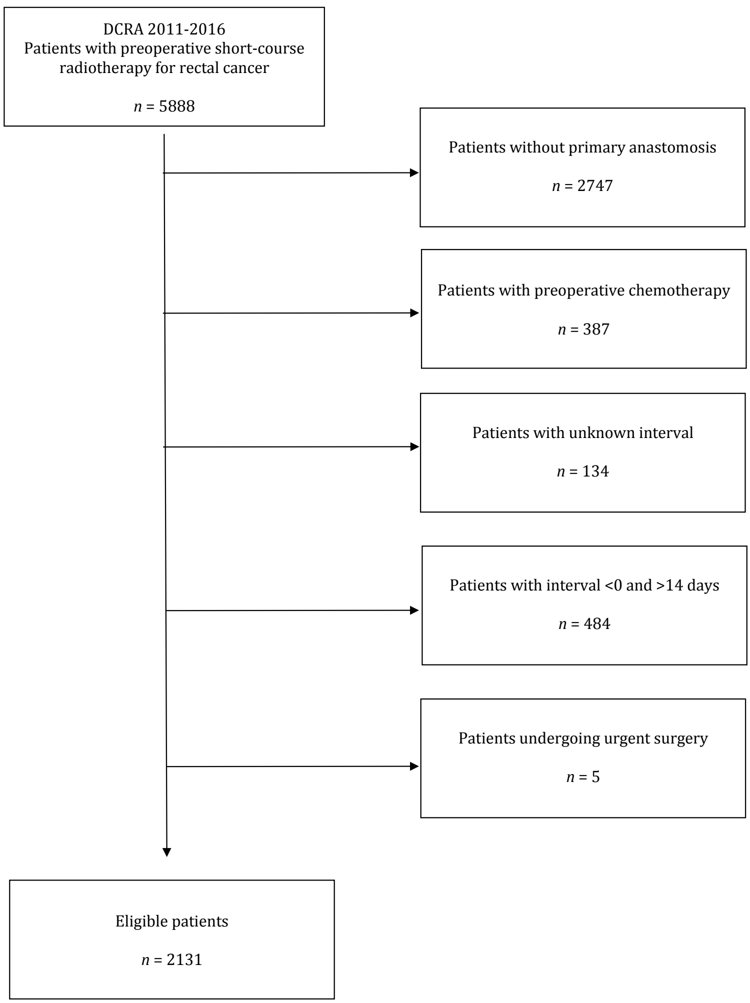

Table 1 shows patient, tumor and treatment characteristics associated with anastomotic leakage. Most patients were male (63.2%) and the median age was 67.0 years. Most patients had a pathological tumor stage of pT3 and a pathological nodal stage of pN0. In total, 79.2% of all procedures were performed laparoscopically and 68.1% of all patients received a diverting ileostomy during operation.

In total, 185 (8.7%) patients suffered from AL. Patients with AL were more often male (p = 0.025) and were significantly younger (p = 0.005). In patients with AL a diverting ileostomy was less frequently constructed during operation (p < 0.000). No statistically significant difference was found for BMI, Charlson Comorbidity index, ASA score, TNM stadium, surgical technique, urgency of operation, additional resection because of tumor growth, CRM and mortality (Table 1).

Table 1. Patient, tumor, and treatment characteristics associated with anastomotic leakage

Characteristic	Number of patients (n = 2131)	Anastomotic leakage (n = 185)	No Anastomotic leakage (n = 1946)	Missing	P value
Patient					
Sex, n (%)					
Male	1347 (63.2)	131 (70.8)	1216 (62.5)	1 (0.0)	0.025*
Female	783 (36.7)	54 (29.2)	729 (37.5)		
Age, y, median (IQR)	67.0 (60.0 – 73.0)	65.0 (59.0 – 71.0)	67.0 (60.0 – 73.0)	0 (0.0)	0.005*
BMI, kg/m^3, median (IQR)	26.0 (23.8 – 28.4)	26.0 (23.6 – 28.3)	26.0 (23.8 – 28.4)	22 (1.0)	0.976
Charlson Comorbidity Index, n (%)					
0	1388 (65.1)	120 (64.9)	1268 (65.2)	0 (0.0)	0.107
I	401 (18.8)	27 (14.6)	374 (19.2)		
≥ II	342 (16.0)	38 (20.5)	304 (15.6)		
ASA score, n (%)					
I-II	1900 (89.2)	162 (87.6)	1738 (89.3)	1 (0.0)	0.454
III-IV	230 (10.8)	23 (12.4)	207 (10.6)		
Tumor					
Distance to anal verge, cm, median (IQR)	10.0 (7.0 – 12.0)	9.0 (7.0 – 10.5)	10.0 (8.0 – 12.0)	46 (2.6)	0.001*
Pathological T stage, n (%)					
pT0	12 (0.6)	0 (0.0)	12 (0.6)	10 (0.5)	0.145†
pT1	171 (8.0)	21 (11.4)	150 (7.7)		
pT2	767 (36.0)	54 (29.2)	713 (36.6)		
pT3	1126 (52.8)	105 (56.8)	1021 (52.5)		
pT4	45 (2.1)	4 (2.2)	41 (2.1)		
Pathological N stage, n (%)					
pN0	1290 (60.5)	108 (58.4)	1182 (60.7)	17 (0.8)	0.697
pN1	563 (26.4)	50 (27.0)	513 (26.4)		
pN2	261 (12.2)	26 (14.1)	235 (12.1)		
Pathological M stage, n (%)					

Table 1. (Continued)

Characteristic	Number of patients (n = 2131)	Anastomotic leakage (n = 185)	No Anastomotic leakage (n = 1946)	Missing	P value
pM0	1983 (93.1)	171 (92.4)	1812 (93.1)	104 (4.9)	0.272†
pM1	44 (2.1)	6 (3.2)	38 (2.0)		
Treatment					
Surgical technique, n (%)					
Open	443 (20.8)	41 (22.2)	402 (20.7)	1 (0.0)	0.632
Laparoscopic	1687 (79.2)	144 (77.8)	1543 (79.3)		
Diverting ileostomy, n (%)					
Yes	1451 (68.1)	96 (51.9)	1355 (69.6)	0 (0.0)	0.000*
No	680 (31.9)	89 (48.1)	591 (30.4)		
Additional resection because of tumor growth, n (%)					
Yes	24 (1.1)	3 (1.6)	21 (1.1)	14 (0.7)	0.457†
No	2093 (98.2)	180 (97.3)	1913 (98.3)		
Interval, n (%)					
<4 days	1055 (49.5)	107 (57.8)	948 (48.7)	0 (0.0)	0.018*
≥4 days	1076 (50.5)	78 (42.2)	998 (51.3)		
Postoperative outcome					
CRM, n (%)					
R0	2067 (97.0)	183 (98.9)	1884 (96.8)	25 (1.2)	0.250†
R1-2	39 (1.8)	1 (0.5)	38 (2.0)		
Mortality, n (%)					
Yes	22 (1.0)	2 (1.1)	20 (1.0)	11 (0.5)	1.000†
No	2098 (98.5)	183 (98.9)	1915 (98.4)		

*Statistically significant
†Fisher's Exact Test
AL, anastomotic leakage
IQR, interquartile range
CRM, circumferential resection margin

Median interval between RT and operation was 4 days (Figure 2). Most patients had the operation on the third day after RT. In total, 1055 (49.5%) patients had operations in <4 days after RT while 1076 (50.5%) patients had operation after ≥4 days after RT (Table 2). The incidence of anastomotic leakage for patients who underwent operation in <4 days was significantly higher than for patients who underwent operation after ≥4 days (10.1% vs 7.2% p = 0.018). In addition, CRM involvement was more frequently observed in patients who underwent operation in <4 days after RT (2.6% vs 1.1% p = 0.013). Hospital stay and mortality were not significantly different for patients who underwent operation <4 days after RT. All other variables were not related to the interval between RT and operation.

Figure 2. Anastomotic leakage and the interval between short-course preoperative radiotherapy and operation. Percentages above the bars represent the incidence of anastomotic leakage.

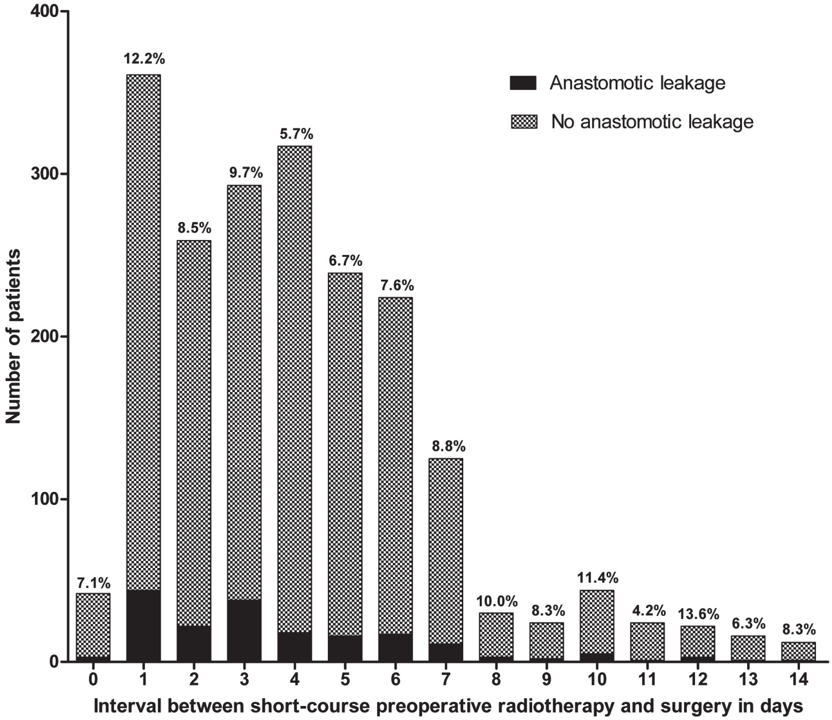

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Table 2. Patient, tumor, and treatment characteristics associated with interval between radiotherapy and operation

Characteristic	Number of patients (n = 2,131)	Interval <4 days (n = 1,055)	Interval ≥4 days (n = 1,076)	Missing	P value
Patient					
Sex, n (%)					
Male	1347 (63.2)	678 (64.3)	669 (62.2)	1 (0.0)	0.331
Female	783 (36.7)	377 (35.7)	406 (37.7)		
Age, y, median (IQR)	67.0 (60.0 – 73.0)	67.0 (60.0 – 73.0)	67.0 (60.0 – 73.0)	0 (0.0)	0.914
BMI, kg/m^3, median (IQR)	25.9 (23.8 – 28.4)	26.1 (23.9 – 28.9)	25.7 (23.7 – 28.1)	22 (1.0)	0.073
Charlson Comorbidity Index, n (%)					
0	1388 (65.1)	677 (64.2)	711 (66.1)	0 (0.0)	0.497
I	401 (18.8)	199 (18.9)	202 (18.8)		
≥ II	342 (16.0)	179 (17.0)	163 (15.1)		
ASA score, n (%)					
I-II	1900 (89.2)	932 (88.3)	968 (90.0)	1 (0.0)	0.205
III-IV	230 (10.8)	123 (11.7)	107 (9.9)		
Tumor					
Distance to anal verge, cm, median (IQR)	10.0 (7.0 – 12.0)	10.0 (8.0 – 12.0)	10.0 (7.0 – 12.0)	46 (2.6)	0.193
Tumor stage, n (%)					
pT0	12 (0.6)	3 (0.3)	9 (0.8)	10 (0.5)	0.407
pT1	171 (8.0)	84 (8.0)	87 (8.1)		
pT2	767 (36.0)	385 (36.5)	382 (35.5)		
pT3	1126 (52.8)	558 (52.9)	568 (52.8)		
pT4	45 (2.1)	19 (1.8)	26 (2.4)		
Pathological N stage, n (%)					
pN0	1290 (60.5)	642 (60.9)	648 (60.2)	17 (0.8)	0.506
pN1	563 (26.4)	268 (25.4)	295 (27.4)		
pN2	261 (12.2)	135 (12.8)	126 (11.7)		
Pathological M stage, n (%)					
pM0	1983 (93.1)	980 (92.9)	1000 (93.9)	104 (4.9)	0.824
pM1	44 (2.1)	21 (2.0)	23 (2.1)		
Treatment					
Surgical technique, n (%)					
Open	443 (20.8)	220 (20.9)	223 (20.7)	1 (0.0)	0.933
Laparoscopic	1687 (79.2)	834 (79.1)	853 (79.3)		
Diverting ileostomy, n (%)					
Yes	1451 (68.1)	711 (67.4)	740 (68.8)	0 (0.0)	0.494
No	680 (31.9)	344 (32.6)	336 (31.2)		
Additional resection because of tumor growth, n (%)					
Yes	24 (1.1)	13 (1.2)	11 (1.0)	14 (0.7)	0.649
No	2093 (98.2)	1036 (98.2)	1057 (98.2)		
Postoperative outcome					
CRM, n (%)					
R0	2067 (97.0)	1017 (96.4)	1051 (97.7)	25 (1.2)	0.013*

Table 2. (Continued)

Characteristic	Number of patients (n = 2,131)	Interval <4 days (n = 1,055)	Interval ≥4 days (n = 1,076)	Missing	P value
R1-2	39 (1.8)	27 (2.6)	12 (1.1)		
Anastomotic leakage, n (%)					
Yes	185 (8.7)	107 (10.1)	78 (7.2)	0 (0.0)	0.018*
No	1946 (91.3)	948 (89.9)	998 (92.8)		
Mortality, n (%)					
Yes	22 (1.0)	8 (0.8)	14 (1.3)	11 (0.5)	0.208
No	2098 (98.5)	1046 (99.1)	1052 (97.8)		

*Statistically significant
CRM, circumferential resection margin
IQR, interquartile range

Univariable and multivariable logistic regression models were performed to estimate the effect of interval between RT and operation on AL (Table 3). In the univariable analysis, an interval of <4 days was associated with AL (OR 1.444 95% CI 1.064 – 1.959 p = 0.018). When sex, age, BMI, diverting ileostomy and distance to the anal verge were added to the model, this significant association was still observed present (OR 1.438 95% CI 1.054 – 1.962 p = 0.028). The area under the receiver operating characteristics curve was 0.667 and the Hosmer-Lemeshow test obtained a Chi-square of 12.168 (p = 0.144).

Table 3. Multivariable logistic regression analysis of factors predicting anastomotic leakage

Characteristic	Univariable OR (95% CI)	P Value	Multivariable OR (95% CI)	P Value
Sex	0.688 (0.494 – 0.956)	0.026*	0.647 (0.462 – 0.906)	0.011*
Age per 10 years	0.843 (0.723 – 0.984)	0.030*	0.849 (0.725 – 0.995)	0.043*
BMI per 10 kg/m^2	1.071 (0.965 – 1.189)	0.199	1.136 (0.994 – 1.298)	0.062
Diverting ileostomy	0.470 (0.347 – 0.638)	0.000*	0.379 (0.275 – 0.524)	0.000*
Distance to anal verge per 2 cm	0.869 (0.792 – 0.953)	0.003*	0.808 (0.733 – 0.889)	0.000*
Interval <4 days	1.444 (1.064 – 1.959)	0.018*	1.438 (1.054 – 1.962)	0.022*

*Statistically significant
OR, odds ratio; CI confidence interval

Discussion

Preoperative RT can be considered a double-edged sword. Choosing a proper interval between short-course preoperative RT and operation can guarantee both its therapeutic effect and control its possible damage. Our study has shown that operation for rectal cancer within <4 days after short-course preoperative RT, which is the most commonly applied interval in the Netherlands, results in significantly more AL. The interval between short-course preoperative RT and operation is usually not determined by a medical-based decision. So, this study warns surgeons that an inappropriate interval between RT and operation may compromise surgical safety.

Initially, RT was developed in squamous cell carcinomas from head and neck regions to decrease local recurrence, to downstage the tumor to allow an operation and to preserve organ functions, which are the same motives for the use in rectal cancer. In contrast to squamous cell carcinomas, adenocarcinomas regress quite slowly as a result of RT(8). In most Western countries, short-course preoperative RT is administrated in patients with a resectable tumor to control local recurrence rather than to achieve downstaging of the tumor. For this reason, the interval between short-course preoperative RT and operation is relatively short. Based upon subgroup analyses of the Stockholm I,II and III and TME trial, operation after short-course RT should be performed within 5 days after RT(9). However, delaying operation for several weeks after short-course RT is recommended to achieve tumor down staging in elderly patients with a nonresectable rectal tumor who are too frail to tolerate conventional chemoradiation(10-12). Today the question is whether this strategy is also applicable to younger patients with regard to oncological outcomes and especially the reduction of postoperative mortality and morbidity. Recently the Stockholm III trial concluded that delayed operation (4-8 weeks) after short-course RT gave similar oncological outcomes compared to short-course RT with immediate operation (<1 week) and that postoperative complications were reduced substantially with delayed operation(13).

The interim analysis of the Stockholm III trial showed that more postoperative complications were seen in patients in the 5x5 group with immediate operation with an interval of 11-17 days between the start of RT and operation(4). In addition, a subgroup analysis of the TME trial showed that elderly patients operated 4–7 days after the last fraction of radiotherapy had higher mortality(14). In contrast, our study showed increased AL in patients operated <4 days after the end of short-course RT. These conflicting data might indicate that is even better to wait longer than the time period which was captured in our study (14 days), which is current clinical practice in The Netherlands, as the results of the Stockholm III trial suggested(13).

Most previous studies did not evaluate the incidence of AL with regard to an optimal timing of operation after neoadjuvant therapy because of the relatively low incidence of AL requiring large sample sizes to provide high level of evidence. Only one study reported that shorter intervals by one week between preoperative chemoradiation and operation for rectal cancer were associated with AL(15). In addition, a meta-analysis found no effect of neoadjuvant therapy for rectal cancer on the incidence of AL(16). This meta-analysis analyzed the effect of chemoradiation and radiation alone separately, however within the group of radiation alone no difference was made for long-term and short-course RT. The relatively long interval between long-term RT and operation might have affected this analysis because possibly enabling the bowel to heal from the damage caused by radiation.

We believe the interval between preoperative short-course RT and operation is of great importance because the interval is an easily adjustable factor in contrast to many well-known AL risk factors(17-19). Therefore, optimal strategies regarding the interval are highly desirable in clinical practice.

This study demonstrated that younger age is associated with AL, which is in line with previous population-based studies. Both the Danish Colorectal Group and the American College of Surgeons National Surgical Quality Improvement Program (NSQIP) concluded that increasing age is related to a lower risk of AL(18, 20, 21). Furthermore, a study from the Michigan Surgical Quality Collaborative cohort found a younger mean age in patients with AL(22). In addition, this study shows that the incidence of AL is lower in diverted patients (6.6% vs 13.1%) although the effect of a diverting ileostomy was not of this extent in previous literature(23). Nevertheless, this study included a homogenous study population in which all patients received short-course preoperative RT and a primary anastomosis.

This study also reported more CRM involvement in patients who underwent operation for rectal cancer within <4 days after RT (Table 2). Nevertheless, this finding was based on relatively small numbers since only 39 patients had a positive CRM. Unfortunately, it was not possible to establish the association with long-term oncological outcomes such as local recurrence and survival because the DCRA only registers until 30 days postoperatively. However, already in 1994 it was shown that CRM involvement is related to local recurrence(24). A few years later it was demonstrated that CRM involvement also influences distant metastasis and survival and therefore CRM involvement is considered an important prognostic marker for selecting patients for adjuvant therapy(25, 26).

With regard to the pathophysiology, we assume that RT not only affects tumor cells but also healthy surrounding tissue possibly compromising anastomotic healing. In animal experiments, anastomotic strength was decreased by long-term preoperative RT but for short-course preoperative RT no difference was observed(27). Another study indicated that long-term preoperative RT resulted in decreased blood flow at the anastomotic site(28). Nevertheless, clinical studies failed to demonstrate an association between preoperative RT and anastomotic leakage(16, 29).

There were some limitations in this study. First, this was an observational study susceptible to bias and confounding. Multivariable analysis was performed to reduce the effect of known confounding factors. Second, the DCRA database does not contain information on the smoking status and preoperative medication use. Therefore, we could not adjust for these factors, which are known to be related to AL. In addition, dichotomization of the interval might be associated with loss of power and residual confounding(30). The strength of this study is that results are based on a nation-wide cohort. In addition, the current study provides the best evidence so far about the effect of the interval on anastomotic leakage. However, a double-blind randomized controlled trial would provide the highest level of evidence, considering the relatively low event rate of AL, this design would require extremely large sample sizes. Nevertheless, other population-based studies could be used to address the same problem.

Conclusions

Today, accumulating evidence is available that delaying operation after short-course preoperative RT for rectal cancer is beneficial, resulting in less postoperative complications and oncological outcomes are similar. This study underlines that especially the incidence of AL, which is the most feared complication after rectal resection, is increased when operation for rectal cancer is performed <4 days after the end of RT. Prospective evaluation is required to assess evidence-based guidelines recommending optimal intervals between short-course preoperative RT and operation for rectal cancer.

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Chapter 4

The effect of age on anastomotic leakage in colorectal cancer surgery: a population-based study*

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Abstract

Background

The aim of this study was to investigate the effect of age on CAL and its associated mortality.

Methods

Data were derived from the Dutch ColoRectal Audit. All patients undergoing resection for colorectal cancer in the Netherlands between January 2011 and December 2016 were included. Univariable and multivariable logistic regressions were performed to test the effect of age on CAL and its associated mortality.

Results

In total, 45 488 patients were included. The incidence of CAL was 6.4% in patients <60 years old, 5.5% in patients 60-69 years old, 5.4% in patients 70-80 years old, and 4.9% in patients ≥ 80 years old ($p < 0.001$). Multivariate analysis showed that age was protective for CAL (OR 0.965 per 5 years 95% CI 0.941 – 0.985 $p < 0.001$). Mortality after CAL was 1.3% in patients <60 years old, 4.8% in patients 60-69 years old, 12.3% in patients 70-80 years old and 27.0% in patients >80 years old ($p < 0.001$). Older age was associated with mortality following CAL (OR 1.497 per 5 years 95% CI 1.364 – 1.647 $p < 0.001$).

Conclusions

This population-based study suggests a protective effect of increased age on CAL after colorectal cancer resection. However, older age is strongly associated with mortality after CAL.

Introduction

Colorectal cancer is the third most common cancer worldwide(1). The Netherlands Cancer Registry (NCR) reported that the incidence of colorectal cancer is rapidly increasing, from 9106 cases in 2000 to 15 427 in 2016(2). Several factors contribute to this increase, including early detection programs and the ageing population(3). In the Netherlands, the incidence of colorectal cancer increases with age, with patients aged 60 years and older accounting for the majority of newly diagnosed cases. Furthermore, about 17% of newly diagnosed patients with colorectal cancer are over 80 years old(4). So, in a progressively aging population the burden of colorectal cancer is rising.

Surgical resection remains the cornerstone of curative treatment for colorectal cancer. Nevertheless, postoperative morbidity and mortality are often increased in elderly patients possibly due to coexisting comorbidities(5). Therefore, it remains challenging for surgeons to decide whether to treat colorectal cancer in elderly patients conservatively or with surgical resection. Previous literature has shown that colorectal surgery in elderly patients is safe and that 1-year mortality is similar to overall life expectancy(6, 7). Increasing age is no longer considered a contraindication for colorectal surgery. Nevertheless, these previous studies did not specifically address colorectal anastomotic leakage (CAL), which is one of the most severe complications after colorectal surgery due to its associated morbidity and mortality(8, 9).

The effect of age on CAL after colorectal cancer resection remains unclear. Most studies identified age as a risk factor, but the results were contradictive. Some studies showed a decreased risk of CAL in older patients (10-14), while others suggest advancing age is a risk factor for CAL(9, 11). In addition, it was previously demonstrated that mortality following CAL is increased in elderly patients (15).

The aim of this study was to investigate the effect of age on CAL and its associated mortality in a population-based study.

Methods

Study design

Data were derived from the Dutch ColoRectal Audit (DCRA), a web-based national registry for primary colorectal cancer resections. All patients undergoing primary colorectal cancer resection with construction of a primary anastomosis between 1st of January 2011 and 31st of December 2016 were included. Patients with other procedures than ileocecal resection, right/left hemicolectomy, sigmoid, low anterior resection or subtotal colectomy were excluded. Patients with a transanal procedure or an end ostomy were excluded. Patients with missing information on age or CAL were also excluded.

The DCRA is a quality improvement project, in which all Dutch hospitals participate(16). Annual comparison with the National Cancer Registration is performed on completeness and data are verified by independent data managers visiting all hospitals. Under Dutch law no ethical approval or informed consent was required for this study, as only de-identified patient information was provided. Details regarding data collection and methodology have been previously published elsewhere(16).

Outcome measures and other variables

Patients were divided into four age groups. Group I were patients aged <60 years, Group II 60-69 years, Group III 70-80 years, and Group IV >80 years old.

The primary outcome was CAL within 30 days after surgery. CAL was defined as a clinically relevant colorectal anastomotic leak leading to radiological or surgical re-intervention. Secondary outcome of interest was mortality following CAL within 30 days after surgery.

Patient, tumor, and treatment characteristics were extracted from the DCRA [gender, age, Body Mass Index (BMI), Charlson Comorbidity Index, American Society of Anesthesiologists (ASA) score, preoperative radiotherapy, preoperative chemotherapy, tumor location, TNM stage, preoperative tumor complications, type of procedure, surgical technique, conversion, urgency of surgery, stoma, perioperative complications, additional resection because of tumor growth, additional resection because of metastasis]. Information on management of CAL was also extracted from the DCRA [type of re-intervention and time to intervention].

Statistical Analysis

Differences in patient, tumor, and treatment characteristics between age groups were examined using one-way analysis of variance (ANOVA) for continuous variables and Chi-square tests for categorical variables. Continuous variables were described as mean with standard deviation, while categorical variables as frequencies with percentages. Multiple imputation was performed to deal with missing values assuming data were missing at random(17). Five imputed datasets were created based on gender, age, BMI, Charlson Comorbidity Index, ASA score, preoperative radiotherapy, preoperative chemotherapy, tumor location, tumor invasion, preoperative tumor complication, type of procedure, surgical technique, urgency of surgery, protective stoma, additional resection because of tumor growth, additional resection because of metastasis, and CAL. Univariable and multivariable regression models were performed. Age was evaluated as a continuous variable and as categorical variable. Tests for non-linearity were performed. Multivariate analysis was performed taking in consideration all clinically relevant variables for the outcome of interest. No variable selection was performed on the data. Additionally, to test whether the effect of age was different for tumor location (colon/rectum) the univariable and multivariable analyses stratified for tumor location. Intervention rates between age groups were tested with Chi-square tests. A p value <0.05 was considered statistically significant. All statistical analyses were performed using the Statistical Package for the Social Sciences version 21.0 for Windows (SPSS IBM, Chicago, IL, USA).

Results

Study population

All patients (46 542) undergoing primary colorectal cancer resection with the construction of a primary anastomosis between 1st of January 2011 and 31st of December 2016 were evaluated. After exclusion of 179 patients with procedures other than ileocecal resection, right/left hemicolectomy, sigmoidectomy, low anterior resection or subtotal colectomy, 174 patients with a trans anal procedure, 455 patients with an end ostomy, 25 patients with missing information on age and 221 patients with missing information on CAL, 45 488 patients were eligible for analysis. Patient, tumor, and surgical characteristics per age group are presented in Table 1.

Table 1. Patient, tumor, and surgical characteristics per age group

		Total	Group I	Group II	Group III	Group IV	P-value	Missing
		45488	**7184**	**15042**	**16651**	**6611**		
Patient characteristics								
Gender	Female	20703 (45.5%)	3414 (47.5%)	6291 (41.8%)	7381 (44.3%)	3617 (54.7%)	<0.001	12 (0.0%)
	Male	24773 (54.5%)	3766 (52.5%)	8746 (58.2%)	9267 (55.7%)	2994 (45.3%)		
Age, mean ± SD, yr		69.4 (±10.6)	52.0 (±6.6)	65.1 (±2.7)	74.8 (±3.1)	84.5 (±3.1)	<0.001	0 (0.0%)
BMI, mean ± SD, kg/m^3		26.4 (±4.5)	26.1 (±4.7)	26.8 (±4.7)	26.5 (±4.3)	25.6 (±4.0)	<0.001	1563 (3.4%)
Charlson Comorbidity Index	0	25155 (55.3%)	5549 (77.2%)	9172 (61.0%)	7792 (46.8%)	2642 (40.0%)	<0.001	0 (0.0%)
	1	9607 (21.1%)	969 (13.5%)	2924 (19.4%)	4000 (24.0%)	1714 (25.9%)		
	≥ 2	10726 (23.6%)	666 (9.3%)	2946 (19.6%)	4859 (29.2%)	2255 (34.1%)		
ASA score	I-II	35723 (78.6%)	6677 (93.1%)	12916 (86.0%)	12320 (74.1%)	3810 (57.7%)	<0.001	58 (0.1%)
	III-V	9707 (21.4%)	494 (6.9%)	2108 (14.0%)	4315 (25.9%)	2790 (42.3%)		
Preoperative radiotherapy		5639 (12.5%)	1604 (22.5%)	2176 (14.5%)	1644 (9.9%)	215 (3.3%)	<0.001	250 (0.5%)
Preoperative chemotherapy		1802 (4.0%)	618 (8.8%)	735 (5.0%)	423 (2.6%)	26 (0.4%)	<0.001	680 (1.5%)
Tumor characteristics								
Tumor location	Colon	37222 (81.9%)	5109 (71.1%)	11780 (78.4%)	14140 (84.9%)	6193 (93.7%)	<0.001	19 (0.0%)
	Rectum	8247 (18.1%)	2072 (28.9%)	3255 (21.6%)	2506 (15.1%)	414 (6.3%)		
Tumor invasion	pT0	672 (1.5%)	194 (2.7%)	270 (1.8%)	195 (1.2%)	13 (0.2%)	<0.001	640 (1.4%)
	pT1	4406 (9.8%)	609 (8.5%)	1881 (12.6%)	1612 (9.8%)	304 (4.6%)		
	pT2	9022 (20.1%)	1321 (18.5%)	3192 (21.4%)	3357 (20.3%)	1152 (17.5%)		
	pT3	25107 (56.0%)	4016 (56.3%)	7815 (52.3%)	9243 (55.9%)	4033 (61.3%)		
	pT4	5641 (12.6%)	922 (12.9%)	1659 (11.1%)	2008 (12.2%)	1052 (16.0%)		
Regional lymph nodes	pN0	26831 (59.6%)	3723 (52.2%)	8819 (58.9%)	10124 (61.2%)	4165 (63.3%)	<0.001	454 (0.9%)
	pN1	10719 (23.8%)	1892 (26.5%)	3532 (23.6%)	3854 (23.3%)	1441 (21.9%)		
	pN2	7484 (16.6%)	1484 (20.8%)	2557 (17.1%)	2504 (15.1%)	939 (14.3%)		
Distant metastasis	pM0	38747 (90.4%)	5864 (83.2%)	12853 (86.8%)	14342 (88.0%)	5688 (87.8%)	<0.001	2624 (5.8%)
	pM1	4117 (9.6%)	903 (12.8%)	1420 (9.6%)	1324 (8.1%)	470 (7.3%)		

Table 1. (Continued)

		Total	Group I	Group II	Group III	Group IV	P-value	Missing
		45488	**7184**	**15042**	**16651**	**6611**		
Preoperative tumor complication		14902 (32.9%)	2330 (32.6%)	3916 (26.2%)	5572 (33.6%)	3084 (46.9%)	<0.001	198 (0.4%)
Surgical characteristics								
Type of procedure	Ileocecal resection	398 (0.9%)	71 (1.0%)	90 (0.6%)	130 (0.8%)	107 (1.6%)	<0.001	147 (0.3%)
	Right hemicolectomy	18214 (40.2%)	1920 (26.8%)	5023 (33.5%)	7304 (44.0%)	3967 (60.%)	<0.001	
	Transversal resection	889 (2.0%)	90 (1.3%)	220 (1.5%)	361 (2.2%)	218 (3.3%)		
	Left hemicolectomy	4023 (8.9%)	635 (8.9%)	1350 (9.0%)	1503 (9.1%)	535 (8.1%)		
	Sigmoidectomy	12933 (28.5%)	2213 (30.9%)	4827 (32.2%)	4609 (27.8%)	1284 (19.5%)		
	Low Anterior Resection	8213 (18.1%)	2064 (28.8%)	3238 (21.6%)	2498 (15.0%)	413 (6.3%)		
	Subtotal Colectomy	671 (1.5%)	162 (2.3%)	252 (1.7%)	197 (1.2%)	60 (0.9%)		
Surgical technique	Open	15405 (33.9%)	2311 (32.2%)	4351 (29.0%)	5751 (34.6%)	2992 (45.4%)	<0.001	83 (0.2%)
	Laparoscopic	30000 (66.1%)	4866 (67.8%)	10664 (71.0%)	10869 (65.4%)	3601 (54.6%)		
Conversion		3453 (7.8%)	483 (6.9 %)	1170 (8.0%)	1327 (8.2%)	473 (7.3%)	0.003	1,037 (2.3%)
Urgency of surgery	Elective	41226 (90.7%)	6432 (89.6%)	13890 (92.4%)	15267 (91.7%)	5637 (85.4%)	<0.001	26 (0.1%)
	Urgent	4236 (9.3%)	746 (10.4%)	1146 (7.6%)	1377 (8.3%)	967 (14.6%)		
Protective stoma		6301 (13.9%)	1570 (22.0%)	2407 (16.1%)	1982 (11.9%)	342 (5.2%)	<0.001	193 (0.4%)
Perioperative complications		1168 (2.6%)	161 (2.3%)	357 (2.4%)	464 (2.8%)	186 (2.8%)	0.026	459 (1.0%)
Additional resection because of tumor growth		3536 (8.0%)	632 (9.1%)	1063 (7.2%)	1256 (7.7%)	585 (9.1%)	<0.001	1,162 (2.6%)
Additional resection because of metastasis		1440 (3.2%)	342 (4.8%)	511 (3.4%)	444 (2.7%)	143 (2.2%)	<0.001	82 (0.2%)

Group I indicates patients aged <60 years, Group II 60-69 years, Group III 70-80 years and Group IV >80 years.

CAL

Overall incidence of CAL was 5.5%. The mean age was lower in patients with CAL compared to patients without CAL (68.6 vs 69.4 years $p < 0.001$). CAL was observed in 6.4% in Group I, 5.5% in Group II, 5.4% in Group III and 4.8% in Group IV ($p < 0.001$) (Table 2). For management of CAL, open surgical re-intervention was used more often. Time to re-intervention was not significantly different between age groups with an overall mean of 9.7 ± 23.8 days (Table 2).

Univariable analysis showed that older age per 5 years was protective for CAL (OR 0.961 per 5 years 95% CI 0.946 – 0.980 $p < 0.001$) and this association remained the same after adjustment for potential confounders in the multivariable analysis (OR 0.965 per 5 years 95% CI 0.941 – 0.985 $p < 0.001$). Both univariable and multivariable showed decreased risk of CAL in Group II, III and IV compared to Group I (Table 3).

Stratification for tumor location showed similar results for colon tumors. For rectal tumors only multivariate analysis with age as a continuous variable reached statistical significance (Supplementary table 1). Tests for non-linearity confirmed a linear association between age and CAL.

Mortality following CAL

In total, mortality following CAL was 9.7%. In Group I mortality following leakage was 1.3%, in Group II 4.8%, in Group III 12.3% and in Group IV 27.2% ($p < 0.001$) (Table 2). Univariable analysis showed that older age per 5 years was associated with increased mortality following CAL (OR 1.677 per 5 years 95% CI 1.539 – 1.818 $p < 0.001$) and this association remained the same after adjustment for potential confounders in the multivariable analysis (OR 1.497 per 5 years 95% CI 1.364 – 1.647 $p < 0.001$) (Table 3). Both univariable and multivariable analysis showed increased mortality following CAL in Group II, III and IV compared to Group I (Table 3). Tests for non-linearity confirmed a linear association between age and mortality following CAL.

Table 2. Details on CAL with intervention strategies and following mortality

		Total	Group I	Group II	Group III	Group IV	P-value	Missing
CAL		2500 (5.5%)	457 (6.4%)	833 (5.5%)	891 (5.4%)	319 4.8%)	<0.001	0 (0.0%)
Re-intervention	Radiological	118 (4.7%)	27 (5.9%)	34 (4.1%)	38 (4.3%)	19 (6.0%)	<0.001	6 (0.2%)
	Surgical	2251 (90.3%)	399 (87.5%)	737 (88.5%)	820 (92.0%)	295 (92.5%)		
	Other	124 (5.0%)	30 (6.6%)	57 (6.9%)	32 (3.6%)	5 (1.6%)		
Surgical re-intervention	Laparoscopic	387 (17.2%)	86 (21.6%)	156 (18.8%)	109 (12.2%)	36 (11.3%)	<0.001	0 (0.0%)
	Open	1864 (82.8%)	313 (78.4%)	581 (70.2%)	711 (79.9%)	259 (81.2%)		
Stoma as treatment		1920 (77.3%)	337 (74.4%)	639 (77.1%)	710 (80.0%)	234 (74.1%)	0.048	15 (0.6%)
Time to intervention, mean ± SD, days		9.7 (±23.8)	9.1 (±21.8)	10.0 (±22.9)	9.9 (±25.0)	9.7 (±23.8)	0.926	552 (22.1%)
Mortality		241 (9.7%)	6 (1.3%)	40 (4.8%)	109 (12.3%)	86 (27.2%)	<0.001	17 (0.7%)

Group I indicates patients aged <60 years, Group II 60-69 years, Group III 70-80 years and Group IV >80 years.
CAL indicates colorectal anastomotic leakage.

Table 3. Results of univariable and multivariable logistic regression analysis of age (continuous and categories) for CAL and mortality following CAL

	CAL		Mortality following CAL	
	Univariable analysis OR (95% CI, p-value)	**Multivariable analysis*** OR (95% CI, p-value)	**Univariable analysis** OR (95% CI, p-value)	**Multivariable analysis†** OR (95% CI, p-value)
Age – continuous				
Age (per 5 years)	0.961 (0.946 – 0.980, <0.001)	0.965 (0.941 – 0.985, 0.001)	1.677 (1.539 – 1.818, <0.001)	1.497 (1.364 – 1.647, <0.001)
Age - categories				
Group I	1	1	1	1
Group II	0.863 (0.767 – 0.971, 0.014)	0.865 (0.767 – 0.976, 0.019)	3.778 (1.589 – 8.981, 0.003)	2.854 (1.185 – 6.873, 0.020)
Group III	0.832 (0.741 – 0.935, 0.002)	0.829 (0.733 – 0.938, 0.003)	10.401 (4.535 – 23.855, <0.001)	6.074 (2.590 – 14.243, <0.001)
Group IV	0.746 (0.644 – 0.865, <0.001)	0.762 (0.649 – 0.895, 0.001)	27.794 (11.966 – 64.559, <0.001)	13.635 (5.666 – 32.809, <0.001)

Group I indicates patients aged <60 years, Group II 60-69 years, Group III 70-80 years and Group IV >80 years.
CAL indicates colorectal anastomotic leakage.
***** Adjusted for gender, BMI, Charlson Comorbidity Index, ASA Score, preoperative radiotherapy, preoperative chemotherapy, tumor invasion, preoperative tumor complications, type of procedure, surgical technique, urgency of surgery, protective stoma.
† Adjusted for Charlson Comorbidity Index, ASA Score, preoperative radiotherapy, tumor location, tumor invasion, preoperative tumor complications, type of procedure, surgical technique, urgency of surgery, perioperative complications, additional resection because of tumor growth, additional resection because of metastasis.

Discussion

The aim of this study was to investigate the effect of age on CAL and its associated mortality after colorectal cancer resection. This population-based study of 45 488 patients showed a protective effect of age on CAL. The incidence of CAL was lowest in patients of >80 years old. However, older age is strongly associated with mortality after CAL. For patients of >80 years old, the mortality following CAL was found to be as high as 27.0%.

Several previous studies identified age as risk factor for CAL. The Danish Colorectal Cancer Group showed that older age is associated with a lower incidence of CAL(12). In addition, studies from the American College of Surgeons National Surgical Quality Improvement Program (NSQIP) also concluded that an increasing age is correlated with a lower risk of CAL(13, 18). Another large prospective multicenter study from Germany which included 17 867 patients found similar results(10). Recently, a study from the Michigan Surgical Quality Collaborative cohort found a younger mean age in patients with CAL(14). These findings were not explicitly evaluated in these studies but were one of the risk factors that were identified. In contrast, another study reported higher risk of CAL with increasing age, but this study was based on a relatively small sample size compared to the previously mentioned national databases(11). In addition, a few other studies demonstrated no significant association between age and risk of CAL(15, 19, 20). Different factors could contribute to these contradictory results, such as small sample sizes(19), investigation of only colon or rectal cancer(15), and specific setting in a Chinese population, which could be substantially different from the Western population(20).

Preoperative selection of patients might have resulted in selection of the fittest. Increased postoperative morbidity and mortality in elderly patients might have influenced surgeons' decision to be more precautious with surgical intervention in elderly patients(15, 21). In addition, the healthy survivor effect might have led to selection of the fittest. This phenomenon describes survivor bias, which selects patients that made it to a specific age while patients who died before reaching this age were not selected. However, in the present study, despite this selection, elderly patients had worse general health as represented by higher Charlson Comorbidity Index and ASA scores.

Right hemicolectomy is associated with low rates of CAL though high rates of mortality, and was the most commonly performed procedure in our elderly cohort (Supplementary Table 2, 3, and 4)(15). This might have influenced the unadjusted comparison of CAL and its associated mortality between the age groups. However, the multivariable model for CAL and mortality following CAL included type of procedure to adjust for this confounding effect.

Previously, a study from the DCRA found high rates of cardiopulmonary complications in elderly patients(4). These complications could be competing risks leading to death even before CAL was clinically present or diagnosed resulting in a lower incidence of CAL in elderly patients.

A more conservative approach with non-interventional treatment of suspected CAL may be adopted more often in elderly patients. This might explain the lower incidence of CAL in elderly patients in this study since AL was defined as clinically relevant AL which required radiological or surgical re-intervention.

In the Netherlands, the smoking rate decreases from the age of 60 years. This might partially explain our results since several studies have shown that active smoking is an independent risk factor for CAL(22, 23). Smoking status was not registered in the DCRA so it was not possible to explore this association. However, in a large study of 17 518 patients younger age was found to be an independent risk factor for CAL even after correcting for smoking status(18).

Inflammatory bowel disease (IBD) increases risk of CAL. This might partially explain increased risk of CAL in younger patients since IBD appears on younger age(24). Nevertheless, just a small percentage of patients with colorectal cancer have IBD at baseline (1-2%)(25). A previous study performed a sensitivity analysis by excluding all patients with IBD showing still a significant protective effect of age on CAL(18).

Our study suggest that older patients truly have a decreased risk of CAL(10, 12, 13, 18). An experimental study found that aging tissues show more chronic inflammation in absence of overt infection(26). It might be possible that this chronic inflammation in aging tissues enables anastomotic healing since anastomotic healing requires a balanced immune response with pro- and anti-inflammatory characteristics preventing an exceeded inflammatory response(27). In addition, this might contribute to the less severe clinical presentation of CAL in elderly patients from subclinical CAL which is not registered in DCRA

This study shows that, despite the protective effect of age on CAL, the mortality following CAL increases with higher age. The mortality rate following CAL is well established in literature, especially in patients aged 80 and over(15, 28). A multicenter study demonstrated a fourfold increase in 30-day mortality following CAL(21). Beside frailty of elderly patients, several other factors might contribute to these high rates of mortality following CAL. Moreover, elderly patients sometimes refuse a second intervention or reintubation or sign a Do Not Resuscitate (DNR) policy before surgery.

Emergency surgery was most often performed in Group IV. This might explain the high mortality rates in group IV because emergency surgery is identified as a risk factor for mortality after colorectal surgery(29).

This study shows multivariable logistic regression models with age as a continuous and categorical variable. Categorization of a continuous variable in a multivariable model has several disadvantages. It could lead to a considerable loss of power, residual confounding and bias due to data-derived cut-off values(30). Therefore, our main conclusion was based on the outcomes of the model with age as a continuous variable which was tested for linearity.

Stratified analyses were performed to explore whether the effect of age was different for tumor location (Supplementary Table 1). No major differences were observed since the multivariable analysis for both colon and rectum showed a statistically significant protective effect of age on CAL. Nevertheless, it needs to be mentioned that stratification compromises the sample size resulting in loss of power. Therefore, it is not possible to perform multivariable analysis for mortality following CAL with stratified data due to small numbers of events (i.e. mortality rate of 22 out of 618 patients with CAL after rectum resection). However, univariable exploration indicated that for both colon and rectum the incidence of mortality after CAL increases with age.

The strength of our study is that it was based on a population-based cohort with a large sample size decreasing the risk of a type II error. However, there were several limitations worth mentioning. Although DCRA registers many variables there are several that are not (smoking, nutritional status, immunosuppression status, medication use) which could have affected the outcomes of this study. Lastly, the DCRA database registers data until 30 days after surgery, unless the initial hospital stay is longer so long-term outcomes are not registered.

Conclusions

This population-based study showed a protective effect of age on CAL after colorectal cancer resection. On the other hand, this study demonstrated that older age is strongly associated with increased mortality following CAL which is reported to be as high as 27.0% in patients >80 years.

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Supplementary materials

Supplementary Table 1. Results of univariable and multivariable logistic regression analysis of age (continuous and categories) for CAL stratified for colon and rectum tumors

Colon	CAL	
	Univariable analysis OR (95%CI, p-value)	**Multivariable analysis*** OR (95%CI, p-value)
Age – continuous		
Age (per 5 years)	**0.995 (0.991 – 1.000, 0.037)**	**0.993 (0.988 – 0.998, 0.005)**
Age - categories		
Group I	1	1
Group II	**0.862 (0.746 – 0.997, 0.045)**	**0.859 (0.741 – 0.997, 0.045)**
Group III	0.897 (0.780 – 1.033, 0.131)	**0.860 (0.742 – 0.997, 0.045)**
Group IV	**0.822 (0.696 – 0.972, 0.022)**	**0.773 (0.645 – 0.925, 0.005)**

Rectum	CAL	
	Univariable analysis OR (95%CI, p-value)	**Multivariable analysis†** OR (95%CI, p-value)
Age – continuous		
Age (per 5 years)	0.970 (0.937 – 1.015, 0.179)	**0.951 (0.913 – 0.995, 0.029)**
Age - categories		
Group I	1	1
Group II	0.955 (0.779 – 1.171, 0.955)	0.884 (0.716 – 1.091, 0.250)
Group III	0.820 (0.656 – 1.023, 0.079)	**0.742 (0.586 – 0.939, 0.013)**
Group IV	0.822 (0.543 – 1.245, 0.355)	0.693 (0.448 – 1.070, 0.098)

Group I indicates patients aged <60 years, Group II 60-69 years, Group III 70-80 years and Group IV >80 years.
CAL indicated colorectal anastomotic leakage.
* Adjusted for gender, BMI, Charlson Comorbidity Index, ASA Score, tumor invasion, preoperative tumor complications, type of procedure, surgical technique, urgency of surgery
† Adjusted for gender, BMI, Charlson Comorbidity Index, ASA Score, preoperative radiotherapy, preoperative chemotherapy, tumor invasion, preoperative tumor complications, type of procedure, surgical technique, urgency of surgery, protective stoma

Supplementary Table 2. CAL per type of surgical procedure

		Total	Group I	Group II	Group III	Group IV
	CAL	2500	457	833	891	319
	Total	45488	7184	15042	16651	6611
	CAL%	5.5%	6.4%	5.5%	5.4%	4.8%
Ileocecal resection	CAL	17	1	3	6	7
	Total	398	71	90	130	107
	CAL%	4.3%	1.4%	3.3%	4.6%	6.5%
Right hemicolectomy	CAL	728	79	182	315	152
	Total	18214	1920	5023	7304	3967
	CAL%	4.0%	4.1%	3.6%	4.3%	3.8%
Transversal resection	CAL	56	5	18	15	18
	Total	889	90	220	361	218
	CAL%	6.3%	5.6%	8.2%	4.2%	8.3%
Left hemicolectomy	CAL	291	56	87	110	38
	Total	4023	635	1350	1503	535
	CAL%	7.2%	8.8%	6.4%	7.3%	7.1%
Sigmoidectomy	CAL	695	127	254	242	72
	Total	12933	2213	4827	4609	1284
	CAL%	5.4%	5.7%	5.3%	5.3%	5.6%
Low anterior resection	CAL	614	167	251	168	28
	Total	8213	2064	3238	2498	413
	CAL%	7.5%	8.1%	7.8%	6.7%	6.8%
Subtotal colectomy	CAL	90	19	35	33	3
	Total	671	162	252	197	60
	CAL%	13.4%	11.7%	13.9%	16.8%	5.0%

Group I indicates patients aged <60 years, Group II 60-69 years, Group III 70-80 years and Group IV >80 years.
CAL indicates colorectal anastomotic leakage.

Supplementary Table 3. Overall mortality per type of surgical procedure

		Total	Group I	Group II	Group III	Group IV
	Mortality	1045	45	160	404	436
	Total	45488	7184	15042	16651	6611
	Mortality%	2.3%	0.6%	1.1%	2.4%	6.6%
Ileocecal resection	Mortality	26	0	2	8	16
	Total	396	71	90	128	107
	Mortality%	6.6%	0.0%	2.2%	6.3%	15.0%
Right hemicolectomy	Mortality	568	17	69	210	272
	Total	18143	1915	5004	7272	3952
	Mortality%	3.1%	0.9%	1.4%	2.9%	6.9%
Transversal resection	Mortality	33	2	4	8	19
	Total	886	89	219	361	217
	Mortality%	3.7%	2.2%	1.8%	2.2%	8.8%
Left hemicolectomy	Mortality	112	8	19	43	42
	Total	4011	633	1346	1498	534
	Mortality%	2.8%	1.3%	1.4%	2.9%	7.9%
Sigmoidectomy	Mortality	178	11	34	75	58
	Total	12900	2209	4814	4596	1281
	Mortality%	1.4%	0.5%	0.7%	1.6%	4.5%
Low anterior resection	Mortality	94	5	23	47	19
	Total	8191	2059	3234	2487	411
	Mortality%	1.1%	0.2%	0.7%	1.9%	4.6%
Subtotal colectomy	Mortality	34	2	9	13	10
	Total	667	159	251	197	60
	Mortality%	5.1%	1.3%	3.6%	6.6%	16.7%

Group I indicates patients aged <60 years, Group II 60-69 years, Group III 70-80 years and Group IV >80 years.
CAL indicates colorectal anastomotic leakage.

Supplementary Table 4. Mortality following CAL per type of surgical procedure

		Total	Group I	Group II	Group III	Group IV
	Mortality	240	6	40	109	85
	Total CAL	2474	449	824	886	315
	Mortality%	9.7%	1.3%	4.9%	12.3%	27.0%
Ileocecal resection	Mortality	4	0	0	2	2
	Total CAL	17	1	3	6	7
	Mortality%	23.5%	0.0%	0.0%	33.3%	28.6%
Right hemicolectomy	Mortality	115	2	15	45	53
	Total CAL	724	78	180	315	151
	Mortality%	15.9%	2.6%	8.3%	14.3%	35.1%
Transversal resection	Mortality	7	0	2	1	4
	Total CAL	55	5	18	15	17
	Mortality%	12.7%	0.0%	11.1%	6.7%	23.5%
Left hemicolectomy	Mortality	29	1	3	19	6
	Total CAL	288	55	87	108	38
	Mortality%	10.1%	1.8%	3.4%	17.6%	15.8%
Sigmoidectomy	Mortality	55	1	12	25	17
	Total CAL	692	127	251	242	72
	Mortality%	7.9%	0.8%	4.8%	10.3%	23.6%
Low anterior resection	Mortality	22	2	5	13	2
	Total CAL	611	166	251	167	27
	Mortality%	3.6%	1.2%	2.0%	7.8%	7.4%
Subtotal colectomy	Mortality	8	0	3	4	1
	Total CAL	87	17	34	33	3
	Mortality%	9.2%	0.0%	8.8%	12.1%	33.3%

Group I indicates patients aged <60 years, Group II 60-69 years, Group III 70-80 years and Group IV >80 years. CAL indicates colorectal anastomotic leakage.

Chapter 5

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PART II

SURGICAL TECHNIQUES AND COLORECTAL ANASTOMOTIC LEAKAGE

Chapter 6

Transanal Total Mesorectal Excision: How are we doing so far?*

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Abstract

Aim

This subgroup analysis of a prospective multicenter cohort study aims to compare postoperative morbidity between transanal total mesorectal excision (TaTME) and laparoscopic total mesorectal excision (LaTME).

Method

This study was designed as a subgroup analysis of a prospective multicenter cohort study. Patients undergoing TaTME or LaTME for rectal cancer were selected. All patients were followed up until the first visit to the outpatient clinic after hospital discharge. Postoperative complications were classified according to Clavien-Dindo classification and Comprehensive Complication Index (CCI). Propensity score matching was performed.

Results

In total, 220 patients were selected from the overall prospective multicenter cohort study. After propensity score matching, 48 patients from each group were compared. The median tumor height for TaTME was 10.0 cm (6.0 – 10.8) and 9.5 cm (7.0 – 12.0) for LaTME ($p = 0.459$). Duration of surgery and anesthesia were both significantly longer for TaTME (221 vs 180 minutes $p < 0.001$ and 264 vs 217 min $p < 0.001$). TaTME was not converted to laparotomy while surgery in 5 patients undergoing LaTME was converted to laparotomy (0.0% vs 10.4% $p = 0.056$). No statistically significant differences were observed for Clavien-Dindo Classification, CCI, readmissions, reoperations and mortality.

Conclusion

This study showed that TaTME is a safe and feasible approach for rectal cancer resection. This new technique obtained similar postoperative morbidity as LaTME.

Introduction

Total mesorectal resection (TME) is the gold standard for rectal resection. This surgical technique, involving resection of the fatty envelope surrounding the rectum, has substantially contributed to local control and survival of rectal cancer(1, 2).

Minimally invasive techniques have been introduced for rectal surgery. Several randomized controlled trials have shown that oncological outcomes are comparable for open and laparoscopic surgery for rectal cancer. The COREAN trial has shown short-term benefits for laparoscopic surgery compared to open surgery and equivalent quality of oncologic resection(3). In the long-term, disease-free survival was similar for the two techniques (4). In addition, The COLOR-II trial has confirmed that laparoscopic and open surgery for rectal cancer provide similar long-term outcomes(5).

Recently, it has been shown that age above 65 years, a BMI greater than 25, and tumor location close to the anal verge are risk factors for the conversion from laparoscopic to open surgery(6). In addition, factors such as a narrow pelvis, or limited views of the distal rectum make the laparoscopic approach difficult. These considerations emphasize the need for a new minimally invasive technique that overcomes the limitations of laparoscopy.

Transanal total mesorectal excision (TaTME) may be the solution. Since its introduction in 2010, TaTME has been shown to be a feasible and safe technique for rectal cancer resections and has subsequently achieved widespread acceptance(7, 8). Nevertheless, to date most evidence has been obtained from cohort studies with small sample sizes and retrospective design(9-13). Therefore, this study is important because it is the first to provide results of a prospective multicenter cohort study. The aim of this study was to compare postoperative morbidity between TaTME and LaTME.

Methods

This study was designed as a subgroup analysis of a prospective multicenter cohort study, the APPEAL-II study. Ten hospitals in The Netherlands and Belgium participated in this study. This study was approved by the medical ethics committee of the Erasmus University Medical Centre in The Netherlands and of the University Hospital Leuven in Belgium. We also obtained approval from local ethics committees of the participating hospitals. This prospective cohort was established between August 2015 and October 2017. Patients aged 18 years and older who underwent partial mesorectal excision (PME) or total mesorectal excision (TME) with construction of a colorectal or coloanal anastomosis were eligible for inclusion. We excluded pregnant women and patients who underwent emergency procedures. All patients received a pelvic drain during surgery that was kept in place for at least the first three postoperative days. Drain fluid was obtained for further analysis according to the study protocol (https://doi.org/10.1186/ISRCTN84052649). Follow-up, for the purposes of this study, was completed at the first visit at the outpatient clinic after hospital discharge. Informed consent was obtained from all patients. For this subgroup analysis, we selected patients who underwent TaTME or LaTME for rectal cancer. Patient selection for TaTME or LaTME was at discretion of the surgeon.

Baseline characteristics (age, gender, BMI, smoking, alcohol abuse (>14 units per week), ASA score, tumor location, neoadjuvant radiotherapy, neoadjuvant chemotherapy, pathological TNM stadium) and surgical characteristics (duration of surgery, duration of anesthesia, conversion, construction of anastomosis, configuration of anastomosis, diverting ileostomy, circumferential resection margin (CRM), distal resection margin (DRM)) were prospectively registered. CRM was considered positive when the margin was <1 mm and for the DRM this was <1 cm(14).

Outcome measures

The outcome measures of this analysis were postoperative complications, readmissions, reoperations, conversions and mortality. Stoma reversals were not considered as reoperations unless it was due to stoma complications. Anastomotic leakage was defined as clinically manifest insufficiency of the anastomosis leading to a clinical state requiring re-intervention (i.e. grade B/C)(15). Anastomotic leakage was confirmed by either endoscopy, CT-scan and/or contrast enema or reoperation. Re-intervention for anastomotic leakage consisted of therapeutic antibiotics, (endoscopic) drainage or a surgical re-intervention. Presacral abscesses were classified as anastomotic leakage if extravasation of the colonic contrast was visible on radiological imaging. Fistulas attached to the anastomosis on CT-scan were also classified as anastomotic leakage. Postoperative complications were classified according to the Clavien-Dindo classification system and grade II or higher was considered to be a severe complication(16, 17). In addition, the comprehensive complication index (CCI) for every patient was calculated using www.assessurgery.com(18).

Statistical analysis

Continuous variables were described as median ± IQR and compared by the Mann-Whitney U test. Categorical variables were described as percentages and compared by the Chi-square test or Fisher's Exact test when needed. Patients were matched based on the propensity score derived from a logistic regression model with approach as dependent covariate and baseline characteristics with p value < 0.1 as independent covariates. In addition, a multivariate penalized logistic/linear regression model was built to investigate the adjusted association between the surgical approach and the outcome measures adjusted for aforementioned risk factors in the unmatched dataset (age, gender, BMI, tumor location, pathological tumor stage, neoadjuvant radiotherapy, neoadjuvant chemotherapy, diverting ileostomy, approach). All clinically relevant variables were added to the model. Statistical significance was defined as p value < 0.050. All analyses were performed using SPSS® software 21.0 (IBM, Armonk, New York, USA) or R Software.

Results

This prospective cohort study of patients undergoing partial mesorectal excision (PME) or total mesorectal excision (TME) included 301 patients. For this analysis, we excluded 74 patients who underwent PME or who had an open approach and 7 patients were operated upon for reasons other than rectal cancer. In total, 220 patients were selected (Figure 1). The median follow-up was 27.0 days (IQR 19.0 – 34.0 days).

Figure 1. Flowchart of patient selection.

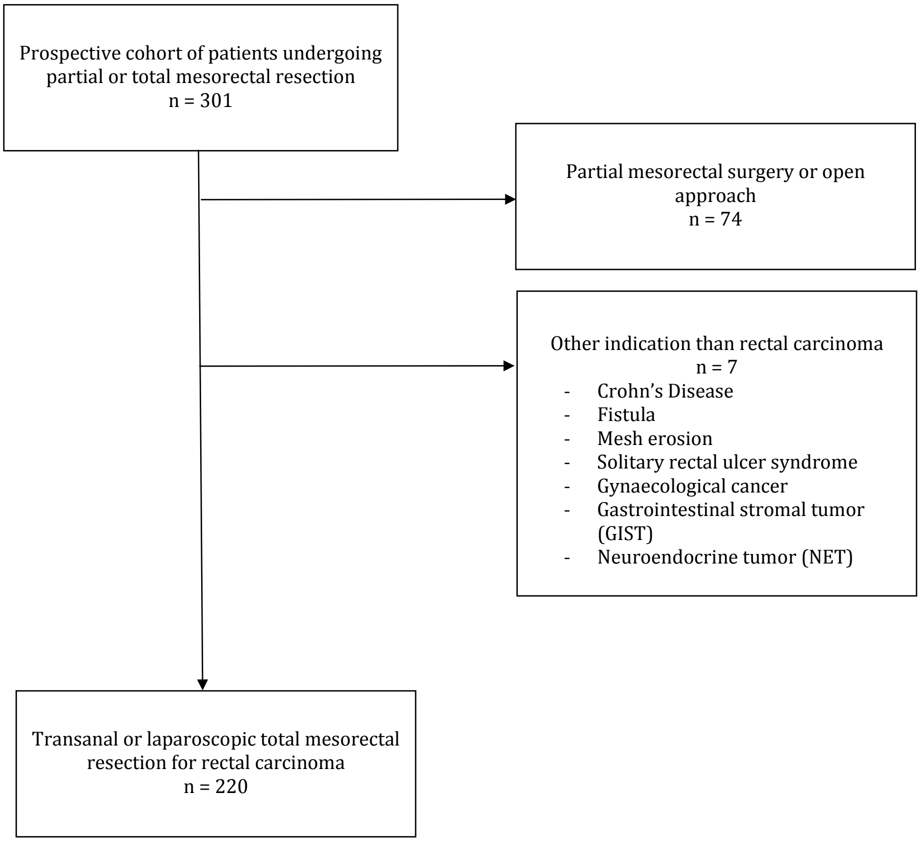

Table 1 shows prematching baseline characteristics of the overall study population of 220 patients. Age, tumor location, pathological T stadium and neoadjuvant chemotherapy were used to calculate the propensity score. After matching for propensity score, 96 patients were eligible for analysis.

Table 1. Demographic characteristics for patients undergoing LaTME and TaTME

		TaTME 119 (54.1%)	LaTME 101 (45.9%)	Missing	P value
Baseline characteristics					
Age, median (IQR†), yr		62.0 (56.0 – 67.0)	66.0 (59.5 – 73.0)	0 (0.0%)	**0.003**
Gender	Male	86 (72.3%)	64 (63.4%)	0 (0.0%)	0.158
	Female	33 (27.7%)	37 (36.6%)		
BMI‡, median ± (IQR†), kg/m²		26.6 (23.7 – 29.7)	25.2 (23.2 – 28.7)	1 (0.5%)	0.162
Smoking	Yes	15 (12.7%)	11 (11.5%)	6 (2.7%)	0.780
	No	103 (87.3%)	85 (88.5%)		
Alcohol abuse	Yes	16 (13.6%)	11 (11.7%)	8 (3.6%)	0.687
	No	102 (86.4%)	83 (88.3%)		
Bowel preparation	Yes	116 (97.5%)	82 (92.1%)	12 (5.5%)	0.102*
	No	3 (2.5%)	7 (7.9%)		
Previous abdominal surgery	Yes	37 (31.1%)	35 (35.0%)	1 (0.5%)	0.540
	No	82 (68.9%)	65 (65.0%)		
ASA§ score	I	11 (9.2%)	16 (16.0%)	1 (0.5%)	0.355*
	II	77 (64.7%)	64 (64.0%)		
	III	30(25.2%)	19 (19.0%)		
	IV	1 (0.8%)	1 (1.0%)		
Tumor distance to anal verge, median (IQR†), cm		5.0 (2.1 – 10.0)	12.0 (9.0 – 15.0)	12 (5.5%)	**<0.001**
pT stage	pT0	21 (17.8%)	6 (6.0%)	7 (3.1%)	**0.027***
	pT1	16 (13.6%)	19 (19.0%)		
	pT2	36 (30.5%)	26 (26.0%)		
	pT3/4	42 (35.6%)	47 (47.0%)		
pN stage	pN0	83 (69.7%)	68 (67.3%)	7 (3.1%)	0.292
	pN1	17 (14.3%)	22 (21.8%)		
	pN2	14 (11.8%)	8 (7.9%)		
	pN3	0 (0.0%)	1 (1.0%)		
Neoadjuvant radiotherapy	Yes	67 (56.3%)	60 (60.0%)	1 (0.5%)	0.581
	Short-course	14	34		
	Long-course	47	25		
	No	52 (43.7%)	40 (40.0%)		
Neoadjuvant chemotherapy	Yes	52 (43.7%)	28 (28.0%)	1 (0.5%)	**0.016**
	No	67 (56.3%)	72 (72.0%)		

* Fisher Exact Test;
† IQR, interquartile range;
‡ BMI, body mass index;
§ ASA, American Society of Anesthesiologists

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Table 2 shows postmatching baseline characteristics of 48 patients undergoing TaTME and 48 patients undergoing LaTME. Patients undergoing LaTME received more often neoadjuvant radiotherapy (43.8% vs 64.6% p = 0.041). The other baseline characteristics were not statistically significant different for TaTME and LaTME. Duration of surgery and anesthesia were both significantly longer for TaTME (221 vs 180 minutes p < 0.001 and 264 vs 217 min p < 0.001). TaTME was not converted to laparotomy while surgery in 5 patients undergoing LaTME was converted to laparotomy (0.0% vs 10.4% p = 0.056) (Table 3). Reasons for conversion were adhesions, obesity, bleeding and insufficient bowel length for stoma creation.

Table 2. Postmatching baseline characteristics

		TaTME 48	**LaTME 48**	**Missing**	**P value**
Age, median (IQR†), yr		65.0 (56.8 – 71.0)	64.0 (59.3 – 73.0)	0 (0.0%)	0.752
Gender	Male	33 (68.8%)	32 (66.7%)		0.827
BMI‡, median ± (IQR†), kg/m²		27.0 (24.5 – 30.7)	26.1 (24.0 – 29.0)	1 (1.0%)	0.221
Smoking		5 (10.4%)	6 (12.5%)	5 (5.2%)	0.661
Alcohol abuse		7 (14.6%)	2 (4.2%)	5 (5.2%)	*0.164
ASA§ score	I	4 (8.3%)	6 (12.5%)	0 (0.0%)	*0.953
	II	29 (60.4%)	28 (58.3%)		
	III	14 (29.2%)	13 (27.1%)		
	IV	1 (2.1%)	1 (2.1%)		
Tumor location, median (IQR†), cm		10.0 (6.0 – 10.8)	9.5 (7.0 – 12.0)	0 (0.0%)	0.459
Neoadjuvant radiotherapy		21 (43.8%)	31 (64.6%)	0 (0.0%)	**0.041**
	Short-course	5 (10.4%)	16 (33.3%)		
	Long-course	15 (31.3%)	14 (29.2%)		
Neoadjuvant chemotherapy		14 (29.2%)	16 (33.3%)	0 (0.0%)	0.660
pT stage	pT0	3 (6.3%)	2 (4.2%)	0 (0.0%)	*0.973
	pT1	7 (14.6%)	7 (14.6%)		
	pT2	15 (31.3%)	14 (29.2%)		
	pT3/4	23 (47.9%)	25 (52.1%)		
pN stage	pN0	32 (66.7%)	34 (70.8%)	0 (0.0%)	0.660
	pN+	16 (33.3%)	14 (29.2%)		

* Fisher Exact Test;
† IQR, interquartile range;
‡ BMI, body mass index;
§ ASA, American Society of Anesthesiologists

Table 3. Post matching surgical characteristics

		TaTME 48	LaTME 48	Missing	P value
Duration of surgery, median (IQR†), minutes		221.0 (187.50 – 263.50)	180.0 (141.0 – 205.0)	3 (3.1%)	**<0.001**
Duration of anaesthesia, median (IQR†), minutes		264.0 (228.8 – 313.3)	217.0 (176.5 – 244.3)	8 (8.3%)	**<0.001**
Conversion		0 (0.0%)	5 (10.4%)	0 (0.0%)	*0.056
Construction of anastomosis	Hand-sewn	7 (14.6%)	0 (0.0%)	0 (0.0%)	***0.012**
	Stapler	41 (85.4%)	48 (100.0%)		
Configuration of anastomosis	Side-to-End	26 (54.2%)	41 (85.4%)	3 (3.1%)	***<0.001**
	End-to-End	20 (41.7%)	4 (8.3%)		
	End-to-Side	0 (0.0%)	2 (4.2%)		
Diverting ileostomy		40 (83.3%)	23 (47.9%)	0 (0.0%)	**<0.001**
CRM involvement		2 (4.2%)	1 (2.1%)	10 (10.4%)	*1.000
DRM involvement		5 (10.4%)	8 (16.7%)	8 (8.3%)	0.322

* Fisher Exact Test
† IQR, interquartile range

No statistically significant differences were observed for hospital stay, anastomotic leakage, ileus, cardiopulmonary complications, wound infections, Clavien-Dindo Classification, CCI, readmissions, reoperations and mortality (Table 4). Readmissions were due to anastomotic leakage, high output stoma, ileus, pancreatic pseudocyst and iatrogenic small bowel perforation. The indications for reoperations were anastomotic leakage and replacement of diverting ileostomy. In the LaTME group, 1 patient died two days after discharge of an unknown reason as autopsy was not performed.

Table 4. Postmatching postoperative course comparison

	TaTME 48	LaTME 48	Missing	P value
Hospital stay, median (IQR†), days	8.0 (6.0 – 13.5)	7.5 (5.0 – 13.8)	0 (0.0%)	0.596
Anastomotic leakage	10 (20.8%)	9 (18.8%)	0 (0.0%)	0.798
Ileus	7 (14.6%)	8 (16.7%)	0 (0.0%)	0.779
Cardiopulmonary complications	0 (0.0%)	3 (6.3%)	0 (0.0%)	*0.242
Wound infection	2 (4.2%)	1 (2.1%)	0 (0.0%)	*1.000
Clavien Dindo Classification >II	9 (18.8%)	10 (20.8%)	0 (0.0%)	0.798
Comprehensive Complication Index, median (IQR†)	14.8 (0.0 – 22.6)	4.4 (0.0 – 22.6)	0 (0.0%)	0.602
Readmission	10 (20.8%)	5 (10.4%)	0 (0.0%)	0.160
Reoperation	8 (16.7%)	7 (14.6%)	0 (0.0%)	0.779
Mortality	0 (0.0%)	1 (2.1%)	0 (0.0%)	*1.000

* Fisher Exact Test
† IQR, interquartile range

In the overall study population of 220 patients, multivariate penalized regression analyses showed that surgical approach is not associated with Clavien-Dindo Classification >II (OR 1.02 95% CI 0.41 – 2.51 p = 0.970), CCI (estimate -0.77 95% CI -6.84 – 5.31 P = 0.805), readmission (OR 1.13 95% CI 0.43 – 2.99 p = 0.802), and reoperation (OR 1.33 95% CI 0.49 – 3.64 p = 0.574) (Table 5).

Table 5. Multivariate penalized logistic regression to test the association between approach and Clavien-Dindo >II, readmission and reoperation

	Clavien-Dindo >II		CCI		Readmission		Reoperation	
	OR 95% CI*	P-value	Estimate 95% CI*	P-value	OR 95% CI*	P-value	OR 95% CI*	P-value
Age, median (IQR†), yr	0.96 0.92 – 0.99	**0.014**	-0.32 -0.55 - -0.08	**0.008**	0.97 0.94 – 1.01	0.181	0.96 0.92 – 1.00	**0.032**
Gender	0.77 0.37 – 1.59	0.482	-0.76 -5.66 – 4.14	0.760	0.88 0.39 – 2.02	0.770	1.01 0.44 – 2.31	0.980
BMI‡, median ± (IQR†), kg/m²	0.98 0.90 – 1.06	0.550	0.06 -0.45 – 0.57	0.820	0.98 0.89 – 1.07	0.618	1.03 0.94 – 1.12	0.588
Location lesion, median (IQR†), cm	1.00 0.92 – 1.08	0.990	0.23 -0.32 – 0.78	0.417	1.06 0.97 – 1.16	0.171	0.96 0.87 – 1.05	0.385
pT	0.88 0.62 – 1.24	0.455	-0.76 -3.03 – 1.51	0.514	0.94 0.64 – 1.39	0.774	1.01 0.68 – 1.50	0.952
Neoadjuvant radiotherapy	0.97 0.41 – 2.26	0.939	1.63 -4.21 – 7.47	0.585	1.05 0.41 – 2.70	0.920	0.86 0.34 – 2.16	0.748
Neoadjuvant chemotherapy	0.67 0.26 – 1.68	0.391	-7.09 -13.30 - -0.88	**0.026**	0.80 0.30 – 2.16	0.664	0.45 0.15 – 1.34	0.153
Diverting ileostomy	0.56 0.26 – 1.23	0.151	1.12 -4.19 – 6.43	0.680	2.22 0.84 – 5.83	0.107	0.41 0.17 – 1.01	0.054
Approach	1.02 0.41 – 2.51	0.970	-0.77 -6.84 – 5.31	0.805	1.13 0.43 – 2.99	0.802	1.33 0.49 – 3.64	0.574

*Odds ratio and 95% confidence interval
† IQR, interquartile range
‡ BMI, body mass index

Discussion and conclusions

This propensity score matched study of a prospective multicenter cohort study aimed to compare postoperative morbidity between TaTME and LaTME. Our results suggest that TaTME is a safe and feasible approach for rectal cancer resection and has similar postoperative morbidity to LaTME.

Nowadays, high conversion rates from laparoscopic to open surgery are reported for rectal resection especially in elderly patients and obese patients contributing to postoperative morbidity(6). Even in the most recent clinical trials comparing laparoscopic versus robotic assisted TME for rectal cancer, conversions were up to 10% in both arms(19). This is one of the main drawbacks of conventional laparoscopic surgery for rectal resection. In the present study, TaTME was not converted at all while LaTME was converted to laparotomy in 10.4%. A recent single center case-matched study reported similar results(20). This low incidence of conversion seems to be the main advantages of this new technique.

With the introduction of minimal invasive techniques, the short-term outcomes of rectal surgery have improved over recent decades. Despite these advances, the incidence of anastomotic leakage has not been reduced(21). Anastomotic leakage is one of the major concerns after rectal resection because of associated morbidity and mortality. A recent study demonstrated that large rectal tumors in obese, diabetic male patients who smoke have the highest risk for anastomotic leakage after TaTME(22). In line with previous literature, we found no difference in leakage rate for TaTME and LaTME (9-11, 13, 23-25). Therefore, the transanal approach does not seem to reduce the incidence of AL after rectal cancer resection.

In contrast to previous studies, our results show that TaTME is associated with more prolonged surgery and anesthesia(7, 8). Previously, it was suggested that TaTME can be performed by two teams simultaneously, however not all hospitals have the capacity to perform TaTME in two teams due to lack of personnel. When TaTME is not performed in two teams simultaneously, this may result in prolonged duration of surgery and anesthesia. Moreover, this study included hospitals in which the TaTME technique was recently introduced. Therefore, a longer duration of surgery might reflect a learning curve. (26). In addition, creation of a diverting ileostomy, which was more often performed in the TaTME group, may also influence duration of surgery and anesthesia.

After matching for propensity score, patients who underwent LaTME received neoadjuvant radiotherapy more frequently than TaTME patients. The ESMO clinical practice guidelines have recently been updated indicating that specific patients with intermediate risk rectal cancer do not need neoadjuvant treatment in order to minimize local recurrence if good-quality TME can be achieved(27). Since the TaTME has recently become more popular, this difference might mirror the update of these guidelines. In addition, this study showed, in the unmatched cohort, that preoperative radiotherapy was not associated with postoperative morbidity (Table 5), and therefore it is unlikely that this difference in baseline characteristics have influenced the results.

In the postmatching TaTME group, more manual and end-to-end anastomoses were observed, even though there were no baseline differences in between both groups on tumor height. A systematic review showed similar results(28).

Diverting ileostomies are common after rectal resection but do not reduce anastomotic leakage or mortality(29). In fact, diverting ileostomies tend to mitigate consequences of anastomotic leakage resulting in less invasive treatment strategies. In the present study, patients who underwent TaTME were more often diverted during primary surgery. A recent single center case-matched study found similar results(25). This difference might reflect surgeons' perception to protect the anastomosis following the new approach while this risk is unsubstantiated.

In the present study, tumor location was derived from endoscopy. There seems to be a significant difference between the tumor location of colorectal cancers reported by endoscopy and the actual location determined during surgery(30). Moreover, the anal verge was the reference for determination of the tumor location. Thus, this distance includes the anal canal of 3-5 cm(31). This may explain the relatively high tumor location in both the TaTME as the LaTME group.

Functional outcomes are of interest for future research. TaTME possibly provides better visualization of the distal rectum which may contribute to preservation of pelvic nerves and vascularity resulting in better urinary and sexual function(23, 32).

At this moment, this subgroup analysis provides the highest level of evidence on postoperative short-term after TaTME and LaTME currently available since the results were based on a multicenter prospective cohort study. Nevertheless, we recognize several limitations of this study. First, the TME procedures in both groups were not standardized so different types of laparoscopic assisting techniques (i.e. single-port or multi-port) were used. Second, cohort studies are sensitive to bias and confounding. Nevertheless, both propensity score analysis and penalized multivariate regression analyses were performed to adjust for confounding effects showing similar results.

This propensity score matched study of a prospective multicenter cohort study aimed to compare postoperative morbidity between TaTME and LaTME. The present study showed that TaTME is a safe and feasible approach for rectal cancer resection. This new technique obtained similar postoperative morbidity. This study is the first to provide evidence based upon prospective data. However, oncological safety in terms of CRM involvement and local recurrence should be obtained in a well-designed randomized controlled trial.

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Chapter 7

Outcomes after elective colorectal surgery by two surgeons versus one in a low-volume hospital*

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Abstract

Background

Improved patient outcomes after colorectal surgery in high-volume hospitals are leading to centralization of colorectal surgery. However, it is desirable to strive for optimal quality of colorectal surgery in low-volume hospitals. This study aimed to assess the effect of the number of surgeons involved in the surgical procedure on patient outcomes in a low-volume hospital.

Methods

All patients who underwent elective colorectal surgery with construction of a primary anastomosis between January 1st 2007 and December 31st 2015 were included in this retrospective cohort. The propensity score was used to adjust for confounding.

Results

A total of 429 patients were included. 143 patients (33.3%) were operated by one surgeon and 286 patients (66.7%) were operated by two surgeons. Patients operated by two surgeons were younger, more often male, and had a higher BMI. A multivariate analysis with propensity scores revealed that surgery with two surgeons was associated with less reoperations (OR 0.4 95%CI 0.2–0.9 p=0.038). Colorectal anastomotic leakage (OR 0.6 95%CI 0.2–1.3 p=0.204) and mortality (OR 0.8 95%CI 0.2–3.7 p=0.807) were not associated with the number of surgeons involved in the surgical procedure.

Conclusion

The present study shows that elective colorectal surgery in a low-volume hospital performed by two surgeons resulted in less reoperations. This might positively influence patient outcomes and might be related to increased surgical quality as compared to procedures performed by only one surgeon.

Introduction

There is a growing interest in quality assessment of colorectal surgery with an increasing need for outcome measures that represent performance of institutes and individual surgeons. Variability in patient outcomes following colorectal surgery has been identified to be assigned to both patient-related factors and institution-related factors(1-3). Previously, several studies have reported improved patient outcomes after colorectal surgery in high-volume hospitals(4). This has led to centralization of colorectal surgery and centers of excellence have been established. However, improvement of patient outcomes after colorectal surgery in low-volume hospitals is not addressed within this strategy. As it may not be possible to implement centralization of colorectal surgery on a national level in the near future, it is still of paramount importance to improve quality of care in low-volume centers. Furthermore, patient outcomes from individual surgeons have come under increased scrutiny. Both volume of surgery and specialization of individual surgeons are associated with improved patient outcomes for colorectal surgery(5-7).

The value of teamwork in the operating room has also earned increasing attention(8). Improvement of teamwork in the operating room may have beneficial effects on patient outcomes(9). Some data suggest that there is an association with teamwork culture and reduction of surgical site infections(10). Nevertheless, the effect of the number of certified surgeons (i.e. not being a resident) involved in the surgical procedure on patient outcomes after colorectal surgery in a low-volume hospital has not been addressed previously, while this might provide an easy possibility to improve patient outcomes after colorectal surgery in low-volume hospitals.

This study aims to determine the effect of the number of surgeons involved in the surgical procedure on quality of colorectal surgery in a low-volume hospital. Our hypothesis was that outcomes of elective colorectal surgery improve when surgical procedures were performed by two surgeons compared to one surgeon in a low-volume hospital.

Materials and methods

Study design

We performed a retrospective, single center, cohort study at the Havenziekenhuis, Rotterdam. The Havenziekenhuis is a low-volume, satellite hospital of the Erasmus University Medical Center Rotterdam, but it is not a teaching hospital. Therefore, no surgical fellows or residents were involved during the surgical procedures and it was possible to compare outcomes between the different numbers of surgeons involved in the surgical procedure. All surgeons involved in the study were formally certified by the Dutch Society of Surgery to perform colorectal surgery and had comparable colorectal expertise. Between January 1st 2007 and December 31st 2015, all patients undergoing elective colorectal surgery with construction of a primary anastomosis, with or without a protective ileostomy, were included. Patients who received an end colostomy or end ileostomy were not included. The STROBE (Strengthening the Reporting of Observational studies in Epidemiology) statement was used for this study(11). Informed consent was waived for participation in this study, because it was a retrospective records review. The study was approved the institutional review board of the Erasmus University Medical Center Rotterdam.

Data collection

Patients were identified by searching hospital database for DBC Codes (Diagnose Behandel Combinatie; Diagnosis Related Groups [DRGs]). Patients' medical records were reviewed and data were collected on patient characteristics: age, sex, Body Mass Index (BMI), American Society of Anesthesiologists (ASA) score, diabetes mellitus, smoking, alcohol abuse (>14 drinks per week), medication use. Surgical characteristics were retrieved and included type of surgical procedure, indication, approach (laparoscopic or open), conversion, stoma construction, additional abdominal resection, intraoperative complications, and duration of surgery.

The number of surgeons involved in the surgical procedures were retrieved from surgical reports. In these surgical reports it was marked which surgeons performed the operation and who were assisting. Only procedures that started and were completed with two surgeons were labeled as 'two surgeons'. If a surgeon, urologist, or gynecologist briefly joined the team to assist with the procedure, it was defined as surgery performed by one surgeon. There was no clear rationale within the unit for deciding which patients involved two surgeons and which patients involved just one. All surgeons performed colorectal resections on their own or together with a colleague.

The postoperative period was restricted to 30 days after the primary procedure and information was obtained regarding postoperative complications. Reoperation, colorectal anastomotic leakage (CAL), mortality and length of hospital stay were registered. Reoperation did not include closure of ileostomy. CAL was defined as an insufficiency of the anastomosis, demonstrated by either imaging studies or reoperation and leading to a clinical state that required intervention such as antibiotic treatment, radiological drainage or surgical intervention.

Statistical analysis

Continuous variables were presented as median with interquartile range (IQR) and univariate testing was performed using Mann-Whitney U test. Dichotomous and categorical variables were presented as numbers with percentages (%) and univariate testing was performed using Pearson's Chi-squared test or Fisher's Exact test depending on size of groups. To adjust for confounding factors, a propensity score was constructed with a multivariable logistic regression model with variables that might determine whether a patient is operated by one or two surgeons. In this model, we included variables related to the number of surgeons involved in surgery that were considered clinically relevant. The propensity score was then added as independent variable to a logistic or linear regression model, depending on the outcome measure, together with the variable that indicated the number of surgeons involved. Sensitivity analysis was performed to explore the effect of surgical approach by stratifying the propensity score analysis for laparoscopic or open approach. A two-sided p-value of <0.05 was considered statistically significant for all tests. All analyses were performed using IBM SPSS Version 21.0.0.1.

Results

We established a retrospective cohort of 441 consecutive patients who were admitted to the Havenziekenhuis Hospital in Rotterdam between January 1st 2007 and December 31th 2015 for elective colorectal resection with construction of a primary anastomosis, with or without construction of protective ileostomy. On average 49 elective colorectal resections with construction of a primary anastomosis were performed yearly. Eleven patients were excluded due to lack of information on the postoperative course. One patient was excluded due to inconclusive information on the number of operators. In total, 429 patients were eligible for analysis, of which 163 underwent right hemicolectomy, 51 left hemicolectomy, 143 sigmoid resection and 72 (low) anterior resection. A total of 204 operations (47.6%) were performed laparoscopically, of which 38 (18.6%) were converted. The median length of hospital stay was 8 days (IQR: 6-13 days) and the incidence of CAL was 8.6% (37 patients). Forty-two patients underwent reoperation. The median hospital stay for patients that underwent reoperation was 16 days and 7 days for patients that did not underwent reoperation ($p<0.001$).

Ten individual surgeons were involved in this study. In 143 patients (33.3%) surgery was performed by one surgeon and in 286 patients (66.7%) by two surgeons. The group of patients operated by two surgeons was younger ($p=0.047$), consisted of more males ($p=0.034$) and had a higher BMI ($p=0.031$) (Table 1). Carcinoma was more often the indication for surgery in patients operated by two surgeons ($p=0.001$). Laparoscopic surgery was more often performed by two surgeons ($p<0.001$). Moreover, in patients operated by two surgeons, a protective ileostomy was constructed more frequently ($p<0.001$), the duration of surgery was significantly longer ($p<0.001$) and more intraoperative complications were recorded ($p=0.049$).

Table 1. Univariate analysis of patient and surgical characteristics with number of surgeons involved.

	One surgeon N = 143 (33.3%)	Two surgeons N = 286 (66.7%)	*P* value
Patient characteristics			
Age (years)	71.8 (65.1-80.2)	68.3 (60.7-76.3)	0.047
Sex			0.034
Male	66 (46.2%)	163 (57.0%)	
Female	77 (53.8%)	123 (43.0%)	
BMI‡ (kg/m²)	24.6 (22.6-27.8)	25.9 (23.4-29.3)	0.031
ASA§ I-II	84 (76.4%)	203 (80.2%)	0.404
ASA§ III-IV	26 (23.6%)	50 (19.8%)	
Diabetes Mellitus			0.577
Yes	18 (15.5%)	227 (86.6%)	
No	98 (84.5%)	35 (13.4%)	
Smoking			0.190
Yes	20 (18.0%)	62 (24.2%)	
No	91 (82.0%)	194 (75.8%)	
Alcohol			0.233
Yes	44 (40.0%)	85 (33.2%)	
No	66 (60.0%)	171 (66.8%)	
Corticosteroids			0.946
Yes	11 (9.0%)	24 (9.2%)	
No	111 (91.0%)	236 (90.8%)	
NSAIDs‖			0.269
Yes	6 (5.0%)	21 (8.1%)	
No	115 (95.0%)	239 (91.9%)	
Surgical characteristics			
Type of surgery			0.326
Right hemicolectomy	50 (35.0%)	113 (39.5%)	
Left hemicolectomy	22 (15.4%)	29 (10.1%)	
Sigmoid resection	50 (35.0%)	93 (32.5%)	
(Low) anterior resection	21 14.7%)	51 (17.8%)	
Carcinoma			0.001
Yes	94 (65.7%)	230 (80.4%)	
No	49 (34.3%)	56 (19.6%)	
Approach			0.000
Laparoscopic	15 (10.5%)	189 (66.1%)	
Open	128 (89.5%)	97 (33.9%)	
Conversion			0.313†
Yes	1 (6.7%)	37 (19.6%)	
No	14 (93.3%)	132 (69.8%)	
Stoma			<0.001†
Yes	2 (1.4%)	40 (14.0%)	
No	141 (98.6%)	245 (86.0%)	
Additional abdominal resection			0.306
Yes	11 (7.7%)	31 (10.8%)	
No	132 (92.3%)	255 (89.2%)	
Intraoperative complications			0.086
Yes	11 (7.7%)	38 (13.3%)	
No	132 (92.3%)	248 (86.7%)	
Duration of surgery, minutes	101 (75 - 133)	127.5 (101 - 164)	<0.001

*Data are patients (%) or median (interquartile range); † Fisher's Exact test; ‡ BMI, body mass index; § ASA, American Society of Anesthesiologists;|| NSAIDs, nonsteroidal anti-inflammatory drug

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For postoperative outcomes, colorectal anastomotic leakage (CAL) was observed in 16 patients (11.2%) operated by one surgeon and in 21 patients (7.3%) operated by two surgeons (p=0.181) (Table 2). Surgery performed by two surgeons was associated with shorter hospital stay (9.0 *versus* 7.0 days, p=0.001) and less reoperations (14.0% *versus* 7.7%, p=0.039). The indication for reoperation was CAL in 31 patients and abdominal wound dehiscence in seven patients. The indication for reoperation in the other four patients was persisting pain and fever, iatrogenic small bowel perforation, ascites and severe postoperative ileus, respectively.

Table 2. Univariate analysis of postoperative outcomes with the number of surgeons involved

Postoperative outcomes	One surgeon N = 143 (33.3%)	Two surgeons N = 286 (66.7%)	*P* value
Reoperation			0.039
Yes	20 (14.0%)	22 (7.7%)	
No	123 (86.0%)	264 (92.4%)	
Colorectal anastomotic leakage			0.181
Yes	16 (11.2%)	21 (7.3%)	
No	127 (88.8%)	265 (92.7%)	
Mortality			0.153†
Yes	5 (3.5%)	4 (1.4%)	
No	138 (96.5%)	282 (98.6%)	
Hospital stay (days)	9.0 (7.0 - 14.0)	7.0 (5.0 - 11.0)	0.001

*Data are patients (%) or median (interquartile range)
† Fisher's Exact test.

For the adjusted analysis, a propensity score was calculated for being operated by one or two surgeons with all variables that had a p-value of <0.1 in the univariate analysis or were considered clinically relevant being age, sex, BMI, carcinoma as indication, surgical approach, protective ileostomy construction, duration of surgery, and intraoperative complications. The area under the curve of the calculated propensity score was 0.842.

After adjustment for the propensity score, the number of surgeons involved in the surgical procedure remained related to post-operative outcomes (Supplementary Table 1). Surgery performed by two surgeons was associated with less reoperations (OR 0.4, 95% CI 0.2–0.9, p=0.038). Surgery performed by two surgeons was also associated with the lower incidence of CAL (OR 0.6, 95% CI 0.2–1.3, p=0.204) and lower mortality (OR 0.8, 95% CI 0.2–3.7, p=0.807), although not statistically significant. The length of hospital stay was not significantly shorter for patients operated by two surgeons (linear regression coefficient -0.8, 95% CI -2.9–1.3, p=0.446).

As a sensitivity analysis, the multivariate analysis was repeated with stratification for surgical approach. It was not justified to stratify for surgical approach for mortality because of the small number of events. All estimated ORs were in the same direction as the un-stratified analyses, but P values were higher due to the inherent reduction of sample sizes (Supplementary Table 2).

Discussion

The purpose of this study was to determine the effect of number of surgeons involved in the surgical procedure on quality of elective colorectal surgery in a low-volume hospital. The results of our study suggested that colorectal surgery performed by two surgeons was associated with less reoperations compared to surgery performed by one surgeon in a low volume hospital. In addition, our study showed a trend towards a decrease of CAL, mortality, and hospital stay in the group of patients operated by two surgeons, although these findings were not statistically significant.

Recently, several studies demonstrated better postoperative outcomes after colorectal surgery in high-volume hospitals(4). Besides, better oncologic outcomes were reported in high-volume hospitals(12, 13). Therefore, nowadays, centralization of care in colorectal surgery is becoming more and more important. However, there is a lack of scientific interest to improve quality of colorectal surgery in low-volume hospitals, whereas centralization of colorectal surgery might not be implemented on a national level soon. This study showed that performing colorectal surgery with two surgeons in a low-volume hospital might improve patient outcomes after colorectal surgery.

The incidence of CAL was 8.6%, which is comparable to previous studies(14, 15). Furthermore, 42 (9.7%) patients underwent reoperation. A recent study evaluating the incidence of reoperation after colorectal surgery as a valid measure for surgical quality reported comparable incidence(16). In the multivariate analyses, surgery performed by two surgeons was associated with less reoperations during the postoperative course, but hospital stay was not shorter for patients operated by two surgeons. Of all 429 included patients, only 42 (9.8%) patients underwent reoperation. Because of the relatively low incidence of reoperations, the overall hospital stay was not strongly affected by the different incidence of reoperation between the two groups.

The present study might have been subject to selection bias. Patients operated by two surgeons had higher BMI which might complicate the surgical procedure and lead to worse postoperative patient outcomes(17, 18). Moreover, protective ileostomies were more often constructed during surgery performed by two surgeons which may have possibly resulted in prolonged duration of surgery. In addition, laparoscopic procedures were more often performed by two surgeons. These findings might implicate that surgical procedures performed by two surgeons were associated with increased complexity and difficulty. Nevertheless, our study has shown that there were less reoperations in the group of patients that was operated by two surgeons.

Some differences in the univariate comparison may be related to the difference in surgical approach. However, a multivariate analysis with propensity scores was performed to eliminate this case-mix problem. In addition, the results of the sensitivity analysis, stratified by surgical approach, were consistent with our primary analysis.

In our study it was not justified to perform a RCT due to clinical equipoise. Most observational studies use multivariable analysis or stratification to adjust for confounding, but propensity score analysis offers a powerful alternative to multivariable analysis, especially in situations with a relatively low event rate(19-21). Propensity score analysis accounts for the conditional probability of treatment-selection, thus allowing for reduction of bias when comparing interventions between treatment groups(22).

The Hawthorne effect is a possible explanation for improved outcomes with two surgeons. This was recently suggested in a study which found that a multidisciplinary, perioperative protocol was associated with reduction in mortality after acute abdominal surgery(23). The Hawthorne effect concerns the awareness of being observed or studied and the resulting possible positive impact on behavior(24). In case of surgery performed by one surgeon, the surgeon was assisted by a surgical assistant while in case of two surgeons there was a constant awareness of being observed by someone with comparable skills and qualities, which might potentially introduce the Hawthorne effect. Additionally, the combined experience of two surgeons might improve surgical quality through increased technical knowledge and awareness. This synergy might be explored in future studies to understand both the technical as well as communication-related mechanisms underlying our observations of improved outcomes with two surgeons.

To our knowledge, this study was the first to investigate the association between the number of surgeons involved in the surgical procedure and the outcomes of colorectal surgery representing quality assessment. We found that surgery performed by two surgeons is associated with less reoperations and, although not statistically significant, with less CAL and mortality, and shorter length of hospital stay. The lack of statistical significance is likely due to low statistical power. This study included a large cohort of patients undergoing elective colorectal surgery, but only 37 patients (8.6%) suffered from CAL and only nine (2.1%) patients died, which introduces a large risk of a type II error resulting from a relatively low event rate. Nevertheless, we can interpret our results with more confidence since the ORs for all outcomes were directing to better outcomes with two surgeons.

There were some limitations in this study that need to be addressed. Although we adjusted for confounding with propensity score analysis, this retrospective observational study was still sensitive to confounding of unknown factors. In the future it might not be possible to explore our hypothesis in a RCT due to lack of clinical equipoise, but the results of this retrospective study justify conducting a prospective cohort study. Moreover, financial aspects of performing colorectal surgery with two surgeons were not taken into account. Even though this strategy might initially increase procedure-related costs, a decrease in the number of reoperations and postoperative burden might potentially compensate these additional costs.

Conclusion

The present study shows that elective colorectal surgery in a low-volume hospital performed by two surgeons resulted in less reoperations. This might positively influence patient outcomes and might be related to increased surgical quality as compared to procedures performed by only one surgeon.

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Supplementary materials

Supplementary Table 1. Adjusted analysis with propensity score for postoperative outcomes and the number of surgeons involved

	OR (95% CI)*	***P* value**
Reoperations	0.4 (0.2 – 0.9)	0.038
Colorectal anastomotic leakage	0.6 (0.2 – 1.3)	0.204
Mortality	0.8 (0.2 – 3.7)	0.807
	Linear regression coefficient	
Hospital stay	-0.8 (-2.9 – 1.3)	0.446

*Odds ratio and 95% confidence interval

Supplementary Table 2. Sensitivity analysis of adjusted analysis with propensity score stratified for surgical approach.

	Open surgery		**Laparoscopic surgery**	
	OR (95% CI)*	*P* value	OR (95% CI)*	*P* value
Reoperations	0.5 (0.2 – 1.2)	0.127	0.4 (0.1 – 1.6)	0.178
Colorectal anastomotic leakage	0.6 (0.2 – 1.6)	0.315	0.6 (0.1 – 3.4)	0.605
	Linear regression coefficient		Linear regression coefficient	
Hospital stay	-1.3 (-3.8 – 1.2)	0.313	0.9 (-3.1 -5.0)	0.445

*Odds ratio and 95% confidence interval

PART III

PREVENTION OF COLORECTAL ANASTOMOTIC LEAKAGE

Chapter 8

Is the intraoperative air leak test effective in the prevention of colorectal anastomotic leakage? A systematic review and meta-analysis*

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Abstract

Objective

The intra-operative air leak test (ALT) is a common intraoperative test used to identify mechanically insufficient anastomosis. This meta-analysis aims to determine whether ALT aids to the reduction of postoperative colorectal anastomotic leakage (CAL).

Methods

A literature search was performed to select studies in acknowledged databases. Full text articles targeting ALT during colorectal surgery were included. Quality assessment, risk of bias and the level-of-evidence of the inclusions were evaluated. ALT methodology, ALT(+) (i.e., leak observed during the test) rate, and postoperative CAL rate of the included studies were subsequently analyzed.

Results

Twenty studies were included for analysis, in which we found substantial risks of bias. A lower CAL rate was observed in patients underwent ALT than those did not; however, the difference was not significant ($p=0.15$). The intraoperative ALT(+) rate greatly varied among the included studies from 1.5% to 24.7%. ALT(+) patients possessed a significantly higher CAL rate than the ALT(-) patients (11.4% vs. 4.2% $p<0.001$).

Conclusions

Based on the available evidence, performing an ALT with the reported methodology has not significantly reduced the clinical CAL rate but remains necessary due to a higher risk of CAL in ALT(+) cases. Unfortunately, additional repairs under current methods may not effectively decrease this risk. Results of this review urge standardization of ALT methodology and effective methods to repair ALT(+) anastomoses.

Introduction

Colorectal anastomotic leakage (CAL) is one of the most dangerous short-term complications after colorectal surgery, attributing to one third of postoperative mortality(1). To prevent CAL, substantial efforts have been made. Among them, the air leak test (ALT) is apparently the most frequently performed intraoperative test to identify a mechanically insufficient anastomosis(2). Typically, certain countermeasures such as additional sutures or a temporary protective stoma construction are performed when a leak (e.g. leakage of air bubbles or dye) was observed during the test.

Though being performed by a majority of colorectal surgeons, it remains inconclusive whether performing ALT and the immediate repair of the ALT(+) cases (i.e. leak of air/dye observed in the test) is beneficial in preventing CAL. This may be due to at least two variables: first, the etiology of CAL is multi-factorial, comprised of communication between intra- and extra-luminal content (e.g., suture dehiscence), anastomotic infection (e.g., peritonitis) and healing disturbances (e.g., ischemia). Performing an ALT may provide limited assistance in detecting CAL due to causes other than anastomotic mechanical failure. Second, various ALT techniques with different outcomes have been reported, which increases the concern that whether such varying techniques may cause different results in detecting mechanically failed anastomosis and eventually lead to different clinical intervention and outcomes. To date, no systematic review or meta-analysis is available providing solid evidence supporting routine ALT application. To this end, we performed this review aiming to determine whether implementing the intraoperative air leak test might aid to reduce CAL.

Methods

Literature Search Strategy

The literature search for this systematic review was performed in January 2015 according to the PRISMA (Preferred Items for Reporting of Systematic Reviews and Meta-Analyses) guidelines in databases including Medline, Embase, Cochrane, Web-of-Science and Google Scholar databases. No restrictions regarding publication date or language have been applied during the search. We restricted our search to human studies, clinical trials and controlled or randomized controlled trials. The following search strategy was used in Embase and modified in other databases accordingly: *((air NEAR/3 (leak* OR pressure* OR insufflat* OR burst* OR tight* OR compress* OR inject* OR deflat*) NEAR/3 test*) OR ((((air OR leak* OR pressure) NEAR/3 test*):ab,ti) AND ('anastomosis leakage'/exp OR 'intestine anastomosis'/exp OR anastomosis/exp OR (anastomo* OR leak*):ab,ti))) AND ('intestine surgery'/exp OR intestine/exp OR 'large intestine disease'/exp OR (intestin* OR colorect* OR colon* OR rectum OR rectal OR bowel* OR sigmoidectom* OR hemicolectom* OR anorectal OR anal OR anus):ab,ti)*

Study Selection

Titles and abstracts of identified articles were independently screened by two authors (R.H. and C.S.) for relevance to the subject. Full text articles were included if they targeted intraoperative air leak test during colorectal surgery and reported the CAL rate accordingly. Reviews, letters to editors, congress and meeting abstracts were excluded. Hereafter, the references of the selected articles were screened for any relevant articles.

Quality Assessment and Data Extraction

Quality Assessment and risk of bias were reviewed by two independent authors (R.H. and C.S.) according to The Cochrane Collaboration's tool for assessing risk of bias(3). The tool assesses the risk of bias and applicability concerns by means of six key domains including sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other sources of bias. Afterwards, the Level of Evidence was evaluated according to the Levels of Evidence (LOE) 2011 from the Centre for Evidence Based Medicine, Oxford(4).

The definition of CAL and the method of performing the air leak test of the included articles were recorded. The clinical endpoints, postoperative clinical or radiological colorectal manifestations of CAL were included for analysis. We assessed ALT performance, intraoperative leakage rate, and the corresponding CAL rates. We also evaluated several subgroups including the analysis of CAL rate in ALT(+) vs. ALT(-) groups. ALT(+) is defined as leak of air/dye observed in the test; ALT(-) is defined as leak of air/dye not observed in the test.

Statistical Analysis

Our primary objective was to determine whether performing ALT reduces CAL. We made a comparison between CAL rates in patients underwent ALT vs. CAL rates in patients that did not undergo the test. We also compared the CAL rate in the ALT(+) patients vs. the ALT(-) ones to determine whether ALT(+) patients have a higher CAL incidence after surgery. For pooling data and calculating a pooled mean for each outcome, the Mantel-Haenszel method was applied using a random-effect model; mean differences with a 95% confidence interval were calculated. Statistical heterogeneity was assessed using Q statistic and I^2 statistics.

Sensitivity analysis

To assess the individual effect of the studies on the overall outcome, a sensitivity analysis was performed. One study was removed at a time to determine whether this would influence the significance of the pooled outcome.

Analyses were performed using Review Manager software (RevMan version 5.3; The Nordic Cochrane Centre, Copenhagen, Denmark).

Results

Literature search results, level of evidence and risk of bias

In total, there were 500 studies identified during the systematic search, of which, 12 studies appeared to be relevant to the study question and were therefore included for analysis. An additional 8 articles were selected from the references, boosting the total to 20 included articles (Figure 1). In total, 5283 patients were included for analysis, with 2395 of them undergoing ALT. The inclusions contained 2 randomized trials, 7 cohort studies, and 11 case series (Table 1). The risk of bias of each inclusion was evaluated and listed in Table 2. Substantial risks of bias were observed among different studies, mostly focusing on the lack of randomization and clear definition of CAL.

Figure 1. Flow chart of the literature search according to the PRISMA guideline

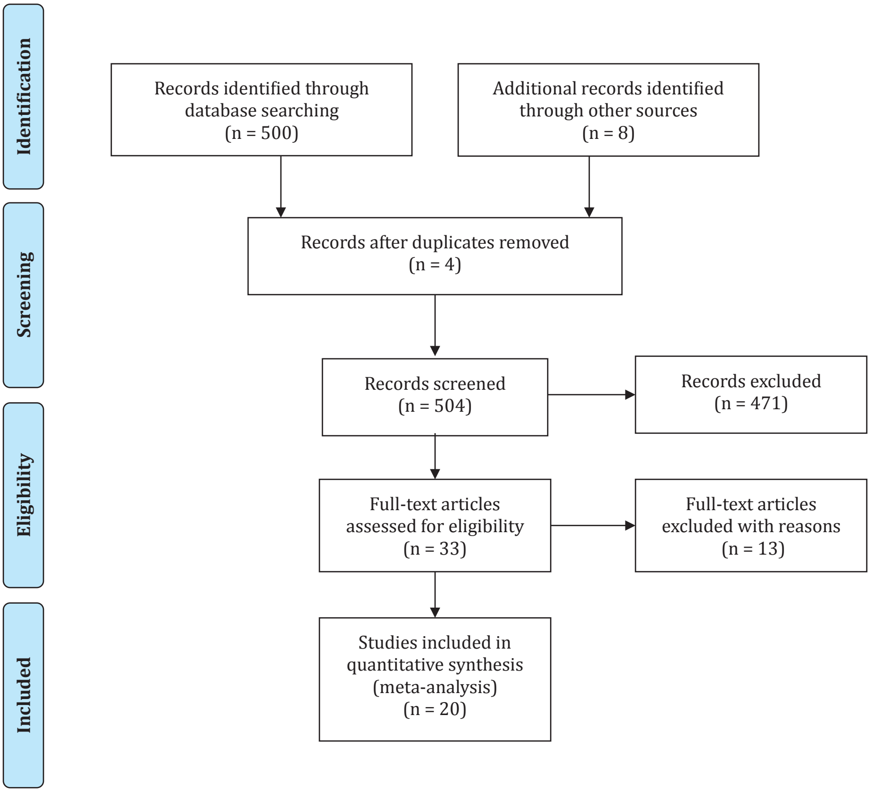

Table 1. Overview of the included studies.

Author	No. of patients	Study design	LOE	AL definition	Method of air leak test	Consequence of ALT(+)
Lazorthes et al.	82	Prospective case series	4	(1) Clinical signs (not defined) (2) Routinely radiological control (enema)	Air insufflation into the rectum using a catheter with the anastomosis under irrigation of saline.	Reinforcing sutures or defunctioning colostoma
Davies et al.	33	Prospective case series	4	(1) Clinical signs: mild (pyrexia, ileus) vs. major (need for colostomy, fistula); (2) Routinely radiological control (enema)	Air insufflation into the rectum using a catheter with the anastomosis under irrigation of saline.	Reinforcement sutures and retested
Beard et al.	143	RCT	1b	(1) Clinical signs (not defined) (2) Routinely radiological control (enema)	Air insufflation into the rectum using an endoscope with the pelvis under irrigation of saline	Oversewing and retested
Griffith et al.	60	Prospective case series	4	Clinical signs (1) faecal fistula, (2)anastomotic breakdown seen at laparotomy or post-mortem examination in association with peritonitis, and (3) clinical features of AL confirmed by sigmoidoscopy or rectal examination	Air insufflation into the rectum using a catheter with the anastomosis under irrigation of saline.	Further stitches until satisfactory ALT
Pritchard et al.	82	Prospective case series	4	Clinical signs (prolonged ileus, unexplained fever, tenderness and distention or rectal discharge). Confirmed by Gastrografin enema. Diagnosis was based on radiography	Air insufflation into the rectum using a catheter with the anastomosis under irrigation of saline.	Defunctioning stoma
Yalin et al.	21	Prospective case series	4	Clinical signs (not defined)	Air insufflation into the rectum using a catheter with the anastomosis under irrigation of saline.	Additional sutures or diverting stoma
Sakanoue et al.	70	Prospective cohort	2b	Clinical signs (not defined)	Air insufflation into the rectum using an endoscope with the anastomosis under irrigation of saline	Reinforcing sutures and diverting stoma
Vignali et al.	55	Prospective case series	4	(1) Clinical signs: fecal fistula to the wound, to the drain tract, or to the vagina or pelvic sepsis supported by radiologic evidence of leak. (2) Routinely radiological control	Insufflation of air into the bowel with the anastomosis under irrigation of saline	Temporary stoma

Table 1. (Continued)

Author	No. of patients	Study design	LOE	AL definition	Method of air leak test	Consequence of ALT(+)
Schmidt et al.	788	Retrospective cohort	2b	Clinical signs: gas, pus or faecal discharge from a drain, pelvic abscess, peritonitis, discharge of pus per rectum or rectovaginal fistula.	Air insufflation into the rectum using an endoscope with the anastomosis under irrigation of saline	Protective stoma
Ishihara et al.	73	Prospective case series	4	Not described	Insufflation of air into the bowel with the anastomosis under irrigation of saline	Additional sutures or redoing of the anastomosis
Lanthaler et al.	122	Prospective cohort	2b	Not described	Insufflation of air into the rectum with the anastomosis under irrigation of saline	Oversewn, protecting loop ileostomy or Hartmann procedure
Ricciardi et al.	998	Retrospective cohort	2b	Clinical signs: the presence of luminal contents through a drain or wound site or abscess cavity causing inflammation (i.e., fever, leukocytosis, or fecal discharge).	Insufflation of air through a proctoscope or flexible endoscope with the anastomosis under irrigation of saline	(1) Repair without diversion, or (2) unplanned proximal diversion, or (3) takedown of anastomosis with new anastomotic construction and no diversion.
Li et al.	244	Retrospective cohort	2b	Clinical signs: peritonitis, feculent substances or gas from the drain, and sepsis or the presence of abscess with demonstrable anastomotic leak by clinical, endoscopic, or radiologic examination.	Transanal insufflation of air using an endoscope with the anastomosis under irrigation of saline	Additional interrupted sutures
Shamiyeh et al.	338	Retrospective cohort	2b	Not described	400cc air insufflation into the colon using a syringe with the anastomosis under irrigation of saline	Oversewn or redoing anastomosis
Ivanov et al.	60	RCT	1b	Clinical signs: gas leakage, pus or faecal discharge from the drain, clinical picture of anastomotic dehiscence (increased body temperature, stomach painful at palpation, auscultatory evidence of absent peristalsis, signs of liquid-gas levels at abdominal x-ray, leukocytosis) with or without a confirmation by sigmoidoscope, and the presence of intra-abdominal abscess verified either by ultrasonography or abdominal CT.	Air insufflation into the rectum using a sigmoidoscope with the anastomosis under irrigation of saline	Repair by single layer extramucosal sutures

Table 1. (Continued)

Author	No. of patients	Study design	LOE	AL definition	Method of air leak test	Consequence of ALT(+)
Lieto et al.	124	Prospective cohort	2b	Clinical signs: presence of signs of peritonitis or abdominal sepsis with or without evidence of luminal content and/or gas through the drain, and demonstrable anastomotic breakdown by endoscopic and/or radiologic examination.	Insufflation of air using an endoscope with the anastomosis under irrigation of saline	Oversewn with interrupted sutures
Kamal et al.	415	Retrospective case series	4	Not described	Air insufflation during sigmoidoscopy	Revision of the anastomosis
Kim et al.	363	Retrospective case series	4	Not described	Not described	Re-resection and re-doing anastomosis with or without diverting stoma, suturing at disrupted site with or without diverting stoma, or only diverting stoma were performed by surgeon's preference.
Xiao et al.	198	Prospective case series	4	Clinical signs: (1) peritonitis and related abnormalities: pelvic or perineal pain or tenderness, tachycardia, fever, and increased white blood cell (WBC) count; (2) gas, fecal, or purulent discharge from the pelvic drain, drain tract, or anus; (3) pelvic abscess or fluid collection; (4) rectovaginal fistula. The diagnosis was verified by clinical, endoscopic, radiologic investigations, or laparotomy	Air insufflation into the rectum using a rectoscope with the anastomosis under irrigation of saline	Repair at the discretion of the operating surgeon, either with additional sutures or redoing anastomosis
Vignali et al.	1014	Retrospective case series	4	Clinical signs: fecal fistula from a wound, drain tract, or vagina; confirmed by sigmoidoscopy or rectal examination; or pelvic sepsis supported by radiologic evidence of leak.	Insufflation of air into the bowel with the anastomosis under irrigation of saline	Reinforcing sutures, if sutures were not possible a defunctioning stoma was formed

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Table 2. Risk of Bias of the included studies.

Author	Sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective outcome reporting	Other sources of bias
Lazorthes et al.	-	-	-	+	+	+
Davies et al.	-	-	-	+	+	+
Beard et al.	+	+	?	+	+	+
Griffith et al.	-	-	-	+	+	+
Pritchard et al.	-	-	-	+	+	+
Yalin et al.	-	-	-	+	?	+
Sakanoue et al.	-	-	-	-	?	-
Vignali et al.	-	-	-	+	+	+
Vignali et al.	-	-	-	+	+	+
Schmidt et al.	-	-	-	+	+	-
Ishihara et al.	-	-	-	+	?	+
Lanthaler et al.	-	-	-	+	+	+
Ricciardi et al.	-	-	-	+	+	+
Li et al.	-	-	-	+	+	+
Shamiyeh et al.	-	-	-	+	+	+
Ivanov et al.	+	?	?	+	+	+
Xiao et al.	-	-	-	+	+	+
Lieto et al.	-	-	-	+	+	+
Kamal et al.	-	-	-	+	+	+
Kim et al.	-	-	-	+	+	+

Among the inclusions, only 11 studies (5-15) provided detailed diagnostic criteria for CAL. Five studies (8-10, 16, 17) diagnosed CAL based on clinical manifestations, while eight studies (5, 7, 8, 12-14, 18, 19) provided both clinical and radiological diagnostic criteria of CAL. There were five studies (20-24) that did not provide any references with regard to the diagnosis of CAL.

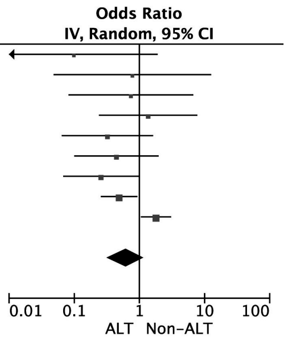
Various methods of ALT tests were used in the included studies. As listed in Table 1, we found that with the exception of one study(24). Despite the fact that all other studies reported their methods of ALT evaluation, the methods themselves varied greatly between studies. Not all studies reported the volume of the inflated gas/dye, while the reported volume varied from 60 ml (6) to 400 ml(22). No study mentioned intraluminal pressure measurements during ALT. When a leak was observed during ALT, i.e. ALT(+), different repair methods were applied varying from reinforcing sutures up to reconstruction of the anastomosis or performing a diverting stoma(17) (Table 1).

As is shown in Figure 2, nine studies reported a comparison of the clinical CAL rate between the patients with ALT and those without ALT. Although a lower CAL rate was found in the patients with ALT, no significant difference was found when compared to the patients without ALT (P = 0.15). The heterogeneity among the studies was significant (P = 0.02, I^2 = 0.55).

Figure 2. Clinical colorectal anastomotic leakage rate in air leak test (ALT) patients vs. non-ALT patients

Study or Subgroup	ALT Events	ALT Total	Non-ALT Events	Non-ALT Total	Weight	Odds Ratio IV, Random, 95% CI
Sakanoue et al. 1993	0	35	4	35	4.1%	0.10 [0.01, 1.90]
Li et al. 2009	1	137	1	107	4.6%	0.78 [0.05, 12.61]
Shamiyeh et al. 2011	1	85	4	253	6.6%	0.74 [0.08, 6.72]
Lanthaler et al. 2008	4	73	2	49	9.2%	1.36 [0.24, 7.74]
Lieto et al. 2011	2	56	7	68	10.1%	0.32 [0.06, 1.62]
Ivanov et al. 2011	3	30	6	30	11.0%	0.44 [0.10, 1.97]
Beard et al. 1990	3	73	10	70	12.4%	0.26 [0.07, 0.98]
Ricciardi et al. 2009	34	825	14	173	20.4%	0.49 [0.26, 0.93]
Schmidt et al. 2003	27	260	32	528	21.7%	1.80 [1.05, 3.07]
Total (95% CI)		**1574**		**1313**	**100.0%**	**0.61 [0.32, 1.18]**
Total events	75		80			

Heterogeneity: $Tau^2 = 0.45$; $Chi^2 = 17.85$, df = 8 (P = 0.02); $I^2 = 55\%$
Test for overall effect: Z = 1.46 (P = 0.15)



Subgroup analysis showed that combining the data of the LOE 1b studies (12, 19) showed a significant difference in the CAL rate between patients with ALT and those without ALT (Figure 3), while such difference was not significant in the LOE 2b studies (Figure 4). The combined CAL rate in the patients with ALT remained stable at 5.8%, 4.7% and 4.9% in the LOE1b, 2b, and 4 respectively. On the contrary, the CAL rate in the patients without ALT was reported as 16% in the LOE 1b studies, which was higher than the rate of 5.3% in the LOE 2b trials.

Figure 3. Clinical colorectal anastomotic leakage rate in air leak test (ALT) patients vs. non-ALT patients: subgroup analysis LOE 1b. LOE = level of evidence

Study or Subgroup	ALT Events	ALT Total	Non-ALT Events	Non-ALT Total	Weight	Odds Ratio IV, Random, 95% CI
Beard et al. 1990	3	30	6	30	44.5%	0.44 [0.10, 1.97]
Ivanov et al. 2011	3	73	10	70	55.5%	0.26 [0.07, 0.98]
Total (95% CI)		**103**		**100**	**100.0%**	**0.33 [0.12, 0.89]**
Total events	6		16			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.29$, df = 1 (P = 0.59); $I^2 = 0\%$
Test for overall effect: Z = 2.20 (P = 0.03)

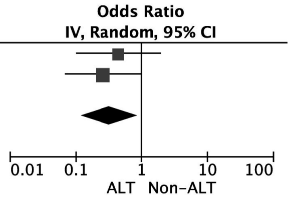
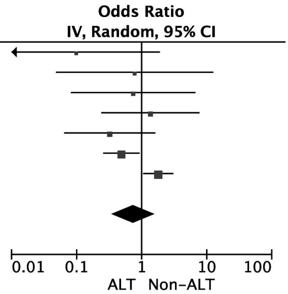


Figure 4. Clinical colorectal anastomotic leakage rate in air leak test (ALT) patients vs. non-ALT patients: subgroup analysis LOE 2b. LOE = level of evidence

Study or Subgroup	ALT Events	ALT Total	Non-ALT Events	Non-ALT Total	Weight	Odds Ratio IV, Random, 95% CI
Sakanoue et al. 1993	0	35	4	35	5.4%	0.10 [0.01, 1.90]
Li et al. 2009	1	137	1	107	6.0%	0.78 [0.05, 12.61]
Shamiyeh et al. 2011	1	85	4	253	8.6%	0.74 [0.08, 6.72]
Lanthaler et al. 2008	4	73	2	49	12.0%	1.36 [0.24, 7.74]
Lieto et al. 2011	2	56	7	68	13.1%	0.32 [0.06, 1.62]
Ricciardi et al. 2009	34	825	14	173	26.5%	0.49 [0.26, 0.93]
Schmidt et al. 2003	27	260	32	528	28.2%	1.80 [1.05, 3.07]
Total (95% CI)		**1471**		**1213**	**100.0%**	**0.74 [0.35, 1.57]**
Total events	69		64			

Heterogeneity: $Tau^2 = 0.45$; $Chi^2 = 13.73$, df = 6 (P = 0.03); $I^2 = 56\%$
Test for overall effect: Z = 0.79 (P = 0.43)



As is shown in Figure 5, the intraoperative positive rate of ALT varies among different studies (1.5% to 24.7%). While the clinical CAL rate in those intraoperative ALT(+) patients was 11.4%, compared to 4.2% in ALT(-) patients. The meta-analysis showed a significant difference (P < 0.001) between these two groups (Figure 6), with no significant heterogeneity between studies (P = 0.84, $I^2 = 0$).

Sensitivity analysis

Except from one study, exclusion of the others had no influence on outcome significance. Exclusion of one heavily weighted article from Schmidt et al. (9) however, resulted in a major change in significance in the clinical CAL rate in ALT patients vs. non-ALT patients evaluation. With this article included, an OR of 0.61 [0.32, 1.19] (P = 0.15) was found. After exclusion, an OR of 0.46 [0.29, 0.74] (P = 0.001) was calculated.

Figure 5. Intraoperative ALT (+) rate, postoperative CAL rate in ALT (+) cases, and overall post-operative CAL rate. Bars in blue indicate the intraoperative positive rate of the air leak test, i.e. ALT(+) rate; bars in red indicate the postoperative CAL rate in the ALT(+) patients; bars in green indicate the overall postoperative CAL rate in all the included patients in each study respectively. CAL = colorectal anastomotic leakage, ALT = air leak test, ALT(+) indicates that leak was observed during the test

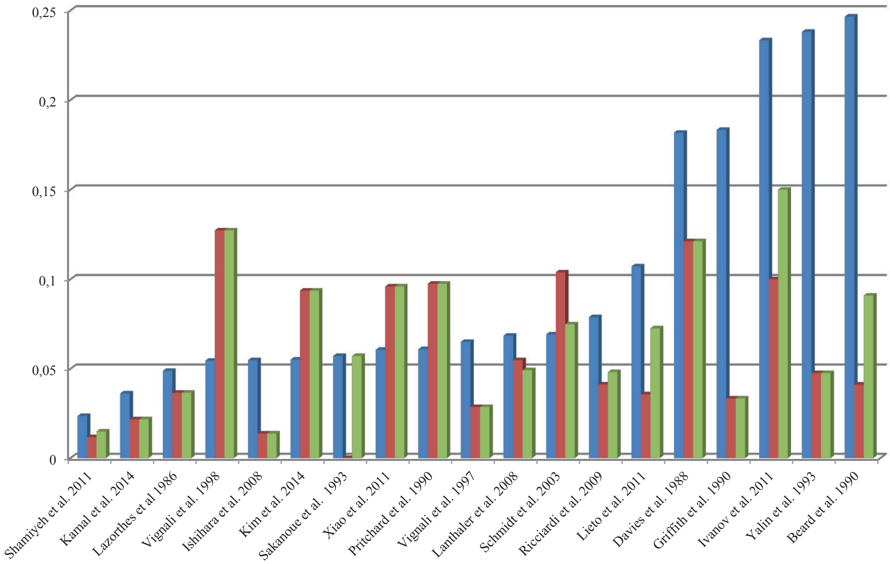
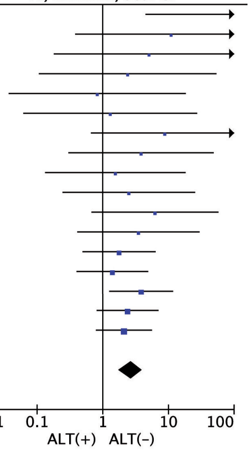


Figure 6. Colorectal anastomotic leakage rate in ALT(+) patients vs. in ALT(-) patients. CAL = colorectal anastomotic leakage, ALT = air leak test. ALT = air leak test, ALT(+) indicates that leak was observed during the test, ALT(-) indicates that no leak was observed during the test

	ALT(+)		ALT(−)			Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI
Li et al. 2009	1	2	1	135	1.6%	134.00 [4.48, 4011.08]
Yalin et al. 1993	1	5	0	16	1.6%	11.00 [0.38, 318.61]
Ishihara et al. 2008	0	4	1	69	1.6%	5.07 [0.18, 143.14]
Lazorthes et al 1986	0	4	3	78	1.9%	2.40 [0.11, 53.85]
Griffith et al. 1990	0	11	2	49	1.9%	0.83 [0.04, 18.41]
Lanthaler et al. 2008	0	5	4	68	1.9%	1.30 [0.06, 27.48]
Ivanov et al. 2011	2	7	1	23	2.7%	8.80 [0.66, 117.23]
Vignali et al. 1998	1	3	6	52	2.8%	3.83 [0.30, 48.93]
Beard et al. 1990	1	18	2	55	3.0%	1.56 [0.13, 18.28]
Pritchard et al. 1990	1	5	7	77	3.3%	2.50 [0.24, 25.57]
Davies et al. 1988	2	6	2	27	3.6%	6.25 [0.67, 57.90]
Kamal et al. 2014	1	15	8	400	3.9%	3.50 [0.41, 29.93]
Kim et al. 2014	3	20	31	343	10.9%	1.78 [0.49, 6.40]
Xiao et al. 2011	3	30	27	368	11.4%	1.40 [0.40, 4.93]
Schmidt et al. 2003	5	18	22	242	14.3%	3.85 [1.25, 11.80]
Vignali et al. 1997	4	66	25	948	15.2%	2.38 [0.80, 7.06]
Ricciardi et al. 2009	5	65	29	760	18.5%	2.10 [0.78, 5.62]
Total (95% CI)		**284**		**3710**	**100.0%**	**2.65 [1.74, 4.05]**
Total events	30		171			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 10.46$, df = 16 (P = 0.84); $I^2 = 0\%$
Test for overall effect: Z = 4.51 (P < 0.00001)



Discussion

ALT is the most frequent performed intraoperative test to detect mechanically insufficient colorectal anastomoses for intraoperative repair. This meta-analysis summarizes the clinical evidence regarding the application of ALT. We found that with current evidence, performing ALT has not significantly reduced the clinical CAL rate after surgery, but it remains necessary due to a significantly higher risk of CAL in patients with a positive leak during the test. The standardization of ALT in future studies is urgently needed to further verify the effectiveness of ALT and its future applications.

As is shown from our data, no significant reduction of CAL rate is seen in the meta-analysis of the CAL rates between patients who underwent ALT and those who did not. Although subgroup analysis showed a significant difference in the RCT (LOE1b) studies, the limited numbers of patients and the extraordinarily high CAL rate in the patients without ALT increases the concern with regards to the reliability of the difference. Particularly since neither of the two LOE1b studies blinded the surgeons during postoperative investigation, the observer bias may influence the diagnosis of CAL after surgery. For future studies, it is important to ensure double blinding when performing a RCT on such topic.

In the sensitivity analysis, the primary comparison in this meta-analysis was heavily influenced by one study with a large number of patients(9). Exclusion of that study resulted in a significant outcome in favor of ALT application. This substantially influenced the statistical analysis and the corresponding p value. Moreover, it increased the uncertainty of the actual ALT effectiveness. However, we chose to include this study in the final analysis because the reporting bias was considered to be limited in the LOE 2b studies since during operation surgeons were not aware of the comparison between patients underwent ALT vs. those who did not. Of course, one possible bias in LOE 2b studies is the selection bias: surgeons may only subject anastomoses that are likely to leak to ALT but not the firm ones, which seems also explain the similar CAL rate between patients with and without ALT. This bias does exist in many of our LOE 2b inclusions, but not in the studies from Shamiyeh et al. (22) and Schmidt et al. (9), which compared historical data (without routine ALT) to recent data (with routine ALT). Our further analysis found similar results when we ruled out the selected ALT cases (data not shown).

According to the current data, whether performing ALT significantly reduces the CAL rate after surgery is, at best, inconclusive. The abovementioned limitations, together with other factors including the heterogeneity in ALT methodology and outcome measurements might all contribute to the inconclusive results. However, such results undoubtedly sound the call for a worldwide standardization of the air leak test.

A direct explanation of our data might be that ALT is not useful in the prevention of CAL and may thus be abandoned. We, probably together with all surgeons, certainly oppose such explanation because any colorectal surgeon would have seen a mechanically failed anastomosis (e.g. anastomotic dehiscence) detected by ALT, in which the avoidance of a ALT would certainly cause catastrophic CAL. Rather than the superficial interpretation, our results have shown one clear cause of the inconclusive effect of ALT: the significantly higher CAL rate in ALT(+) patients demonstrates that ALT(+) patients are still under higher risk of developing CAL even though a repair procedure was performed in most cases. We recognize that it is certainly reasonable to assume that ALT(+) may have an even higher CAL rate without the repairing procedures. However, since ALT simply detects the mechanical insufficiency, our data at least demonstrates that the current repairing strategies in the ALT(+) cases, varying from additional sutures to performing a diverting stoma, have not effectively eliminated the mechanical risks of CAL in those positive cases. The high CAL rate in ALT(+) patients may extensively attenuate the preventive effect of ALT, resulting in the similar CAL rate between patients with and without ALT.

Though having been performed for decades, no standardized methodology or consensus has been reached, which is confirmed by our results. The fact that one inflated 60 mL of air during the test while another injected 400 mL of saline is disturbing and raises the question whether we are performing the same ALT. Unfortunately, the results from our study are not encouraging in this regard. Despite the lack of detailed methods, intraoperative ALT resulted in a positive rate varying from 1.5% to 24.7% among different studies(11, 19). Considering that intraoperative repair was applied in most ALT(+) patients, we should be aware that such a diverse range of positive rate strongly implies the possibility of overtreatment in many patients, particularly in centers with a high rate of ALT(+) cases. We intended to further explore whether there is any difference among the intraoperative repairing methods in reducing postoperative CAL rate, while unfortunately such analysis was not possible with the current data since it requires much detailed information that are not reported in most inclusions.

From a biomechanical point of view, a standardized volume of the injected air or water is difficult to establish because of the variation in patients' anatomy. Thereby, pressure should be considered as a means for standardization. It is important to note that an anastomosis (either handsewn or stapled) may not sustain intraluminal pressure as high as one may imagine. Although systematic evaluation of the burst pressure is not yet available, studies report that a newly constructed colorectal anastomosis bursts at the pressure around 70 to 184 mmHg(25). Compared to this pressure, injecting 400 mL of saline seems dangerous if not properly controlled. Therefore, a pressure indicator might be suggested during ALT. Actually measuring the intra-luminal pressure has been included as a very standard method in measuring the early-stage anastomotic strength in animal studies (26, 27). Although such technique is not presently available for human patients, we believe it is urgently needed. A barometer can be combined then with endoscopy or certain inflating devices to ensure a safety and ease of application.

Conclusion

In conclusion, currently available evidence regarding the value of ALT in prevention of CAL contains substantial risks of bias. Based on the evidence, performing ALT with the reported methodology has not effectively reduced the clinical CAL rate after surgery. This is partly because a positive result in ALT still predicts a higher risk of postoperative CAL, and additional repairs with current methods do not decrease this risk. However, the evidence also suggests that performing ALT is necessary to identify patients with a higher risk of CAL. Being the quality control step of colorectal anastomosis, the air leak test is in dire need for worldwide standardization. Future studies with a higher level of evidence (e.g. double-blind RCT) should be initiated to verify the effectiveness of ALT.

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PART IV

EARLY DETECTION OF COLORECTAL ANASTOMOTIC LEAKAGE

Chapter 9

Cytokines as early markers of colorectal anastomotic leakage: a systematic review and meta-analysis*

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Abstract

Purpose

Colorectal anastomotic leakage (CAL) is one of the most severe complications after colorectal surgery. This meta-analysis evaluates whether systemic or peritoneal inflammatory cytokines may contribute to early detection of CAL.

Methods

Systematic literature search was performed in the acknowledged medical databases according to the PRISMA guidelines to identify studies evaluating systemic and peritoneal levels of TNFα, IL1β, IL6 and IL10 for early detection of CAL. Means and standard deviations of systemic and peritoneal cytokine levels were extracted, respectively, for patients with and without CAL. The meta-analysis of the mean differences was carried out for each postoperative day using Review Manager.

Results

Seven articles were included. The meta-analysis was performed with 5 articles evaluating peritoneal cytokine levels. Peritoneal levels of IL6 were significantly higher in patients with CAL compared to patients without CAL on postoperative day 1, 2 and 3 ($P < 0.05$). Similar results were found for peritoneal levels of TNFα but on postoperative day 3, 4 and 5 ($P < 0.05$). The articles regarding systemic cytokine levels did not report any significant difference accordingly.

Conclusion

Increased postoperative levels of peritoneal IL6 and TNFα are significantly associated with CAL and may contribute to its early detection.

Introduction

Despite the progress made in surgical techniques and perioperative management, morbidity and mortality after colorectal surgery remain problematic. One of the major causes is colorectal anastomotic leakage (CAL), which contributes to one-third of all postoperative deaths after colorectal surgery(1). CAL occurs in 3% to 20% of patients after colorectal surgery(2-4). It is a defect of the colorectal wall at the anastomotic site leading to communication between the intra- and extra luminal compartments(5). Localized signs such as abdominal pain and postoperative ileus, though being considered as abdominal manifestations of CAL, are very common after colorectal surgery and therefore provide limited diagnostic value(6). Moreover, systemic manifestations or parameters such as fever, increase leukocyte count, or increased C-reactive Protein (CRP) levels are actually also frequently observed and therefore not sensitive in diagnosing CAL(7).

With the current postoperative regimes, CAL is usually confirmed by imaging studies such as endoscopy or CT-scan. The median day of diagnosis varies between postoperative day 8 and 13(8-10). A recent review shows that more than 50% of CAL was at the highest severity when diagnosed, which requires re-laparotomy(11). This indicates that many early stages of CAL are not diagnosed until progressed to a severe state. So, the current regimes seem to be ineffective and insufficient in many cases based on the high rates of invasive re-intervention(8, 9). To this end, methods for early detection of CAL require extensive further exploration.

Occurrence of CAL is a dynamic and progressive process. Before systemic symptoms including fever, leukocytosis, and other septic symptoms become manifest, localized infection at the site of the anastomosis first takes place(12), which involves varying immune cells and cytokines(13). Some cytokines such as TNFα, IL1β and IL6 are pro-inflammatory cytokines that mediate inflammatory response, whereas IL10 is considered as an anti-inflammatory cytokine modulating the inflammation(14, 15). Although the surgical trauma also influences levels of these cytokines, abnormal changes of the cytokines still indicate occurrence of the infectious complications including anastomotic leakage. Previous studies have suggested that monitoring cytokine levels in drain fluid or in blood samples may contribute to early detection of CAL, while firm evidence is not available yet. Therefore, this meta-analysis aims to evaluate the value of peritoneal and systemic cytokine levels for early detection of CAL.

Methods

The methods of this meta-analysis followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) statement(16).

Literature search

The literature search was performed in Medline, Embase, Cochrane, Web-of-science, and Google scholar libraries in August 2014 and updated in July 2015 by two authors. No restrictions regarding publication date or language were applied during the search strategy. The search was restricted to human studies.

Study selection

Titles and abstracts were screened for relevance by two authors (Z.W. and A.D.) independently. All full text articles evaluating the predictive value of TNFA, IL1β, IL6 and IL10 in early detection of CAL after colorectal surgery were selected. Articles without a comparison between patients with and without CAL were excluded; reviews, letters to editor, and congress abstracts were excluded as well.

Quality assessment

Two authors independently judged the quality of included articles using the QUADAS-2 (Quality-Assessment in Diagnostic Accuracy Studies) method, which evaluates the risk of bias and the applicability according to four key domains including patient selection, index test, reference standard, and flow and timing(17). Level of evidence was estimated according to Levels of Evidence 2011 from the Centre for Evidence Based Medicine(18).

Data extraction

Two authors independently extracted means and standard deviations (SD) of cytokine levels of each postoperative day for patients with and without CAL respectively. Any discrepancies were resolved by re-examination of data until consensus was reached. The mean and SD of cytokine levels per postoperative day were not provided in the articles of Matthiessen et al. (19) and Yamamoto et al. (20). Primary data of these articles were obtained from the authors themselves. The unit of levels of cytokines was not reported by Fouda et al. in their results(21), but was confirmed according to the methods and the instruction of their ELISA kit(22). All cytokine data were converted into the same unit ng/mL in the meta-analysis.

Statistical analysis

Quantitative statistical analysis for binary outcomes was carried out using mean differences with 95% confidence interval. The random-effects model was applied to obtain the 95%

confidence interval. Statistical heterogeneity was calculated with the I^2 statistic, which represents the percentage of variation in study estimates due to heterogeneity and tested by the Cochran Q test (modified χ^2 test). All statistical analyses were performed using Review Manager version 5.3, the Nordic Cochrane Centre, Copenhagen, Denmark.

Results

Results of study selection and evaluation

Seven articles met final inclusion criteria (Figure 1). All included studies evaluated peritoneal or systemic cytokine levels after colorectal surgery for the diagnosis of CAL (Table 1). All included studies were found to be at high risk of bias while the applicability was considered to be positive (Table 2). The high risk of bias was related to poor patient selection. Furthermore, study designs of included studies led to a low level of evidence.

Figure 1. PRISMA flow chart representing selection of articles for review

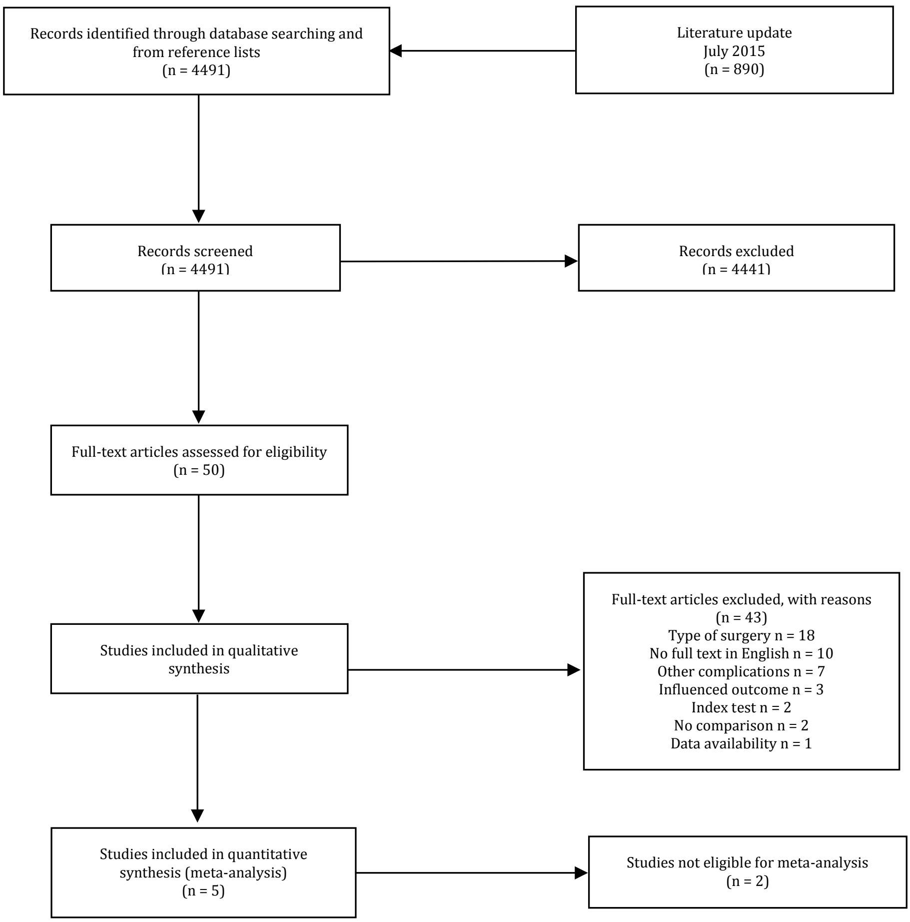


Table 1. Study characteristics of included studies, including Levels of Evidence 2011 according to the Centre for Evidence Based Medicine

Author	Year	Patients	Study design	Location	Surgery type	Follow-up	Index test	Complication	Level of evidence
Bertram	2003	25	Case-Control	Peritoneal	Colorectal surgery	7 days	TNF, IL6	CAL (n=3)	4
Fouda	2010	56	Case-Control	Peritoneal	Elective low anterior resection for rectal cancer	5 days	TNF, Il-6, IL-10	CAL (n=8)	4
Herwig	2002	24	Case-Control	Peritoneal	Colorectal surgery	4 days	TNF, IL-1B, IL6	CAL (n=12)	4
Matthiessen	2007	23	Case-Control	Peritoneal	Anterior resection of the rectum for cancer	2 days	TNF, Il-6, IL-10	CAL (n=7)	4
Yamamoto	2010	100	Case-Control	Peritoneal	Elective resection for carcinoma of the sigmoid/rectum	3 days	TNF, IL-1B, IL6	Peritonitis (n=8)	4
Ellebaek	2014	50	Case-Control	Systemic	Low anterior resection for rectosigmoid cancer	5 days	TNF, IL-1B, IL6, IL10	CAL (n=4)	4
Reisinger	2014	84	Case-Control	Systemic	Colorectal surgery	7 days	IL6	CAL (n=8)	4

Table 2. Quality assessment of the included studies by judging risk of bias and applicability using Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) + = low risk of bias; - = high risk of bias; ? = not specified

		Risk of Bias			
Author	**Year**	**Patient Selection**	**Index Test**	**Reference Standard**	**Flow and timing**
Bertram	2003	-	+	-	-
Fouda	2010	-	+	+	-
Herwig	2002	-	+	+	-
Matthiessen	2007	-	+	+	-
Yamamoto	2010	-	+	+	-
Ellebaek	2014	-	+	?	-
Reisinger	2014	-	+	+	-
		Applicability			
Author	**Year**	**Patient Selection**	**Index Test**	**Reference Standard**	**Flow and timing**
Bertram	2003	+	+	-	-
Fouda	2010	+	+	+	-
Herwig	2002	+	+	+	-
Matthiessen	2007	+	+	+	-
Yamamoto	2010	+	+	+	-
Ellebaek	2014	+	+	?	-
Reisinger	2014	+	+	+	-

Meta-analysis is a statistical method for pooling the results of several studies reporting similar outcomes in order to gain a better estimate of the effect size of an intervention. It is appropriate to perform a meta-analysis when outcomes are comparable and can be pooled meaningfully. Comparators should be at least similar enough to be combined. All the included studies reported cytokine levels on a similar scale except for the studies of Ugras et al. (23) and Alonso et al. (24). The peritoneal cytokine level reported by Ugras et al. (23) are approximately 10 to 1000 times higher than the data from the other studies, while the data from Alonso et al. (24) are approximately 50 to 100 times lower than the other inclusions'. Despite both studies met final inclusion criteria, they were not included in the meta-analysis for peritoneal cytokines.

Definitions of CAL

The definitions of CAL were inconsistent between included studies (Table 3). The studies from Fouda et al. (21) and Bertram et al. (25) based the definition of CAL on clinical signs, mostly focusing on the aspect of drain fluid; the study from Yamamoto et al. (20) included additional imaging studies; the studies from Herwig et al. (26) and Reisinger et al. (27) defined CAL by the necessity of re-intervention. The definitions of CAL in the studies from Matthiessen et al. (19) and Ellebaek et al. (28) mainly focused on a demonstrated defect of the intestinal wall.

Table 3. Definition of anastomotic leakage of included studies, CAL = colorectal anastomotic leakage

Author	Year	Complication	Definition
Bertram	2003	CAL	Patients were considered uneventful if recovery occurred without signs of anastomotic leakage within 14 days after operation
Fouda	2010	CAL	AL was defined clinically as gas, pus, or fecal discharge from the drain, fecal discharge from the operative wound, pelvic abscess, peritonitis, and rectovaginal fistula
Herwig	2002	CAL	Diagnosis of AL was confirmed by endoscopy, contrast enema, abdominal CT scan, microbiologic examination and finally by intraoperative findings during relaparotomy
Matthiessen	2007	CAL	Peritonitis caused by leakage, pelvic abscess, discharge of feces from the abdominal drain, or rectovaginal fistula, and leakage from all staple lines
Yamamoto	2010	Peritonitis	The diagnosis of postoperative peritonitis was based on clinical findings along with imaginary data and the colour of abdominal exudates
Ellebaek	2014	CAL	Anastomotic leakage was defined as a demonstrated defect of the intestinal wall at the anastomotic site leading to a communication between the intra- and extra luminal compartment's
Reisinger	2014	CAL	Clinically relevant AL was defined as extra luminal presence of contrast fluid on contrast CT scans and/or leakage when relaparotomy was performed, requiring re-intervention

Enzyme-linked immunosorbent assay (ELISA)

Although most studies used ELISA to determine the cytokine levels, different methods of measuring, handling and storing the samples were used in the included studies (Table 4).

Table 4. Specifying the methodology of cytokine level measurement of included studies NS = not specified ELISA = enzyme-linked immunosorbent assay

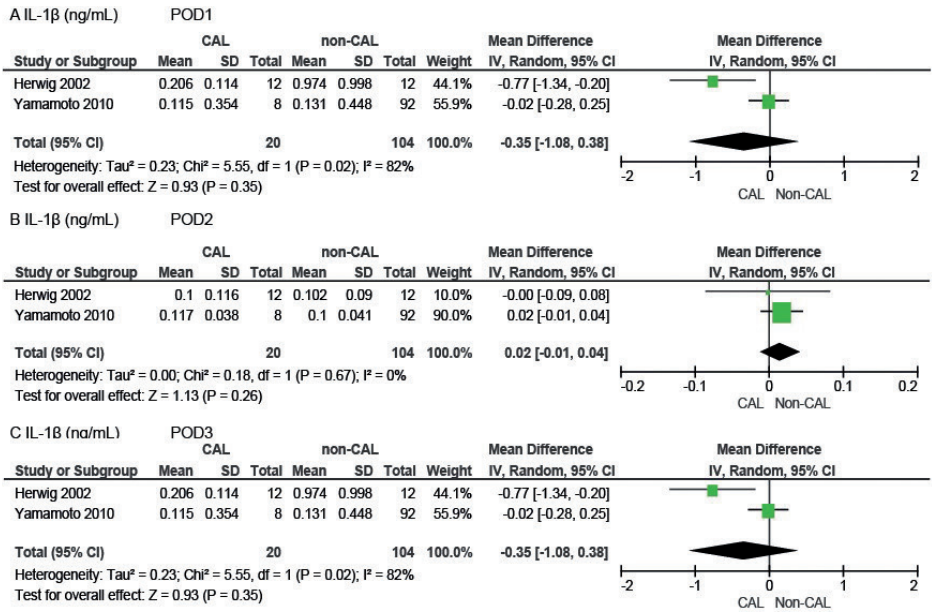
Author	Year	Cytokines	Location	Centrifugation	Storage	Cytokine measuring	Producer
Bertram	2003	TNF, IL-6	Peritoneal	3000 rpm for 10 min at 4 °C	- 80 °C	ELISA	Immulite, DPC Biermann GmbH, Bad Nauheim, Germany
Fouda	2010	TNF, IL-6, IL-10	Peritoneal	3000 rpm for 10 min at 4 °C	20 °C	ELISA	NS
Herwig	2002	TNF, IL-1β, IL-6	Peritoneal	2000 rpm for 10 min	-70 °C	ELISA	Coulter-Immunotech Diagnostics, Hamburg, Germany
Matthiessen	2007	TNF, IL-6, IL-10	Peritoneal	NS	NS	ELISA	DPC, Los Angeles, CA, USA
Yamamoto	2010	TNF, IL-1β, IL-6	Peritoneal	3000 rpm for 10 min	- 80 °C	ELISA	R&D system, Minneapolis, MN, USA
Ellebaek	2014	TNF, IL-1β, IL-6, IL-10	Systemic	3600 rpm for 10 min at 4 °C	- 80 °C	ELISA	Bio-Rad Laboratories, Hercules, CA, USA
Reisinger	2014	IL-6	Systemic	3500 rpm for 15 min	- 80 °C	ELISA	NS

Peritoneal cytokines

In total we included 5 studies in the meta-analysis for peritoneal levels of TNFA, IL6 and IL1β. The meta-analysis regarding peritoneal levels of cytokines included 228 patients who underwent colorectal surgery between 1996 and 2010. The mean level of cytokines on each postoperative day is reported in Figure 2 by calculating the weighted mean of each included study. As is shown in Figure 2 the peritoneal level of the cytokines varied after surgery. TNFA and IL6 levels substantially increased in patients with CAL while there was no or mild increase in patients without CAL.

Peritoneal levels of TNFA showed significant differences between patients with and without CAL at POD3 ($P = 0.04$), POD4 ($P = 0.0002$), and POD5 ($P < 0.00001$) (Figure 3). The meta-analysis of POD3 included 4 studies while the meta-analyses of POD4 and POD5 only included 2 studies. Peritoneal levels of IL6 were different between patients with and without the CAL on POD1 ($P = 0.05$), POD2 ($P = 0.03$), and POD3 ($P = 0.002$) (Figure 4). All analyses for IL6 were based on 4 or 5 independent studies on the first three days. Nevertheless, peritoneal levels of IL1β and IL10 were only reported in one or two studies. Although we still the meta-analysis when possible, the results did not show significant differences between patients with and without CAL on each respective day (Figure S1).

Figure S1. Forest plot with 95% confidence interval (CI) of the mean difference of peritoneal levels of IL-1β (ng/mL) between colorectal anastomotic leakage (CAL) patients and non-CAL patients per postoperative day (POD) 1 (=A), 2 (=B) and 3 (=C).



Systemic cytokines

Two studies were included for evaluation of systemic cytokine levels after colorectal surgery (27, 28). Moreover, the primary data was not available in the articles. Therefore, we did not perform a meta-analysis for the systemic levels of cytokines. However, neither of the studies showed any significant difference in the systemic cytokine levels (TNFA, IL1β, IL6 and IL10) between patients with and without CAL.

Figure 2. Weighted means of peritoneal levels of TNF (2.A, ng/mL), IL-6 (2.B, ng/mL) and IL-1β (2.C, ng/mL) on each postoperative day (POD) comparing colorectal anastomotic leakage (CAL) patients with non-CAL patients; TNF (=A), IL-6 (=B), IL-1β (=C). The p values of differences are illustrated when relevant.

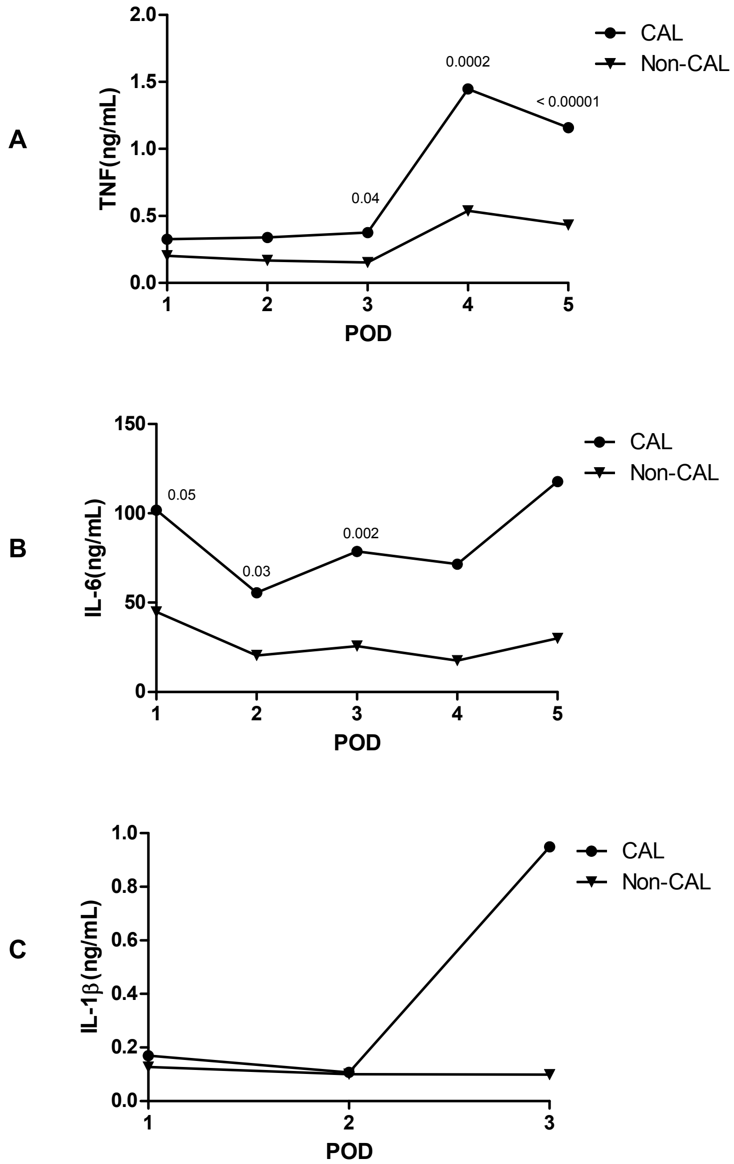
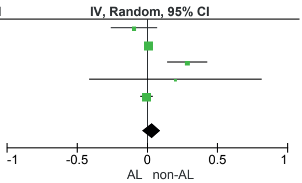


Figure 3. Forest plot with 95% confidence interval (CI) of the mean difference of peritoneal levels of TNF (ng/mL) between colorectal anastomotic leakage (AL) patients and non-CAL patients per postoperative day (POD) 1 (=A), 2 (=B), 3 (=C), 4 (=D) and 5 (=E).

A TNF POD1

Study or Subgroup	AL Mean	AL SD	AL Total	non-AL Mean	non-AL SD	non-AL Total	Weight	Mean Difference IV, Random, 95% CI
Bertram 2003	0.101	0.077	3	0.196	0.328	22	10.9%	-0.10 [-0.26, 0.07]
Fouda 2010	0.17	0.009	8	0.162	0.016	48	39.9%	0.01 [0.00, 0.02]
Herwig 2002	0.461	0.168	12	0.176	0.179	12	13.6%	0.29 [0.15, 0.42]
Matthiessen 2007	0.504	0.706	7	0.304	0.646	16	1.0%	0.20 [-0.41, 0.81]
Yamamoto 2010	0.206	0.052	8	0.212	0.085	92	34.5%	-0.01 [-0.05, 0.03]
Total (95% CI)			**38**			**190**	**100.0%**	**0.03 [-0.03, 0.09]**

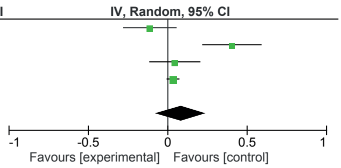
Heterogeneity: Tau² = 0.00; Chi² = 17.67, df = 4 (P = 0.001); I² = 77%
Test for overall effect: Z = 0.98 (P = 0.33)



B TNF POD2

Study or Subgroup	AL Mean	AL SD	AL Total	Non-AL Mean	Non-AL SD	Non-AL Total	Weight	Mean Difference IV, Random, 95% CI
Bertram 2003	0.054	0.014	3	0.167	0.394	22	23.3%	-0.11 [-0.28, 0.05]
Herwig 2002	0.555	0.319	12	0.151	0.063	12	22.0%	0.40 [0.22, 0.59]
Matthiessen 2007	0.158	0.146	4	0.114	0.148	19	23.9%	0.04 [-0.11, 0.20]
Yamamoto 2010	0.214	0.049	8	0.181	0.073	92	30.8%	0.03 [-0.00, 0.07]
Total (95% CI)			**27**			**145**	**100.0%**	**0.08 [-0.07, 0.24]**

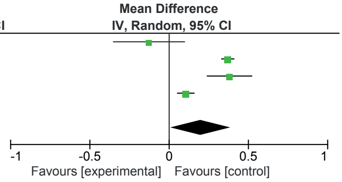
Heterogeneity: Tau² = 0.02; Chi² = 18.46, df = 3 (P = 0.0004); I² = 84%
Test for overall effect: Z = 1.03 (P = 0.30)



C TNF POD3

Study or Subgroup	AL Mean	AL SD	AL Total	Non-AL Mean	Non-AL SD	Non-AL Total	Weight	Mean Difference IV, Random, 95% CI
Bertram 2003	0.121	0.01	3	0.248	0.535	22	20.3%	-0.13 [-0.35, 0.10]
Fouda 2010	0.511	0.055	8	0.141	0.007	48	27.8%	0.37 [0.33, 0.41]
Herwig 2002	0.428	0.233	12	0.047	0.084	12	24.4%	0.38 [0.24, 0.52]
Yamamoto 2010	0.255	0.072	8	0.15	0.071	92	27.5%	0.11 [0.05, 0.16]
Total (95% CI)			**31**			**174**	**100.0%**	**0.20 [0.01, 0.39]**

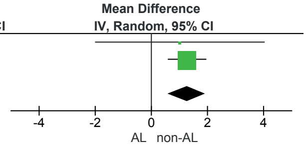
Heterogeneity: Tau² = 0.03; Chi² = 79.51, df = 3 (P < 0.00001); I² = 96%
Test for overall effect: Z = 2.04 (P = 0.04)



D TNF POD4

Study or Subgroup	AL Mean	AL SD	AL Total	Non-AL Mean	Non-AL SD	Non-AL Total	Weight	Mean Difference IV, Random, 95% CI
Bertram 2003	1.602	2.64	3	0.585	0.788	22	4.7%	1.02 [-1.99, 4.02]
Herwig 2002	1.408	1.178	12	0.135	0.077	12	95.3%	1.27 [0.61, 1.94]
Total (95% CI)			**15**			**34**	**100.0%**	**1.26 [0.61, 1.91]**

Heterogeneity: Tau² = 0.00; Chi² = 0.03, df = 1 (P = 0.87); I² = 0%
Test for overall effect: Z = 3.79 (P = 0.0002)



E TNF POD5

Study or Subgroup	AL Mean	AL SD	AL Total	Non-AL Mean	Non-AL SD	Non-AL Total	Weight	Mean Difference IV, Random, 95% CI
Bertram 2003	2.58	3.727	3	1.204	1.445	22	0.0%	1.38 [-2.88, 5.64]
Fouda 2010	0.825	0.114	8	0.078	0.02	48	100.0%	0.75 [0.67, 0.83]
Total (95% CI)			**11**			**70**	**100.0%**	**0.75 [0.67, 0.83]**

Heterogeneity: Tau² = 0.00; Chi² = 0.08, df = 1 (P = 0.77); I² = 0%
Test for overall effect: Z = 18.49 (P < 0.00001)

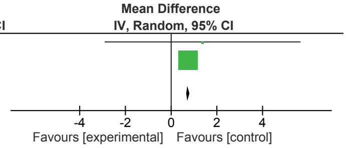


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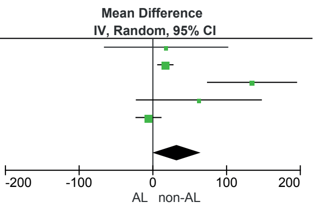
Figure 4. Forest plot with 95% confidence interval (CI) of the mean difference of peritoneal levels of IL-6 (ng/mL) between colorectal anastomotic leakage (CAL) patients and non-CAL patients per postoperative day (POD) 1 (=A), 2 (=B), 3 (=C), 4 (=D) and 5 (=E).

A IL-6 POD1

Study or Subgroup	AL Mean	AL SD	AL Total	non-AL Mean	non-AL SD	non-AL Total	Weight	Mean Difference IV, Random, 95% CI
Bertram 2003	64.9	68.2	3	46.9	76.8	22	10.4%	18.00 [-65.58, 101.58]
Fouda 2010	52.5	14.4	8	35.5	9.5	48	32.9%	17.00 [6.67, 27.33]
Herwig 2002	162.5	105.8	12	27.9	13.9	12	15.5%	134.60 [74.22, 194.98]
Matthiessen 2007	160.2	81.3	4	97.8	64.4	19	10.2%	62.40 [-22.37, 147.17]
Yamamoto 2010	34.5	23.6	8	40.4	21.2	92	31.1%	-5.90 [-22.82, 11.02]
Total (95% CI)			**35**			**193**	**100.0%**	**32.84 [0.59, 65.10]**

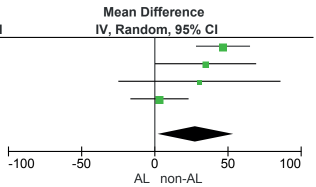
Heterogeneity: Tau² = 796.19; Chi² = 22.23, df = 4 (P = 0.0002); I² = 82%
Test for overall effect: Z = 2.00 (P = 0.05)



B IL-6 POD2

Study or Subgroup	AL Mean	AL SD	AL Total	non-AL Mean	non-AL SD	non-AL Total	Weight	Mean Difference IV, Random, 95% CI
Bertram 2003	72.7	14.4	3	26.1	18.8	22	32.2%	46.60 [28.51, 64.69]
Herwig 2002	60.2	58.8	12	25.5	14.1	12	22.7%	34.70 [0.49, 68.91]
Matthiessen 2007	62.6	54.8	4	32.1	26.8	19	13.8%	30.50 [-24.54, 85.54]
Yamamoto 2010	38.9	27.5	8	35.7	20.3	92	31.3%	3.20 [-16.30, 22.70]
Total (95% CI)			**27**			**145**	**100.0%**	**28.07 [2.57, 53.58]**

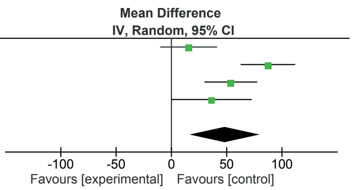
Heterogeneity: Tau² = 441.20; Chi² = 10.43, df = 3 (P = 0.02); I² = 71%
Test for overall effect: Z = 2.16 (P = 0.03)



C IL-6 POD3

Study or Subgroup	AL Mean	AL SD	AL Total	non-AL Mean	non-AL SD	non-AL Total	Weight	Mean Difference IV, Random, 95% CI
Bertram 2003	33.7	20.9	3	18.1	20.9	22	25.7%	15.60 [-9.61, 40.81]
Fouda 2010	115.5	34.9	8	28.2	4.8	48	26.0%	87.30 [63.08, 111.52]
Herwig 2002	75.8	39.9	12	22	11	12	26.3%	53.80 [30.38, 77.22]
Yamamoto 2010	63	51.5	8	26.8	18.4	92	22.0%	36.20 [0.32, 72.08]
Total (95% CI)			**31**			**174**	**100.0%**	**48.83 [17.28, 80.39]**

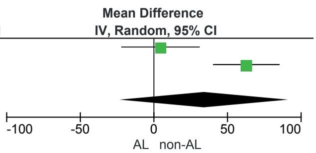
Heterogeneity: Tau² = 843.22; Chi² = 16.91, df = 3 (P = 0.0007); I² = 82%
Test for overall effect: Z = 3.03 (P = 0.002)



D IL-6 POD4

Study or Subgroup	AL Mean	AL SD	AL Total	non-AL Mean	non-AL SD	non-AL Total	Weight	Mean Difference IV, Random, 95% CI
Bertram 2003	19.9	22.3	3	15.4	17.7	22	49.2%	4.50 [-21.80, 30.80]
Herwig 2002	84.5	37.2	12	21.7	12.8	12	50.8%	62.80 [40.54, 85.06]
Total (95% CI)			**15**			**34**	**100.0%**	**34.09 [-23.04, 91.21]**

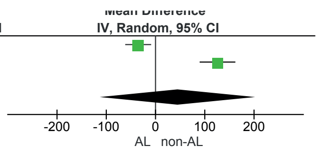
Heterogeneity: Tau² = 1544.96; Chi² = 11.00, df = 1 (P = 0.0009); I² = 91%
Test for overall effect: Z = 1.17 (P = 0.24)



E IL-6 POD5

Study or Subgroup	AL Mean	AL SD	AL Total	non-AL Mean	non-AL SD	non-AL Total	Weight	Mean Difference IV, Random, 95% CI
Bertram 2003	12	8.9	3	47.2	55.3	22	50.3%	-35.20 [-60.41, -9.99]
Fouda 2010	148.1	50.8	8	22.2	1.8	48	49.7%	125.90 [90.69, 161.11]
Total (95% CI)			**11**			**70**	**100.0%**	**44.86 [-113.01, 202.73]**

Heterogeneity: Tau² = 12732.58; Chi² = 53.18, df = 1 (P < 0.00001); I² = 98%
Test for overall effect: Z = 0.56 (P = 0.58)



Discussion

CAL remains a dangerous complication after colorectal surgery. This meta-analysis summarizes previous literature of early detection for CAL by measuring peritoneal and systemic cytokine levels. Our data show that peritoneal levels of pro-inflammatory cytokines (i.e. IL6 and TNFA) were higher in patients with CAL during early postoperative days, suggesting the diagnostic value of measuring the peritoneal cytokine level after surgery.

Among the candidate cytokines, TNFA and IL6 showed a statistically significant increase in CAL patients. These inflammatory cytokines are mainly secreted by macrophages and neutrophils, which infiltrate to the anastomotic area at the first days after construction of anastomosis. Our previous animal studies have demonstrated that a significantly larger amount of iNOS+ (Inducible Nitric Oxide Synthase) producing cells (mainly macrophages subtype 1) infiltrate into the anastomotic area in the CAL cases than in those without CAL within the first postoperative days(29). In accordance with previous evidence, current data confirm the localized mechanism during the early stage of CAL, suggesting the importance of these two cytokines, especially IL6, in the early detection of CAL.

Nowadays the diagnosis of CAL still relies on clinical presentation and imaging studies. Early clinical presentation is often heterogeneous and nonspecific, resulting in delay of CAL diagnosis(9). In many cases, CAL does not turn clinically apparent until approximately the eighth postoperative day(30); in some cases, CAL may even become manifest until a median of the twelfth postoperative day when many patients have already been discharged(8). As shown in our results, increased peritoneal levels of pro-inflammatory cytokines were observed on postoperative day 1-5, which is much earlier than the current median day of CAL diagnosis(8). Especially IL6 was higher in CAL patients since the first postoperative day, indicating the possibility of early detection of CAL by monitoring of intra-peritoneal cytokines. Such possibility has been reported by the previous literature. The studies from Salgado et al. (31, 32) reported that the increase of peritoneal cytokine levels is prior to the clinical manifestations of anastomotic leakage or increase of leukocytes in bariatric surgery. Similar investigations in the field of colorectal surgery are also warranted.

We also attempted to explore whether the systemic cytokine level could contribute to the early detection of CAL, since postoperative drainage is not often applied in colonic surgeries nowadays(33-35). Measurement of systemic cytokines might be of great assistance to early detection of CAL in patients without drainage if their early changes can be determined as well. Unfortunately, our data show that higher levels of cytokines were only observed in the peritoneal drainage but not in the blood sample. Despite the lack of high level-of-evidence studies, our findings are in line with the previous study from Wiik et al. who reported a more extensive release of pro- and anti-inflammatory cytokines into the peritoneal cavity after abdominal surgery compared to the systemic response(12). This could be due to the fact that lymphocytes and monocytes at the site of CAL secrete these cytokines(36). In addition, other studies have demonstrated a poor diagnostic value of serum CRP or white blood cell count in the early detection of CAL(37). Accumulated evidence verified that the systematic changes of CAL are rather latent during the first postoperative days. Changes in systemic levels of cytokines seem to only occur when a critical condition emerges such as sepsis(38).

For the purpose of determining a reference level in colorectal surgery, we used exact values rather than the comparative risk ratios in statistical analysis, which was previously reported by Cini et al. (39). According to our data, it seems that although many included studies reported a significant risk of CAL with high cytokine levels, the repeatability of the cytokine levels among different studies still seems unsatisfactory. The variations in cytokine levels may be caused by several reasons. As mentioned above, the definition of CAL varies substantially among the included studies (Table 3). The included articles used different definitions of CAL, which corresponds to different grades of CAL according to the International Study Group on Rectal Cancer, varying between subclinical CAL to the ones requiring surgical intervention. This induced a mix of outcomes in this meta-analysis.

Due to the relatively low rate of infectious complications after colorectal surgery, studies with high level-of-evidence and a large number of patients on such topic are difficult to implement. It is understandable that in this early stage, most included studies yield very low level-of-evidence and high risks of bias. (Nested) case control studies are highly sensitive to bias, especially to the selection bias, which may influence reliability of the study results. Moreover, the included studies have to deal with a limited sample size, which also decreases the reliability. On the basis of these limitations the studies are sensitive to the type II error (i.e. false negative). However, this type II error has limited influence on the positive results of our analysis (for TNFA and IL6), supporting higher peritoneal cytokine levels in CAL patients compared to uncomplicated cases. Unfortunately, previous studies do not provide further data regarding the sensitivity and specificity of the peritoneal cytokine evaluation. Studies with high level-of-evidence and large amount of inclusions to determine the role of peritoneal cytokines in the early diagnosis of CAL are in the need, which is also one main focus of our on-going study.

Conclusions

In this meta-analysis, we investigated both peritoneal and systemic cytokine levels after colorectal surgery. Our data demonstrate levels of the peritoneal pro-inflammatory cytokines (i.e. TNFA and IL6) substantially increase in CAL patients during the first postoperative days, suggesting their potential diagnostic value, while the systemic cytokines have limited additional value in this regard. High level-of-evidence studies are warranted to determine the accuracy of peritoneal cytokines in the early diagnosis of CAL.

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Chapter 10

A multicenter cohort study of serum and peritoneal biomarkers to predict anastomotic leak after rectal cancer resection*

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Abstract

Aim

Anastomotic leakage (AL) is one of the most feared complications after rectal resection. This study aimed to assess a combination of biomarkers for early detection of AL after rectal cancer resection.

Method

This study was an international multicenter prospective cohort study. All patients received a pelvic drain after rectal cancer resection. On the first 3 postoperative days, drain fluid was collected daily and CRP was measured. MMP2, MMP9, glucose, lactate, IL1β, IL6, IL10, TNFα, Escherichia coli, Enterococcus faecalis, LBP and amylase were measured in drain fluid. Prediction models for AL were built for each postoperative day using multivariate penalized logistic regression. Model performance was estimated by c-index for discrimination. The model with best performance was visualized with a nomogram and calibration was plotted.

Results

In total, 292 patients were analyzed; 38(13.0%) patients suffered from AL, with a median interval to diagnosis of 6.0(IQR 4.0–14.8) days. AL occurred less often after partial than after total mesorectal excision (4.9% vs 15.2% $p = 0.035$). Of all patients with AL, 26(68.4%) patients required reoperation. AL was more often treated by reoperation in patients without a diverting ileostomy (18/20 vs 8/18 $p = 0.03$). The prediction model for postoperative day 1 included MMP9, TNFα, diverting ileostomy and surgical technique (c-index = 0.71). The prediction model for postoperative day 2 only included CRP (c-index = 0.69). The prediction model for postoperative day 3 included CRP and MMP9 and obtained best model performance (c-index = 0.78).

Conclusion

The combination of serum CRP and peritoneal MMP9 may be useful to predict AL earlier after rectal cancer resection. In clinical practice, this combination of biomarkers should be interpreted in clinical context as with any other diagnostic tool.

Introduction

With the introduction of minimally-invasive techniques, the short-term outcomes of rectal surgery have improved over the last decades(1, 2). Despite these advances, the incidence of anastomotic leakage (AL) has not been reduced(3). Moreover, standardized recovery programs have shortened hospital stay, yet with the downside of AL becoming clinically apparent after discharge resulting in readmission and delayed management(4). Nowadays, 20% of AL is diagnosed after discharge with a mean time to diagnosis of 6 to 15 days(5, 6).

Current diagnostic strategy, consisting of on demand CT-scanning, fails to detect AL at an early stage as half of all leakages require reoperation(7, 8). Delayed reintervention after false-negative CT scanning is associated with increased mortality and prolonged hospital stay(9). In addition, delay in diagnosis of 2.5 days is associated with an increase in mortality from 24% to 39%(10). Hence, early detection is of paramount importance in order to minimize postoperative morbidity and mortality.

Previously, biomarkers in drain fluid have been proposed as an innovative strategy for early detection of AL. Elevated peritoneal levels of inflammatory cytokines and lactate as well as decreased pH seemed to be associated with AL and measurements of such parameters is thus of interest for early detection of AL(11). Furthermore, promising results were shown for lipopolysaccharide-binding protein (LBP) and *Enterococcus faecalis* in drain fluid(12, 13). However, implementation in clinical practice is lagging behind as previous studies were based on small sample sizes and were lacking estimation of predictive accuracy.

A systematic review concluded that combining biomarkers yielded improved predictive accuracy compared to separate analysis of biomarkers(14). Therefore, we aimed to assess a combination of biomarkers for prediction of AL after rectal cancer resection and to determine its predictive accuracy.

Method

Patients

This study was designed as an international multicenter prospective cohort study. Ten hospitals in the Netherlands and Belgium participated in this study. Patients were included between August 2015 and October 2017. The medical ethics committee of the Erasmus MC University Medical Center in The Netherlands and of the University Hospital Leuven in Belgium approved this study. Ethical approval was also obtained in the other participating hospitals. This study was registered at www.ISRCTN.org (Study ID: 84052649).

Patients aged 18 years and older who underwent partial mesorectal excision (PME) or total mesorectal excision (TME) with construction of a colorectal or coloanal anastomosis were eligible for inclusion. Pregnant women and patients who underwent an emergency procedure were excluded. In addition, patients in whom no drain fluid was obtained or who underwent surgery for another indication than adenocarcinoma were excluded. All patients gave written informed consent. The follow-up ended at the first outpatient clinic visit after hospital discharge.

Drain fluid collection and storage

All patients received a pelvic drain during surgery. Drain fluid was collected every morning on the first 3 postoperative days. Drain fluid was collected respecting rules of sterility with a syringe including a needle and deposited in a 10 mL EDTA tube. The drain fluid reservoir was replaced after collecting drain fluid. The EDTA tube was transported to the laboratory and the drain fluid samples were centrifuged (1955×g) for 10 minutes at 4°C. Subsequently the supernatant was removed. Drain fluid was aliquoted in five cryotubes of 2 mL and stored at -80°C until further analysis. C-reactive protein (CRP) was measured in peripheral blood samples at the hospitals' clinical laboratory on the first 3 postoperative days.

Drain fluid analysis

Samples were thawed, vortexed and centrifuged for 1 minute at 10,000×g at 4°C before analyzing. All biomarkers were measured in duplicate and the means were taken for further analysis. Matrix metalloproteinases (MMP2 and MMP9) and cytokines (IL1β, IL6, IL10 and TNFα) were measured using ProcartaPlex® Multiplex Immunoassay (ThermoFisher Scientific) on a Luminex Magpix machine. For cytokine measurement, high sensitivity assays were used. Levels of α-amylase, glucose and lactate were measured using Roche/Hitachi cobas c systems from Roche Diagnostics, Indianapolis, USA. LBP was measured with enzyme linked immunosorbent assay (ELISA; R&D Systems, Minneapolis, USA) according to manufacturer's instruction. *Escherichia coli* and *Enterococcus faecalis* were measured using a semi-quantitative real time PCR strategy. Prior to DNA isolation, 500 µl of drain fluid was spiked with 5 µl Phocine Herpes Virus (PhHV) as an internal control from European Virus Archive (EVAg). Samples were spinned for 5 minutes at 8000g and the pellets resuspended in 180µl buffer (20 mM Tris, 2 mM EDTA, 1% Tween 80 and 50 mg/ml lysozyme). The samples were incubated at 37°C, shaking at 600 rpm for 30 minutes after which 25 µl proteinase K was added followed by a 2-hour incubation at 56°C at 700 rpm. DNA extraction was performed using Macherey-Nagel NucleoSpin® Tissue kit (Bioké, Leiden, Nederland). Template DNA was eluted in elution buffer in a total volume of 100 µl. Subsequently, primers for *Escherichia coli* and *Enterococcus faecalis* were added in accordance to the previously published protocol(15). The StepOnePlus Real-Time PCR System (Applied Biosystems, Bleiswijk, Nederland) was used for RT-PCR. Threshold cycles (Ct) were corrected for differences in extraction efficiency using the threshold cycle of the internal control PhHV.

Clinical data assessment

Patient characteristics (age, gender, BMI, medication use, bowel preparation, smoking, alcohol abuse, ASA score, previous abdominal surgery, indication for surgery, preoperative radiotherapy, preoperative chemotherapy, location of lesion) and surgical characteristics (surgical procedure, surgical technique, conversion, construction of anastomosis, configuration of anastomosis, diverting ileostomy) were prospectively registered. The creation of the anastomosis was registered as 'stapler' or 'manual'. Manual anastomosis was performed using interrupted colo-anal sutures with a hand-sewn technique. If the anastomosis was constructed with a stapler and additional manual sutures were added this was registered as stapled. Transanal TME was defined as follows: part of a TME being performed with transanal assistance. This includes a semi-rigid platform with rigid instruments to perform a down-to-up TME.

AL was the primary outcome of interest being defined as a clinically manifest insufficiency of the anastomosis, leading to a clinical state requiring treatment (i.e. grade B/C)(7). AL was confirmed by either endoscopy, CT-scan and/or contrast enema or reoperation. Fistulae communicating with the anastomosis on CT-scan were classified as AL together with presacral abscesses if extravasation of the colonic contrast was visible on radiological imaging. In addition, postoperative indicators (time to discharge, postoperative complications with their respective treatment strategies, readmission, reoperation and mortality) were prospectively registered. Elective stoma reversals were not registered as reoperation.

Statistical analysis

Continuous variables were described as median ± interquartile range (IQR) and compared with the Mann-Whitney U test. Categorical variables were described as percentages and compared with the Chi-square test or Fisher's Exact test when needed. Comparisons of biomarkers were corrected for multiple testing using Holm's method per postoperative day(16). Multiple imputation procedure was performed to impute missing data based on 10 completed datasets. For each postoperative day, multivariate penalized logistic regression models were constructed including clinically relevant baseline characteristics (age, gender, NSAIDS, corticosteroids, diverting Ileostomy, surgical procedure, approach) and all biomarkers. Prediction models for each postoperative day were built including covariates with a p-value < 0.1. Internal validation using the Bootstrap method was used to obtain corrected estimates of model performance to avoid overfitting. Model performance was estimated by Harrell's concordance index (c-index). The c-index measures how adequate the model discriminates between the outcome of interest and represents the probability that, in a randomly selected pair of patients, the model assigns a higher risk to the patient who is truly high risk compared with the patient who is truly low risk. C-index of 0.5 indicates no association between prediction and true outcome and a value of 1.0 indicates perfect association. C-indexes >0.75 are considered clinically useful(17). Calibration plot of the model with best c-index was built showing the relationship between observed probability of the outcome and predicted probability. The observed and expected rates are similar in a well calibrated model. The final model was visualized using a nomogram and captured in an online calculator (https://www.evidencio.com/models/show/1537). Two-sided p-values <0.05 were considered statistically significant. Analyses were performed using SPSS version 22 (IBM Corp., Armonk, NY, USA) and NLME, LATTICE, ARM, AOD and RMS package in R version 3.3.3 (http://www.r-project.org).

Results

Study population

A total of 310 patients were included. Nine patients were excluded because no drain fluid was obtained, and 9 patients were excluded due to another surgery indication than rectal adenocarcinoma. In the end, 292 patients were eligible for analysis.

Table 1 represents baseline characteristics of the study population. The median time of follow-up was 28.0 days (IQR 17.0 – 35.0). The median time to discharge was 7.0 days (IQR 5.0 – 11.0). In total, 42 (14.4%) patients were readmitted to the hospital and 38 (13.0%) patients underwent reoperation. Infection at the drain insertion site was reported in 3 (1.0%) patients. No other complications of the pelvic drain were reported. Two (0.7%) patients died. One patient died of AL and the other patient died two days after hospital discharge of an unknown reason as no autopsy was performed.

Anastomotic leakage

In total, 38 (13.0%) patients suffered from AL. No differences in patient characteristics were observed for patients with and without AL. The incidence of AL was not different for patients with and without diverting ileostomy (11.4% vs 14.9% p= 0.371). AL occurred less often after PME than after TME (4.9% vs 15.2% p = 0.035) (Table 1).

AL was clinically manifest as a presacral abscess in 5 patients. Median time to diagnosis was 6.0 days (IQR 6.0 – 14.8). Patients with AL had a significantly longer hospital stay (16.0 days vs 6.0 days p ≤ 0.001). Drain fluid production was not different for patients with and without AL (day 1 155 mL vs 180.0 mL p = 0.664, day 2 97.5 vs 100.0 p = 0.435, day 3 60.0 vs 90.0 p= 0.141).

Table 1. Patient and surgical characteristics of patients with and without anastomotic leakage (AL).

		Total 292	No AL 254 (87.0%)	AL 38 (13.0%)	Missing	P value
Patient characteristics						
Age, median ± IQR†, yr		63.0 (57.0 – 71.0)	63.5 (57.5 – 71.0)	60.5 (53.8 – 68.5)	0 (0.0%)	0.135
Gender	Male	193 (66.1%)	167 (65.7%)	26 (68.4%)	0 (0.0%)	0.745
	Female	99 (34.0%)	87 (34.4%)	12 (31.6%)		
BMI‡, median ± IQR†, kg/m^2		25.8 (23.5 – 28.7)	25.8 (23.3 – 28.7)	25.9 (24.2 – 29.2)	1 (0.3%)	0.546
Corticosteroids		17 (5.8%)	14 (5.5%)	3 (7.9%)	2 (0.7%)	0.475*
NSAIDS		8 (2.7%)	7 (2.8%)	1 (2.6%)	2 (0.7%)	1.000*
Bowel preparation		244 (83.6%)	209 (82.3%)	35 (92.1%)	25 (8.6%)	1.000*
Smoking		38 (13.0%)	31 (12.2%)	7 (18.4%)	10 (3.4%)	0.304*
Alcohol abuse		39 (13.4%)	32 (12.6%)	7 (18.4%)	10 (3.4%)	0.378
ASA§ score	I	45 (15.4%)	37 (14.6%)	8 (21.1%)	2 (0.7%)	0.468*
	II	181 (62.0%)	156 (61.4%)	25 (65.8%)		
	III	62 (21.2%)	57 (22.4%)	5 (13.2%)		
	IV	2 (0.7%)	2 (0.8%)	0 (0.0%)		
Previous abdominal surgery		100 (34.2%)	90 (35.4%)	10 (26.3%)	1 (0.3%)	0.263
Clinical tumor stage	T1	14 (4.8%)	13 (5.1%)	1 (2.6%)	44 (15.1%)	0.871*
	T2	72 (24.7%)	62 (24.4%)	10 (26.3%)		
	T3	144 (49.3%)	123 (48.4%)	21 (55.3%)		
	T4	18 (6.2%)	16 (6.3%)	2 (5.3%)		
Clinical nodal stage	N0	101 (34.6%)	86 (33.9%)	15 (39.5%)		0.600
	N≥1	139 (47.6%)	119 (46.9%)	17 (44.7%)		
Preoperative radiotherapy		155 (53.1%)	135 (53.1%)	20 (52.6%)	1 (0.3%)	0.933
- Short course		58 (37.4%)	52 (38.5%)	6 (30.0%)		
- Long course		89 (57.4%)	77 (57.0%)	12 (60.0%)		
Preoperative chemotherapy		102 (34.9%)	87 (34.3%)	15 (39.5%)	1 (0.3%)	0.540
Location lesion from anal verge, median ± IQR, cm		10.0 (6.0 – 13.0)	10.0 (6.0 – 14.0)	9.0 (5.0 – 12.0)	16 (5.5%)	0.169
Surgical characteristics						

Table 1. (Continued)

		Total 292	No AL 254 (87.0%)	AL 38 (13.0%)	Missing	P value
Procedure	PME	61 (20.9%)	58 (22.8%)	3 (7.9%)	0 (0.0%)	**0.035**
	TME	231 (79.1%)	196 (77.2%)	35 (92.1%)		
Surgical technique	Open	11 (3.8%)	10 (3.9%)	1 (2.6%)	0 (0.0%)	0.736*
	Laparoscopic	161 (55.1%)	142 (55.9%)	19 (50.0%)		
	Transanal	120 (41.1%)	102 (40.2%)	18 (47.4%)		
Conversion		8 (2.7%)	8 (3.1%)	0 (0.0%)	0 (0.0%)	0.598*
Construction of anastomosis	Manual	43 (14.7%)	39 (15.4%)	4 (10.5%)	2 (0.7%)	0.423
	Stapler	247 (84.6%)	213 (83.9%)	34 (89.5%)		
Configuration of anastomosis	Side-to-Side	4 (1.4%)	4 (1.6%)	0 (0.0%)	31 (10.6%)	0.861*
	Side-to-End	173 (59.2%)	147 (57.9%)	26 (68.4%)		
	End-to-End	79 (27.1%)	70 (27.6%)	9 (23.7%)		
	End-to-Side	5 (1.7%)	5 (2.0%)	0 (0.0%)		
Diverting ileostomy		158 (54.1%)	140 (55.1%)	18 (47.4%)	0 (0.0%)	0.371

* Fisher Exact Test;
† IQR, interquartile range;
‡ BMI, body mass index;
§ ASA, American Society of Anesthesiologists

In 30 (78.9%) patients AL was confirmed by a CT-scan, in 5 (13.2%) by proctoscopy and in 1 (2.6%) patient by reoperation. Of all patients with AL, 26 (68.4%) patients required reoperation whereas 12 (31.6%) patients were treated more conservatively (antibiotics, drainage or endosponge). AL was more often treated by reoperation in patients without a diverting ileostomy (18/20 vs 8/18 $p = 0.03$).

Biomarkers

Table 2 shows comparison of levels of biomarkers for patients with and without AL per postoperative day. Table 3 represents outcomes of multivariate penalized logistic regression analyses per postoperative day. Prediction models for each postoperative day were built including covariates with a p-value < 0.1 in the multivariate analysis. The prediction model for postoperative day 1 included MMP9, TNFα, diverting ileostomy and surgical technique. The prediction model for postoperative day 2 only included CRP. The prediction model for postoperative day 3 included both CRP and MMP9.

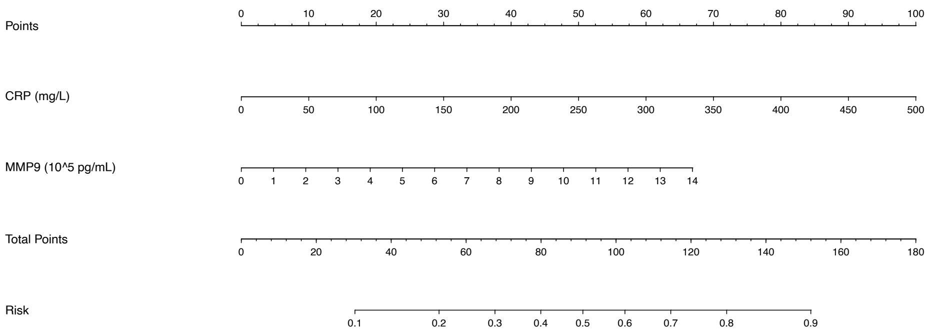
Table 2. Comparison of biomarker levels for patients with and without anastomotic leakage (AL).

		Postoperative day 1					Postoperative day 2					Postoperative day 3				
	AL	**N***	**Median**	**Q1†**	**Q3‡**	**P value**	**N***	**Median**	**Q1†**	**Q3**	**P value**	**N***	**Median**	**Q1†**	**Q3‡**	**P value**
MMP2×10^5 (pg/mL)	**Y**	37	0.7	0.5	1.2		31	1.0	0.6	1.4	1.000	31	1.1	0.7	2.1	1.000
	N	248	0.7	0.4	1.1	1.000	236	1.0	0.6	1.4		230	1.2	0.7	1.7	
MMP9×10^5 (pg/mL)	**Y**	37	3.2	0.9	10.8		31	1.7	0.4	7.0	1.000	32	2.0	0.5	5.0	**0.011**
	N	247	2.0	0.9	4.1	0.450	235	1.0	0.5	2.0		231	0.6	0.3	1.5	
Glucose (mmol/L)	**Y**	37	2.0	0.4	3.8		38	0.2	0.1	2.4	**<0.001**	35	0.3	0.1	3.1	**0.011**
	N	247	3.4	1.5	4.6	0.252	241	2.4	0.1	4.7		238	2.9	0.1	5.0	
Lactate (mmol/L)	**Y**	37	10.5	6.9	14.5		38	12.5	9.1	19.7	1.000	37	11.3	8.1	19.2	0.444
	N	248	9.1	6.2	13.2	1.000	242	11.1	6.4	17.3		243	9.2	5.2	14.9	
CRP (mg/mL)	**Y**	36	69.5	35.0	105.8		36	152.5	83.5	215.5	**<0.001**	37	170.0	113.8	290.5	**<0.001**
	N	241	50.0	30.9	80.0	0.459	213	86.0	47.1	135.9		215	78.0	41.0	125.0	
IL1β (pg/mL)	**Y**	37	61.1	31.7	263.5		32	138.1	46.7	536.8	**0.011**	31	190.0	28.6	3271.1	**<0.001**
	N	247	47.1	19.6	132.3	0.341	236	39.8	13.4	151.5		232	30.3	9.3	142.9	
IL6 (pg/mL)	**Y**	36	69717.7	19267.2	76184.2		32	73454.5	23889.4	76334.1	1.000	31	46178.8	17483.5	76070.8	0.301
	N	246	51635.3	23484.4	76070.8	1.000	236	41860.7	17483.5	75786.4		232	24738.2	11239.9	68858.8	
IL10 (pg/mL)	**Y**	37	249.7	141.3	594.6		32	176.3	84.4	630.8	0.080	31	128.3	38.6	554.2	0.072
	N	247	204.8	109.7	405.5	0.584	236	99.1	51.8	220.8		232	62.4	30.0	136.4	
TNFα (pg/mL)	**Y**	37	37.3	23.6	128.8		32	23.1	12.9	67.2	1.000	31	45.2	14.2	79.7	**0.036**
	N	246	30.1	16.4	59.1	0.156	237	21.5	12.0	39.8		231	17.7	9.9	34.0	
E. Coli (Ct)	**Y**	37	34.2	32.4	35.8		33	34.8	31.4	37.5	1.000	30	34.3	26.7	36.4	1.000
	N	247	34.6	32.4	37.0	1.000	231	34.6	32.4	36.7		227	34.7	32.9	36.6	
E. Faecalis (Ct)	**Y**	38	26.3	25.2	26.9		33	26.5	25.4	27.5	1.000	32	26.2	25.1	27.4	1.000
	N	248	26.2	25.1	27.1	1.000	234	26.0	25.0	27.0		228	25.9	25.1	27.0	
LBP (μg/mL)	**Y**	38	3.6	1.9	5.0		34	5.5	3.5	6.6	1.000	31	6.2	4.6	7.0	1.000
	N	248	3.2	2.2	4.4	1.000	237	5.1	4.0	6.1		231	5.6	4.5	6.7	
Amylase (U/L)	**Y**	36	36.0	14.3	84.8		38	30.5	13.5	47.0	1.000	37	24.0	17.5	45.0	1.000
	N	243	24.0	13.0	41.0	0.584	243	28.0	18.0	45.0		244	25.0	15.0	37.0	

*N, number of patients; † Q1, first quartile; ‡ Q3, third quartile

The prediction model of postoperative day 1 had a c-index of 0.71 whereas the prediction model of postoperative day 2 had a c-index of 0.69. So, these prediction models were lacking discrimination and therefore, were not considered to be clinically useful. On the contrary, the prediction model of postoperative day 3, including CRP and MMP9, had a c-index of 0.78. This c-index indicated that in 78% of the time, the model assigned a higher probability to a patient with AL than a patient without AL. For the prediction model of postoperative day 3, a nomogram was constructed facilitating the calculation of the individual risk of AL after rectal cancer resection based on CRP and MMP9 on postoperative day 3 (Figure 1). An online calculator was built for this nomogram at https://www.evidencio.com/models/show/1537.

Figure 1. Nomogram of the prediction model of postoperative day 3 (c-index = 0.78). This nomogram can estimate the risk of anastomotic leakage (AL) after rectal resection on postoperative day 3 with serum CRP and peritoneal MMP9.



Calibration was determined to estimate model performance with a calibration plot. In a calibration plot the predicted probability is plotted against the corresponding observed probability in the dataset. Ideally, this depicts a diagonal line and calibration is quantified by the mean absolute error. Figure 2 shows the calibration plot of the prediction model of postoperative day 3 (mean absolute error = 0.025).

Figure 2. Calibration plot for nomogram predicting anastomotic leakage (AL) with serum CRP and peritoneal MMP9 on postoperative day 3. This plot represents the relationship between predicted probability from the nomogram and observed probability in the dataset. The bootstrap method was used to obtain corrected probabilities.

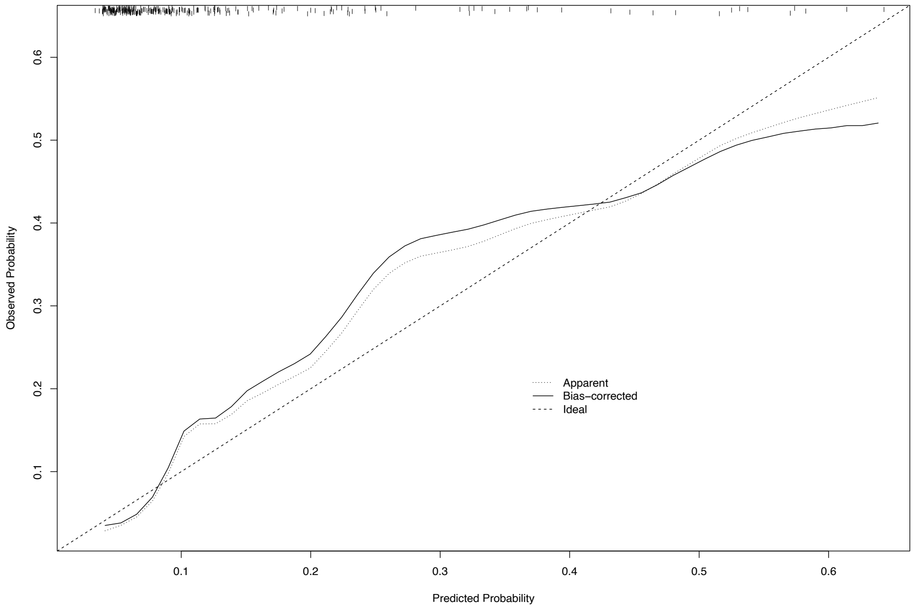


Table 3. Outcomes of multivariate penalized logistic regression for anastomotic leakage (AL) per postoperative day.

	Postoperative day 1				Postoperative day 2				Postoperative day 3			
	OR*	95% CI† lower	95% CI† upper	P value	OR*	95% CI† lower	95% CI† upper	P value	OR*	95% CI† lower	95% CI† upper	P value
MMP2 (pg/mL)	1.011	0.962	1.063	0.661	1.020	0.955	1.090	0.556	1.025	0.986	1.066	0.216
MMP9 (pg/mL)	1.106	0.995	1.229	0.063‡	1.094	0.952	1.257	0.203	1.130	0.982	1.301	0.088‖
Glucose (mmol/L)	0.939	0.751	1.176	0.585	0.916	0.728	1.152	0.453	0.920	0.734	1.152	0.466
Lactate (mmol/L)	0.990	0.890	1.101	0.854	0.993	0.912	1.081	0.869	0.987	0.917	1.063	0.737
CRP (mg/mL)	1.068	0.981	1.162	0.128	1.057	1.005	1.111	0.030§	1.064	1.013	1.118	0.013‖
IL1β (pg/mL)	1.002	0.992	1.012	0.702	0.999	0.992	1.006	0.787	1.001	0.999	1.003	0.522
IL6 (pg/mL)	0.980	0.847	1.135	0.787	1.052	0.899	1.230	0.529	0.939	0.788	1.119	0.481
IL10 (pg/mL)	0.999	0.980	1.019	0.954	1.044	0.940	1.159	0.424	1.110	0.959	1.284	0.161
TNFα (pg/mL)	1.037	0.998	1.077	0.062‡	0.991	0.969	1.014	0.453	1.011	0.996	1.026	0.136
E. Coli (Ct)	0.975	0.852	1.115	0.707	0.947	0.830	1.081	0.422	1.029	0.905	1.169	0.664
E. Faecalis (Ct)	1.072	0.756	1.520	0.697	1.179	0.820	1.695	0.373	1.009	0.703	1.448	0.960
LBP (µg/mL)	0.913	0.704	1.184	0.492	0.910	0.708	1.170	0.462	0.888	0.686	1.149	0.365
Amylase (U/L)	1.000	0.998	1.003	0.827	1.001	0.998	1.003	0.648	1.000	0.999	1.001	0.547
Age	0.978	0.944	1.013	0.222	0.973	0.936	1.010	0.154	0.986	0.948	1.027	0.503
Gender	0.931	0.415	2.088	0.862	0.866	0.367	2.044	0.743	0.698	0.275	1.772	0.449
NSAIDS	0.719	0.131	3.953	0.704	0.454	0.051	4.042	0.479	1.018	0.172	6.028	0.985
Corticosteroids	1.066	0.263	4.315	0.928	1.132	0.252	5.093	0.871	1.087	0.267	4.430	0.908
Diverting ileostomy	0.478	0.205	1.116	0.088‡	0.485	0.195	1.208	0.120	0.575	0.219	1.511	0.261
Procedure	2.829	0.888	9.014	0.079‡	2.540	0.787	8.193	0.119	2.229	0.603	8.239	0.229
Surgical technique	0.756	0.151	3.787	0.733	0.804	0.152	4.252	0.797	1.047	0.197	5.557	0.957

*OR, odds ratio
† CI, confidence interval
‡ These variables were added to the prediction model of postoperative day 1
§ These variables were added to the prediction model of postoperative day 2
‖ These variables were added to the prediction model of postoperative day 3

Discussion and conclusions

This international multicenter prospective cohort study showed that the combination of serum CRP and peritoneal MMP9 may be useful to predict AL early after rectal cancer resection. The combination of these biomarkers can estimate the individual risk of AL after rectal cancer resection on the third postoperative day which was three days earlier than the median time to diagnosis (6 days).

As with any other biomarker in clinical practice, this tool only assesses the risk of AL requiring confirmation through additional imaging. However, this tool might enable timely intervention and subsequently minimize morbidity and mortality. For example, if this tool shows that a patient has high risk of AL on the third postoperative day and AL is subsequently confirmed by additional imaging even before the leak becomes clinically apparent, early reintervention could minimize the consequences of AL. So, this tool facilitates decision making for surgeons even before clinical symptoms occur(18).

Serum CRP is already a useful negative predictor for AL after anterior resection(19, 20). Nevertheless, serum CRP monitoring lacks specificity and positive predictive value for AL, because CRP level also rises due to other inflammatory complications(21). Previous research on biomarkers for AL showed that local biomarkers from peritoneal fluid were more specific than systemic biomarkers(22). The present study showed that peritoneal MMP9 was predictive for AL and therefore this biomarker has additional value in prediction of AL over serum CRP alone. Furthermore, the c-index of 0.78 of this combination showed adequate discrimination which is important in a diagnostic setting where the classification of patients into different groups is of main interest.

MMP9 is a matrix metalloproteinase which plays a role in degradation of extracellular matrix proteins, especially of collagen, and is actively involved in inflammation reaction and wound healing process(23, 24). Previously, experimental studies have investigated the association between MMPs and colorectal AL. MMPs negatively affect anastomotic healing(25, 26) whereas MMP inhibitors provided enhanced breaking strength of colonic anastomoses(27). The most pronounced collagen loss provoked by MMP9 was seen in the suture-holding zone of a colonic anastomoses(28). In addition, anastomotic MMP9 activity was increased 3 days after operation in an experimental model of bacterial peritonitis(29). Translation to clinical research obtained similar results. Patients with elevated levels of MMP1, MMP2 and MMP9 in perioperative biopsies from the colon had more often AL(30). Actually, peritoneal MMP9 had already been evaluated as biomarker for AL. For colorectal resection, contradictory literature exists(31, 32). But for rectal resection, a pilot study showed that peritoneal MMP9 levels measured 4 hours after surgery were increased in patients who developed AL(33).

However, it remains unknown whether this association represents a causal relationship or resembles consequential effects of AL.

In rectal cancer surgery, diversion is commonly applied to protect the anastomosis from leaking(34). However, the incidence of AL was not different for patients with and without a diverting ileostomy (11.4% vs 14.9%). Nevertheless, in patients without a diverting ileostomy, AL was more often treated by reoperation than in patients with a diverting ileostomy (18/20 vs 8/18 p = 0.03). These results suggested that a diverting ileostomy allows less invasive treatment strategies. Accordingly, it was previously shown from population-based data of the Dutch ColoRectal Audit (DCRA) that a high tendency towards stoma construction in rectal cancer surgery did not reduce the incidence of AL(35).

The reported incidence of AL of 13.0% is high compared to several previous studies (3.0% - 11.1%)(36, 37). We hypothesize that the prospective design and inclusion of only rectal resections contribute to this relatively high incidence of AL. Another explanation is that the definition of AL varies and that some atypical presentations of leakages such as presacral abscesses or rectovaginal fistulas are not always included. In addition, The Dutch Snapshot study reported a comparable incidence of 13.4% within 30 days postoperatively(4).

Over the last decade, our research group has been involved in the search for a reliable biomarker for AL after colorectal resection. In a clinical trial (APPEAL study), we demonstrated that PCR in drain fluid for *Enterococcus faecalis* could be predictive for AL after colorectal resection(13). However, the relatively low positive predictive value (PPV) of 30.2% on the third postoperative day indicated a substantial number of false positives. Therefore, the present study was conducted aiming to obtain a combination of biomarkers with increased predictive accuracy. In addition, the previous study showed that an increase of 1 standard deviation of the average level of LBP of postoperative day 1 is associated with an increased risk of leakage of 1.6(12). LBP is an acute phase protein that binds to lipopolysaccharide (LPS) to elicit an immune response to gram-negative bacteria(38). However, the present study did not confirm these results possibly due to different drain locations as the previous study obtained drain fluid from intra-abdominal drains whereas the present study used pelvic drains which were positioned extraperitoneal. Furthermore, the different microbiome of patients with colon and rectal cancer may be another explanation as the previous study also included colonic resections(39, 40). This previous study showed promising results for drain fluid analysis of the first 3 postoperative days. Therefore, we decided to limit drain fluid collection to this interval.

The GRECCAR 5 trial has shown that pelvic drainage after rectal excision for rectal cancer does not reduce AL(41). On the other hand, pelvic drainage was not found to be detrimental(42). In this study, only 3 (1.0%) patients suffered from infection at the drain insertion site which could be managed without invasive treatment strategies. So, the opportunity to detect AL early after rectal resection with innovative drain fluid analysis might justify pelvic drainage after rectal resection.

MMP9 measurements can easily be implemented as Luminex is a commonly used method in clinical laboratories. It is a fast method and relatively cheap. However, there were some limitations. First of all, dislocation of the drain may have influenced drain fluid composition(43). Secondly, intraoperative spill could have affected drain fluid composition by eliciting an inflammatory response. In addition, the emerging transanal technique may impact pelvic contamination although no evidence exists.

Since prediction models tend to perform better on data on which the model was constructed, external validation is essential before implementing prediction models in clinical practice(44). Furthermore, a phase II diagnostic study is required confirming that this tool truly predicts AL in a time changing direction which runs from the diagnostic test forward to diagnosis(45). In this manner, the effect on time to diagnosis can prospectively be assessed. In the end, the effect of early detection on morbidity and mortality requires phase III diagnostic research.

This international multicenter prospective cohort study showed that the combination of serum CRP and peritoneal MMP9 may be useful to predict AL earlier after rectal cancer resection. Nevertheless, it is important to mention that this tool should never replace clinical observations implying that the outcomes of this tool should be interpreted in clinical context as with any other diagnostic tool.

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Chapter 11

Discussion and future perspectives

Discussion

Anastomotic leakage (AL) remains the most feared complication after colorectal resection. The incidence varies from 4-33% and about one-third of the postoperative mortality after colorectal surgery is due to AL(1). Until today, the pathophysiology remains largely unknown leaving the surgeon in the dark in designing specifically targeted strategies to overcome this severe postoperative complication.

Part I: Risk assessment

In Part I risk assessment of AL after colorectal resection was investigated. Previously, many efforts have been devoted to identifying risk factors for AL after colorectal resection. However, as many surgeons may have experienced, it is not uncommon for patients without any apparent predisposition to develop AL. Therefore, it seems that selecting patients on risk factors may have limited value. Nevertheless, exploration of risk factors may increase knowledge on pathophysiology of AL. In addition, identification of adjustable risk factors may provide tools for optimization of prevention strategies.

Several previous studies suggested that early and late AL are different entities(2-8). However, there is no consensus in literature on the definition of late AL. Patients with early AL are more likely to undergo re-laparotomy as intervention(6, 8). On the other hand, the long-term stoma retention rate is higher in patients with late AL(7).

In **Chapter 2** risk factors for early and late colorectal AL were identified in a nation-wide audit (Dutch ColoRectal Audit)(9). Male sex and rectal cancer were associated with both early and late AL. Higher BMI, laparoscopy, emergency surgery and no diverting ileostomy were risk factors for early AL while Charlson Comorbidity Index ≥II, ASA ≥3, preoperative tumor complications, extensive additional resection because of tumor growth and preoperative radiation were risk factors for late AL. These results supported the hypothesis that early AL might originate from a technically failed anastomosis resulting in immediate anastomotic dehiscence whereas late AL might be the result of delayed healing of a well-constructed anastomosis.

In **Chapter 3** the same nation-wide audit (Dutch ColoRectal Audit) was used to explore whether the interval between preoperative short-course radiotherapy and surgery for rectal cancer influenced the incidence of AL. Previously, the TME trial has shown that preoperative short-course radiotherapy reduces 10-year local recurrence rate compared to surgery alone, without any survival benefit in patients with resectable rectal cancer(10). Although no clear evidence is available, short-course radiotherapy with surgery within 1 week is common practice. This study showed that elective surgery for rectal cancer <4 days after preoperative short-course radiotherapy resulted in an increase of AL. A proper interval between radiotherapy and surgery should not only guarantee optimal surgical outcomes, but also optimal oncological outcomes as preoperative short-course radiotherapy is administrated to reduce local recurrence(10). Therefore, to establish an optimal interval regarding both surgical and oncological outcomes, prospective evaluation is required.

In **Chapter 4** the effect of age on AL after colorectal cancer resection was explored. The incidence of colorectal cancer increases with age, with patients aged 60 years and older accounting for the majority of newly diagnosed cases in the Netherlands with 17% of newly diagnosed patients with colorectal cancer being 80 years and older(11). Several previous studies identified age as a risk factor for AL, however results were contradictive with some studies reporting a reduced incidence of AL in older patients, while others showed an increased incidence(12-17). In this study, data were derived from the same nation-wide audit (Dutch ColoRectal Audit). This population-based study showed that greater age was protective for AL. However, this study demonstrated that in patients >80 years, mortality following AL was 27.0%. These results support preoperative informed decision making, especially in octogenarians.

In **Chapter 5**

Part II: Surgical techniques

In Part II the effect of surgical techniques on AL was discussed. With the introduction of minimally invasive surgery, the outcomes of colorectal surgery have improved(18-20). However, these advancements have not reduced the incidence of AL after colorectal surgery.

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For rectal cancer resection, total mesorectal resection (TME) is the gold standard. This surgical technique, involving resection of the fatty envelope surrounding the rectum, has substantially contributed to local control and survival of rectal cancer(21, 22). Lately, minimally invasive techniques have been introduced for rectal surgery(18-20). The COREAN trial and the COLORII trial have shown short-term and long-term benefits for laparoscopic TME compared to open approach(23-25). Nevertheless, male sex and high Body Mass Index (BMI) are unfavorable patient characteristics for a laparoscopic approach(26). In addition, the limited view of the distal margin of the tumor and conversion rates to open surgery remain unsatisfactory emphasizing the need for an innovative approach to overcome these limitations of laparoscopy(27-29). Transanal total mesorectal excision (TaTME) might be the solution. Since its introduction in 2010, TaTME has been proven to be a feasible and safe technique for rectal cancer resections and subsequently achieved widespread acceptance(30, 31). TaTME has been suggested to result in lower rates of AL due to the avoidance of cross stapling(32, 33). Nevertheless, evidence is scarce and is mainly obtained from observational studies with retrospective design(34-38).

In **Chapter 6** postoperative morbidity after laparoscopic total mesorectal excision (LaTME) and transanal total mesorectal excision (TaTME) were compared. This study reported no difference in postoperative morbidity. More specifically, the incidence of AL was similar for LaTME and TaTME and the main advantage of TaTME seems to be the lower conversion rate to open surgery. This study is the first providing evidence from prospective observational data. However, oncological safety in terms of circumferential resection margin (CRM) involvement and local recurrence should be obtained in a well-designed RCT(39).

In **Chapter 7** the effect of the number of surgeons involved in the surgical procedure on postoperative morbidity after colorectal resection was investigated in a low-volume hospital. The hypothesis was that outcomes of elective colorectal surgery might improve when the surgical procedures were performed by two surgeons compared to one surgeon. Elective colorectal surgery in a low-volume hospital performed by two surgeons had no effect on the incidence of AL, however, it resulted in less reoperations.

Part III: Prevention

In Part III prevention of AL was addressed. Prevention of this postoperative complication remains the ultimate goal.

In **Chapter 8** a systematic review and meta-analysis were described exploring whether the intraoperative air leak test (ALT) prevents colorectal AL. Although convincing evidence is scarce, ALT is the most commonly used method to identify mechanically failure of the anastomosis(40). The positive ALT rate varied greatly among the included studies and this meta-analysis showed a higher incidence of AL in patients with a positive ALT compared to patients with a negative ALT. This finding indicated that current repair strategies of a failed anastomosis identified by the ALT may not be effective. Standardization of ALT and repair of a failed anastomosis seem necessary.

Part IV: Early detection

In Part IV innovative techniques for early detection of AL were evaluated. Current diagnostic strategy, consisting of on demand CT-scan, fails to detect AL in an early stage as 50% of all leakages are of the highest severity (i.e. Grade C) requiring reoperation(41-43). Hence, innovative strategies for early detection are under scrutiny and the search for reliable biomarkers is warranted(44).

In **Chapter 9** available literature on systemic and peritoneal inflammatory cytokines measurement for early detection of colorectal AL was evaluated. Systemic measurement was not associated with AL while peritoneal IL6 and TNFα levels were associated with AL after colorectal resection. This systematic review and meta-analysis raised the question whether a combination of specific biomarkers, rather than one single marker, could provide a clinically useful tool(45). To this end, high level-of-evident studies were warranted to determine the accuracy of peritoneal cytokines in the early diagnosis. Therefore, an international multicenter prospective cohort study was performed which is shown in the next chapter.

In **Chapter 10** a multicenter prospective cohort study showed that the combination of serum CRP and peritoneal MMP9 on postoperative day 3 was predictive for AL while the median time to diagnosis was 6 days. Adequate model performance of this prediction model justifies further clinical evaluation. Nevertheless, it is important to mention that this tool should not replace clinical observation implying that the outcomes of this tool should be interpreted in clinical context as with any other diagnostic tool. This study showed that peritoneal MMP9 has additional value in predicting AL after rectal resection over serum CRP alone. MMP9 is a matrix metalloproteinase which plays a role in degradation of extracellular matrix proteins, especially of collagen, and is actively involved in the inflammation reaction and the process of wound healing(46, 47). Previously, experimental studies have already investigated the role of MMP in anastomotic healing. MMPs negatively affect anastomotic healing(48, 49) whereas MMP inhibitors provided enhanced breaking strength of colonic anastomoses(50). The most pronounced collagen loss provoked by MMP9 was seen in the suture-holding zone of a colonic anastomosis(51). Translation to clinical research obtained similar results. Patients with elevated levels of MMP9 in perioperative obtained biopsies from the colon more often had AL(52). Actually, peritoneal MMP9 levels have already been evaluated as being a biomarker for AL. A pilot study showed that peritoneal MMP9 levels, measured 4 hours after surgery, were increased in patients who had AL after rectal resection(53). However, it remains unknown whether this association represents a causal relationship or resembles consequential effects.

Future perspectives

To date, colorectal anastomotic leakage (AL) remains the most dreaded complication after colorectal resection resulting in high morbidity and mortality. In the future, because of the aging population, it can be expected that the incidence of colorectal cancer will increase and thereby the number of patients at risk for AL after colorectal resection(54). The etiology remains largely unknown as it remains unclear why some anastomoses leak while others do not, possibly because the process of anastomotic healing is not completely understood yet. Full understanding of the pathophysiology is key in determining innovative strategies for early detection and prevention of AL(55). Nevertheless, exploration of new clinical perspectives also contributes to our knowledge on the etiology of AL.

Early detection

Despite that absolute prevention of AL is ideal, early detection of AL is of paramount importance in order to minimize associated postoperative morbidity and mortality(56). Early diagnosis of AL allows timely remedial intervention and could therefore reduce morbidity and mortality(56). The difficulty is represented by the fact that AL presents in a variety of ways, ranging from rapid fulminant sepsis to a more insidious onset with failure to progress in the postoperative period. In addition, the challenge arises from the multifactorial etiology of AL(57). Future research should not only focus on development of innovative strategies for early detection, but once predictive accuracy is assured, clinical implementation should be strived for. Before clinical implementation, a phase II diagnostic study is required confirming that this tool truly predicts AL in a time changing direction which runs from the diagnostic test forward to diagnosis(58). In this manner, the effect on time to diagnosis can be assessed prospectively. In the end, the effect of early detection on morbidity and mortality requires phase III diagnostic research.

Drain fluid

Drain fluid analysis might contribute to early detection of AL after colorectal surgery. This thesis showed that the combination of serum CRP and peritoneal MMP9 on postoperative day 3 is predictive for AL after rectal resection. In addition, this thesis provides a clinical useful tool estimating the individual risk for AL from serum CRP and peritoneal MMP9 on postoperative day 3. Development in medical technology may bring a revolution in detection of AL after colorectal resection. The future may lie in biosensor technology with a biochip with suitable biochemical recognition methods integrated in abdominal or pelvic drain systems(59, 60). Moreover, this might enable continuous measurement of biomarkers providing inside in biomarkers profiles and facilitating early detection. Creation of such a sensor for biomarkers is a realistic aim(61).

By exploring drain fluid i.e. the surroundings of the anastomosis, we might gain insight in the pathophysiology of AL because the composition of drain fluid might not only resemble the effect of anastomotic dehiscence but per se it might also affect anastomotic healing. Exploring drain fluid might provide insight in the local inflammatory response to AL. Moreover, determining the effect of the local response on anastomotic healing could be of interest as local inflammation impairs wound healing by prolonging the inflammatory phase, and inducing the expression of tissue proteases(62).

Microbiome

Future research could further focus on the association between the microbiome and AL after colorectal surgery as the intraluminal content might affect anastomotic healing(55). Evidence is available that AL can occur when the microbiome is depleted and specific pathogenic bacterial strains predominate(63). In addition, intestinal microbes with the capacity to produce tissue proteases may break down collagen in the intestinal tissue contributing to anastomotic dehiscence. *Enterococcus faecalis* possesses this characteristic and it has been demonstrated that *Enterococcus faecalis* contributes to AL by activating MMP9, a matrix metalloproteinase which plays a role in degradation of extracellular matrix proteins, especially collagen(47, 63).

Study design

In this era of evidence-based medicine, randomized controlled trials (RCTs) provide the highest level of evidence after meta-analysis and systematic reviews. However, RCTs investigating AL after colorectal surgery as primary outcome measure are scarce as they would require large sample sizes due to, from a statistical point of view, the relatively low incidence compromising power to detect a statistically significant difference. Nevertheless, population-based observational studies offer the possibility to provide information about rare diseases. These population-based observational studies assure generalizability (external validation) as patients and providers are carefully selected in trials and therefore do not resemble the general population and current clinical practice(64). Results from these population-based observational studies are thought to reflect clinical practice more accurately. In addition, observational data suffice for determination of risk factors. However, as allocation in these studies is not randomized, these studies are prone to confounding bias. The rapidly expanding field of big data analytics might play a pivotal role in the evolution of clinical practice and research(65).

Finally, all future research efforts on colorectal AL, on a national and international basis, should be ever more coordinated by all scientific societies of colorectal surgery, medical industry and clinical centers, specifically dedicated to colorectal surgery, guaranteeing for better standardization, knowledge and inspiration.

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Chapter 12

Summary

Summary

Anastomotic leakage (AL) remains the most dreaded complication after colorectal resection. This thesis aimed to explore new clinical perspectives of colorectal AL in order to minimize the incidence and the consequences of this postoperative complication.

Part I Risk assessment

In **Chapter 2**, risk factors for early and late colorectal AL were identified in a nation-wide audit (Dutch ColoRectal Audit). A total of 36,929 patients who underwent colorectal cancer resection with the construction of primary anastomosis in The Netherlands between 2011 and 2015 were analyzed. In total, 1,537 (4.1%) patients suffered from AL. Male sex and rectal cancer were associated with both early and late leakage. Higher Body Mass Index (BMI), laparoscopy, emergency surgery and no diverting ileostomy were risk factors for early leakage while Charlson Comorbidity Index ≥ II, American Society of Anesthesiologists (ASA) score ≥ 3, preoperative tumor complications, extensive additional resection because of tumor growth and preoperative radiation were risk factors for late leakage. These results support the hypothesis that that early leakage might be related to technical failure of the anastomosis while late leakage seems be related to healing deficiencies.

In **Chapter 3**, the same nation-wide audit (Dutch ColoRectal Audit) was used to explore whether the interval between preoperative short-course radiotherapy and surgery for rectal cancer influenced the incidence of AL. In total, 2,131 patients who underwent rectal cancer resection with the construction of a primary anastomosis in the Netherlands between 2011 and 2016 were analysed and 185 (8.7%) patients suffered from AL. Elective surgery for rectal cancer < 4 days after preoperative short-course radiotherapy resulted in an increase of AL.

In **Chapter 4**, the association between age and AL after colorectal resection was assessed. Data were derived from the same nation-wide audit (Dutch ColoRectal Audit). A total of 45,488 patients who underwent surgery for colorectal cancer in the Netherlands between 2011 and 2016 were analysed. The incidence of AL was lowest in patients ≥ 80 years (6.4% in patients < 60 years, 5.5% in patients 60-69 years, 4.9% in patients ≥ 80 years). Multivariate logistic regression showed that greater age was protective for AL. On the other hand, this population-based study showed that greater age was strongly associated with mortality after AL. In patients > 80 years old, mortality following AL was 27.0%.

In **Chapter 5** p.

Part II Surgical techniques

In **Chapter 6**, postoperative morbidity after laparoscopic total mesorectal excision (LaTME) and transanal total mesorectal excision (TaTME) was compared. This study was designed as a subgroup analysis of a prospective multicenter cohort study (Chapter 9). In total, 220 patients undergoing LaTME or TaTME were selected from the overall multicenter prospective cohort study. After propensity score matching, 48 patients for each group were compared. This study reported no difference in postoperative morbidity.

In **Chapter 7**, the effect of the number of surgeons involved in the surgical procedure on postoperative morbidity after colorectal resection was investigated in a low-volume hospital. A total of 429 patients were included and 143 patients (33.3%) were operated by one surgeon whereas 286 patients (66.7%) were operated by two surgeons. Patients operated by two surgeons were younger, more often male, and had a higher BMI. A multivariate analysis with propensity scores revealed that surgery with two surgeons was associated with less reoperations. Colorectal anastomotic leakage and mortality were not associated with the number of surgeons involved in the surgical procedure.

Part III Prevention

In **Chapter 8**, a systematic review and meta-analysis was described exploring whether the intraoperative air leak test (ALT) prevents colorectal AL. This review stated that available evidence was prone to substantial risk of bias. The positive ALT rate varied from 1.5% to 24.7% and a higher incidence of AL was found in patients with a positive ALT compared to patients with a negative ALT.

Part IV Early detection

In **Chapter 9,** available literature about systemic and peritoneal inflammatory cytokines for early detection of colorectal AL was evaluated. This systematic review and meta-analysis included 7 studies that evaluated systemic and peritoneal levels of TNFα, IL1β, IL6 and IL10 after colorectal resection. Systemic cytokine levels were not associated with AL. Peritoneal levels of IL6 were significantly higher in patients with leakage on postoperative day 1,2 and

3 whereas peritoneal levels of TNFα were significantly higher in patients with leakage on postoperative day 3,4 and 5.

In **Chapter 10**, an international multicenter prospective cohort study was described which assessed a combination of biomarkers for early detection of AL after rectal resection. Systemic CRP and peritoneal MMP2, MMP9, glucose, lactate, IL1β, IL6, IL10, TNFα, Escherichia coli, Enterococcus faecalis, LBP and amylase were analyzed. In total, 292 patients were analyzed and 38 (13.0%) patients suffered from AL. The prediction model, including CRP and MMP9 on postoperative day 3, obtained best model performance with adequate discrimination (c-index = 0.78) and calibration (mean absolute error = 0.025). A nomogram was built in an online calculator. This study showed that that the combination of serum CRP and peritoneal MMP9 on postoperative day 3 was predictive for AL while the median time to diagnosis was 6 days.

In **Chapter 11**, the results of this thesis were discussed.

Chapter 13

Nederlandse samenvatting

Nederlandse samenvatting

Naadlekkage is thans de meest gevreesde complicatie na colorectale chirurgie. Dit proefschrift richt zich op de verschillende klinische aspecten van colorectale naadlekkage om de incidentie in kaart te brengen en om de gevolgen van deze postoperatieve complicatie te verminderen.

Deel I Risicobeoordeling

In **Hoofdstuk 2** werden risicofactoren voor vroege en late colorectale naadlekkage geïdentificeerd in een landelijke audit, namelijk in de *Dutch ColoRectal Audit* (DCRA). In dit onderzoek werden 36.929 patiënten geanalyseerd, die in Nederland tussen 2011 en 2015 een resectie ondergingen vanwege een colorectaal carcinoom en bij wie een primaire naad oftewel anastomose werd aangelegd. In totaal ontwikkelden 1.537 (4,1%) patiënten postoperatief een naadlekkage. Het mannelijk geslacht en een rectumcarcinoom waren geassocieerd met het ontstaan van vroege en late naadlekkage. Hoge *Body Mass Index (BMI),* laparoscopie, spoedoperatie en geen ontlastend ileostoma waren risicofactoren voor vroege naadlekkage. *Charlson Comorbidity Index* ≥ II, *American Society of Anesthesiologists (ASA) score* ≥ 3, preoperatieve tumorcomplicatie, uitgebreide resectie vanwege tumorgroei en neo-adjuvante radiotherapie waren risicofactoren voor late naadlekkage. Deze resultaten bevestigen de hypothese dat een vroege naadlekkage gerelateerd is aan het technisch falen van de anastomose terwijl een late naadlekkage gerelateerd is aan een verminderde wondgenezing.

In **Hoofdstuk 3** werd in dezelfde landelijke audit van de DCRA onderzocht of het interval tussen neo-adjuvante kortdurende radiotherapie en chirurgie voor een rectumcarcinoom invloed had op de incidentie van naadlekkage. In dit onderzoek werden 2.131 patiënten geanalyseerd, die in Nederland tussen 2011 en 2015 een operatie ondergingen vanwege een rectumcarcinoom en bij wie een primaire anastomose werd aangelegd. In totaal ontwikkelden 185 (8,7%) patiënten een naadlekkage. Uit dit onderzoek is gebleken dat een operatie binnen 4 dagen na kortdurende radiotherapie leidt tot een toename van het aantal naadlekkages.

In **Hoofdstuk 4** werd onderzocht wat de invloed van de leeftijd is op het ontstaan van naadlekkage na een colorectale resectie. Data werden verkregen uit dezelfde landelijke audit van de DCRA. In dit onderzoek werden 45.488 patiënten geanalyseerd, die in Nederland tussen 2011 en 2016 een resectie ondergingen vanwege een colorectaal carcinoom en bij wie een primaire anastomose werd aangelegd. De incidentie van naadlekkage was het laagst bij patiënten ≥ 80 jaar (6,4% bij patiënten < 60 jaar; 5,5% bij patiënten 60-69 jaar; 4,9% bij patiënten ≥ 80 jaar). Multivariabele logistische regressie toonde aan dat een hogere leeftijd beschermend was voor naadlekkage. Daartegenover toonde deze landelijke studie dat hogere leeftijd sterk geassocieerd was met mortaliteit na naadlekkage. Bij patiënten > 80 jaar was de mortaliteit na naadlekkage maar liefst 27,0%.

In **Hoofdstuk 5**

Deel II Chirurgische technieken

In **Hoofdstuk 6** werd de postoperatieve morbiditeit na laparoscopische totale mesorectale excisie (LaTME) en transanale totale mesorectale excisie (TaTME) vergeleken. Deze studie was een subgroep analyse van een multicenter prospectieve cohortstudie (Hoofdstuk 9). In totaal werden er 220 patiënten die LaTME of TaTME ondergingen geselecteerd uit de cohortstudie. Na matchen op basis van de *propensity score*, werden in totaal 48 patiënten in de LaTME groep en 48 in de TaTME groep vergeleken. In deze studie werden geen verschillen in naadlekkage incidentie gevonden. De postoperatieve morbiditeit was vergelijkbaar voor LaTME en TaTME.

In **Hoofdstuk 7** werd onderzocht of het aantal chirurgen dat betrokken was bij een colorectale ingreep van invloed was op de postoperatieve uitkomsten in een klein ziekenhuis. In totaal werden 429 patiënten geïncludeerd, daarvan werden 143 patiënten (33,3%) door één chirurg geopereerd en 286 patiënten (66,7%) door twee chirurgen. Patiënten die door twee chirurgen werden geopereerd waren jonger, vaker van het mannelijk geslacht en hadden een hogere BMI. Een multivariabele logistische regressie met de *propensity score* liet zien dat het geopereerd worden door twee chirurgen geassocieerd was met minder heroperaties. Naadlekkage en mortaliteit waren niet geassocieerd met het aantal chirurgen dat betrokken was bij de chirurgische ingreep.

Deel III Preventie

In **Hoofdstuk 8** werd een systematische review en meta-analyse uitgevoerd, waarin onderzocht werd of de fietsbandproef tijdens een colorectale resectie naadlekkage voorkomt. Er werd geconcludeerd dat de beschikbare literatuur gevoelig was voor bias. De frequentie van een positieve fietsbandproef varieerde van 1,5% tot 24,7%. Er werd een hogere naadlekkage incidentie gevonden bij patiënten met een positieve fietsbandproef dan bij patiënten met een negatieve fietsbandproef.

Deel IV Vroegtijdige detectie

In **Hoofdstuk 9** werd de beschikbare literatuur bestudeerd betreffende de waarde van systemische en peritoneale inflammatoire cytokines voor de vroege detectie van naadlekkage na een colorectale resectie. Dit systematische review omvatte 7 studies die TNFα, IL1β, IL6 en IL10 evalueerden. Systemische cytokines waren niet geassocieerd met naadlekkage. IL6 in drainvocht was significant hoger bij patiënten met naadlekkage op dag 1, 2 en 3 postoperatief. TNFα in drainvocht was significant hoger bij patiënten met naadlekkage op dag 3, 4 en 5 postoperatief.

Hoofdstuk 10 betreft een internationale multicenter prospectieve cohortstudie waarin gezocht werd naar een combinatie van biomarkers die voorspellend was voor naadlekkage na resectie van een rectumcarcinoom. Serum CRP en MMP2, MMP9, glucose, lactaat, IL1ß, IL6, IL10, TNFa, Escherichia coli, Enterococcus faecalis, LBP en amylase werden geanalyseerd in drainvocht op de eerste 3 dagen na de operatie. In totaal werden 292 patiënten geanalyseerd en 38 (13,0%) patiënten hadden naadlekkage. Het predictiemodel, inclusief CRP en MMP9 op postoperatieve dag 3, liet een adequate discriminatie (c-index = 0,78) en kalibratie (gemiddeld absoluut error = 0,025) zien. Deze studie toonde aan dat de combinatie van serum CRP en MMP9 in drainvocht op postoperatieve dag 3 voorspellend was voor naadlekkage, terwijl de mediane tijd tot diagnose 6 dagen was.

In **Hoofdstuk 11** werden de resultaten van dit proefschrift bediscussieerd.

Chapter 14

List of publications
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List of publications

Outcomes after elective colorectal surgery by 2 surgeons versus 1 surgeon in a low-volume hospital.
Sparreboom CL, Lambrichts DPV, Menon AG, Kleinrensink GJ, Lingsma HF, Lange JF
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Dis Colon Rectum. 2018 November

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Zaimi I, **Sparreboom CL**, Lingsma HF, Doornebosch PG, Menon AG, Kleinrensink GJ, Jeekel J, Wouters M, Lange JF
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Sparreboom CL, Wu Z, Lingsma HF, Menon AG, Kleinrensink GJ, Nuyttens JJ, Wouters MW, Lange JF
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J Biomed Mater Res B Appl Biomater. 2014 April

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Dankwoord

Dit proefschrift was niet tot stand gekomen zonder de bijdrage van velen. Ik wil een aantal mensen in het bijzonder bedanken.

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Professor Bouvy, Professor Kleinrensink en dr. Menon, geachte leden van de grote commissie, dank voor de bereidheid om zitting te nemen in de grote commissie. Het zal ongetwijfeld een interessante discussie worden. Professor Kleinrensink, het is zo ver, mijn proefschrift is af. De strijdbijl kan worden neergelegd en de kogelwerende vesten weer terug in de mottenballen. Dank voor uw begeleiding, vrolijkheid en uw voorliefde voor Rotterdam. Anand, dank voor de begeleiding en gezelligheid!

Zhouqiao Wu, dear Ciao, it has already been 7 years ago that our friendship started over operating rats and it has resulted in several publications and a phenomenal trip to China visiting your Gastric Cancer Congress and the Chinese Wall. Thank you for your support. I am looking forward to our next lunch at Jaffa!

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Pap en mam, woorden schieten tekort als ik moet beschrijven hoe dankbaar ik jullie ben. Dankbaar voor de steun die ik altijd heb gehad bij de keuzes die ik de afgelopen jaren heb gemaakt. Dankbaar voor de veilige thuishaven die jullie mij gegeven hebben en dankbaar voor de Rotterdamse opvoeding waar ik van jongs af aan heb geleerd dat hard werken wordt beloond. Ik zou dit graag voor jullie terug doen. Bedankt voor alles.

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Curriculum Vitae

Cloë Lean Sparreboom was born on February 13th 1992. She grew up in Rotterdam and graduated from Erasmiaans Gymnasium in Rotterdam in 2010. After this, she moved to London, United Kingdom to study English.

She returned and commenced medical school at the Erasmus University Rotterdam in 2011. During medical school, she undertook an internship in Suriname. In 2014 she acquired the bachelor's degree in medicine and started the clinical research master at the Netherlands Institute for Health Sciences (NIHES) for which she attended a summer school at Johns Hopkins University School of Public Health in Baltimore, United States.

The first steps for her thesis were taken during the clinical research master program at the department of surgery, Erasmus MC University Medical Center under supervision of Prof. dr. J.F. Lange, Prof. dr. J. Jeekel and Prof. dr. G.J. Kleinrensink. In 2015 she got the opportunity to proceed with her research project as a PhD candidate. In 2017 she restarted medical school. Currently she is involved in clinical rotations and she expects to graduate in February 2020.

PhD Portfolio

PhD Student:	C.L. Sparreboom
Promotor:	Prof. dr. J.F. Lange
	Prof. dr. A. D'Hoore
Co-promotor:	Prof. dr. J.J. Jeekel
	Dr. N. Komen
Erasmus MC Department:	Surgery
PhD Period	2015 – 2019

PhD courses	year	ECTS
Systematic literature search in PubMed	2015	1.0
Endnote	2015	1.0
ICH-GCP (Good Clinical Practice)	2015	1.5
Biomedical English writing	2016	2.0
Research Integrity	2017	0.3
(Inter)national conferences		
Najaarsdag NVvH, Hilversum	2015	1.0
Taskforce Naadlekkage, Nijmegen	2016	1.0
Wetenschapsdag Heelkunde Erasmus MC, Rotterdam	2016	1.0
Chirurgendagen NVvH, Veldhoven (chair)	2016	1.0
Taskforce Naadlekkage, Rotterdam (oral presentation)	2016	1.0
Wetenschapsdag Heelkunde Erasmus MC, Rotterdam	2017	1.0
Taskforce Naadlekkage, Veldhoven	2017	1.0
12th International Gastric Cancer Congress, Beijing (oral presentation)	2017	1.0
European Hernia Society, Vienna (oral presentation)	2017	1.0
EIT Health EU Grant proposal conference, Munich (oral presentation)	2017	1.0
European Society for Surgical Research, Amsterdam (oral presentation)	2017	1.0
Taskforce Naadlekkage, Veldhoven (oral presentation)	2017	1.0
11th European Colorectal Congress, St Gallen (2 poster presentations)	2017	2.0
Wetenschapsdag Heelkunde Erasmus MC, Rotterdam	2017	1.0
Belgium Surgical Week, Ostend (oral presentation)	2018	1.0
12th European Colorectal Congress, St Gallen (poster presentation)	2018	1.0
Chirurgendagen NVvH, Veldhoven	2017	1.0
Teaching		
Teaching anatomy to medical students	2015 - 2017	2.0
Supervising Master students		
Master thesis Health Sciences	2016 – 2017	2.0
Other		
EIT Health EU Grant proposal with Medtronic	2016 – 2017	3.0
Total		30.8