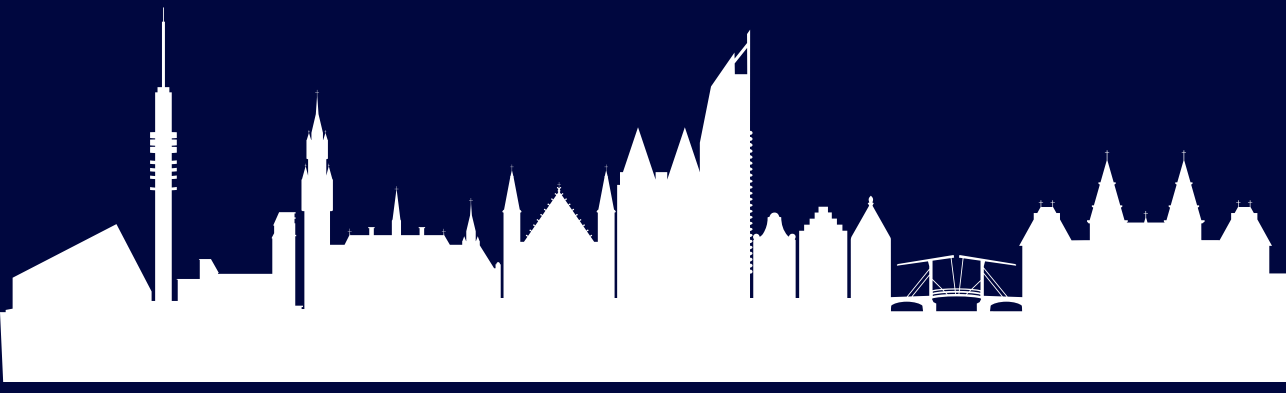
Complications and salvage surgery following restorative and non-restorative rectal cancer resection

Emma Westerduin



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GENERAL INTRODUCTION AND OUTLINE OF THE THESIS

General introduction

Colorectal carcinoma is the third most common type of cancer worldwide with approximately 18 million new cases annually of which 13.700 cases in the Netherlands with 4000 new rectal cancer patients every year.[1, 2] Although often grouped together with colon cancer, rectal cancer is considered a separate entity with its own treatment strategies. The treatment of rectal cancer is multidisciplinary, with an important role of precise clinical staging using MRI, need for neoadjuvant chemo- and radiotherapy in the locally advanced cases, and with high complex surgery because of the intricate pelvic anatomy. Despite evolving treatment strategies, resection of rectal cancer still remains the cornerstone of curative treatment.

One of the greatest developments in rectal cancer surgery was the introduction of the total mesorectal excision (TME), which was first described by Heald in 1986.[3] Heald showed extraordinary results by sharp, en bloc resection of the tumour, with complete pararectal lymph node dissection performed by resection of the visceral mesorectum. In his first series, he reported a cumulative 5-year local recurrence rate of 2.7% and an overall corrected 5-year survival of 87.5%, numbers unrivalled before that time.[4] Therefore, TME is now the standard principle for rectal cancer resection.

In the early 2000s, laparoscopic surgery for rectal cancer resection was introduced in the Netherlands and was proven a safe technique when considering both oncological and postoperative outcomes by the COLOR II trial.[5, 6] Nowadays, more than 80% of patients are operated for rectal cancer using laparoscopy.[7] Over the last decade, a modified surgical technique, combining the abdominal approach of the TME with transanal minimally invasive surgery, also referred to as TAMIS, has gained popularity.[8] It facilitates dissection deep down in the pelvis, which can especially be challenging in distal tumours in males because of the narrow pelvis. It has shown to be a feasible and safe approach compared to conventional laparoscopic TME when considering postoperative and short-term oncological outcome.[9-12]

There are also surgical treatment options preserving the rectum. Parks popularized transanal local excision in the 1950s using an anal retractor. With this technique, the tumour is resected locally and thereby the rectum is preserved. This was brought to the next level with the introduction of transanal endoscopic microsurgery (TEM) using a complex surgical system with insufflation and stereoscopic visualization in the 1980s by Buess.[13] Nowadays, the complex rigid TEM system is increasingly replaced by a flexible transanal platform that make use of the normal laparoscopic instruments, as used in TAMIS. There are many developments in rectal preserving treatment strategies, including 'watch and wait' approach for clinical complete response after neoadjuvant

chemoradiotherapy, as well as multimodality strategies including radiotherapy, systemic therapy and transanal local excision for early stage rectal cancer.[14]

Restorative and non-restorative rectal cancer resection
Curative surgery for rectal cancer without preservation of the rectum can be divided into restorative and non-restorative rectal cancer resection. The decision for either type of resection depends on a large number of variables; age, comorbidity, preoperative sphincter function, distance of the tumour from the anal verge, expected resection margins in relation to the sphincter complex and of course, patient preference.

In restorative rectal cancer resection, the part of the rectum including the tumour is excised according to the TME principle or using partial mesorectal excision (PME) depending on distance of the tumour from the anal verge. Per definition, this always constitutes a sphincter preserving resection. Subsequently, bowel continuity is restored by connecting the efferent colon to the remaining rectal remnant or directly to the sphincter complex by creation of an anastomosis. This anastomosis can be either stapled or hand-sewn and the abdominal approach can be performed through laparotomy or laparoscopy. This type of surgery, called anterior or low anterior resection (LAR) depending on tumour location and level of distal rectal transection, is the most commonly used technique in rectal cancer resection.

Non-restorative rectal cancer resection can either consist of a sphincter or non-sphincter preserving option. The sphincter preserving non-restorative option is the low Hartmann's resection (LHR), a technique in which the distal rectum is cross-stapled, leaving a rectal remnant in situ. The non-sphincter preserving option is the abdominoperineal excision (APR). In APR, the rectum is also excised according to the TME principles. Depending on the location of the tumour it can be necessary, especially in very distal rectal cancer, to excise the entire sphincter complex and part of the pelvic floor in order to achieve an oncological safe resection margin. In this type of APR, an extensive perineal wound is created, with a risk of perineal wound problems such as perineal wound infection and presacral abscess formation, with incisional perineal herniation in the long run.[15] When it is not oncologically necessary to resect the sphincter complex and pelvic floor, options are either to perform a LHR, or an intersphincteric resection of the rectal remnant, referred to as an intersphincteric abdominoperineal resection (iAPR). In all types of non-restorative rectal cancer resection, a definitive end colostomy is created.

Anastomotic leakage and pelvic abscess

The most feared complication in restorative rectal cancer resection is anastomotic leakage with reported incidences of up to 19%.[5, 16, 17] In this thesis, anastomotic leakage was defined as disruption of the anastomosis, identified through extravasation of contrast during radiological imaging, at reoperation or endoscopy, and irrespective of the presence of symptoms. Also, an abdominal abscess or a free pelvic fluid collection was considered an occult leak.[18] TME leaves a large presacral cavity, prone for accumulation of pus and debris when anastomotic leakage occurs after restorative rectal cancer resection. But also in non-restorative rectal cancer, a pelvic abscess can develop because of blow-out of the rectal remnant.

Anastomotic leakage requires early diagnosis and management including faecal diversion, transanal or percutaneous drainage, treatment with endo-SPONGE®, or endo-SPONGE® assisted transanal closure of the anastomotic defect. Anastomotic leakage can result in severe complications such as sepsis, chronic sinus or even septic coxartritis, necrotising fasciitis of the leg or ureteric strictures. Particularly patients who had neoadjuvant radiotherapy are prone for late complications.[19, 20] Delayed diagnosis and treatment decreases the chance of healing of the anastomosis.[21] Also, anastomotic leakage is associated with impaired functional outcomes, since prolonged inflammation can cause fibrosis and a decrease in pliability of the neorectum.[22-25]

Salvage surgery

When conservative treatment of anastomotic leakage following LAR fails, patients are confronted with a dilemma; do they want another attempt at restoration of bowel continuity and are they willing to, and most importantly, able to cope with possible new complications?

The first, and most common option for salvage surgery, is dismantling of the leaking anastomosis. There is no consensus about the best way of dismantling a low pelvic anastomosis. Often, the leaking efferent colonic limb is brought out as an end colostomy, and the rectal stump is closed whenever possible using stapling or sutures. However, this rectal remnant can be the source of persisting pelvic sepsis, for which reason an intersphincteric completion proctectomy (ICP) can be performed.[26] In this type of surgery, ICP is combined with extensive debridement of the septic pelvic cavity and the pelvic dead space is completely obliterated with well vascularized tissue (omentoplasty, musculocutaneous or fasciocutaneous flap) in order to reduce the chance of recurrent pelvic sepsis.

In these non-restorative types of salvage surgery for anastomotic leakage, patients will have to live with a stoma for the rest of their lives. Another option is the creation of a new (redo) anastomosis following resection of the leaking anastomosis. This is complex surgery, because of the distorted anatomy and pelvic adhesions following primary surgery, prolonged pelvic sepsis and fibrosis following radiotherapy. Also, the location of the leaking anastomosis deep down in the pelvis is a complicating factor. A redo anastomosis is only rarely performed in mostly only tertiary referral centres, and only few and small series have been described in literature.[27-29] It is, however, often a patient's last chance for restoration of bowel continuity and life without a stoma and is therefore offered to only highly motivated and selected patients.

Outline of the thesis

This thesis aims to assess the incidence of major complications with special focus on septic complications such as anastomotic leakage and pelvic abscess formation following rectal cancer resection and salvage surgery for septic complications. **Part I** focusses on restorative rectal cancer resection and **Part II** on non-restorative rectal cancer resection. In the **third** part, salvage surgery following anastomotic leakage after restorative rectal cancer resection is addressed.

Part I - Restorative rectal cancer resection

Since anastomotic leakage is the most feared complication following restorative rectal cancer resection, the incidence of anastomotic leakage following LAR as well as predisposing factors and long-term outcomes are described in **Chapter 1** based on a large cohort of patients from a collaborative Snapshot study involving 71 Dutch hospitals.

A deviating ileostomy has long been thought to reduce the rate of anastomotic leaks. However, it also delays the diagnosis of anastomotic leakage because the leak will often be asymptomatic in diverted patients. This may decrease the chance of healing of the anastomosis. Furthermore, the majority of patients never benefitted from their diverting stoma, but had all the disadvantage of having a stoma, and were exposed to the risks of complications associated with closing the stoma. In **Chapter 2** an institutional shift from routine use of a deviating ileostomy to only highly selective defunctioning is evaluated.

Part II - Non-restorative rectal cancer resection

In non-restorative rectal cancer resection, APR and LHR have been previously described as valid surgical techniques.[30, 31] Since the distal bowel resection margin in rectal cancer resection was lowered to 1 cm in order to be oncologically safe, more patients are eligible for sphincter saving surgery.[32, 33] Therefore, conventional or extralevator APR with creation of a large perineal wound became obsolete in many cases, introducing *intersphincteric* APR with end colostomy as an alternative surgical technique. In **Chapter 3**, the use of iAPR and LHR for rectal cancer resection without the desire to restore bowel continuity is assessed among Dutch surgeons. **Chapter 4** describes a cohort study in which complications following iAPR and LHR are compared between groups, with emphasis on pelvic abscess. In **Chapter 5**, outcomes following iAPR and LHR are compared as well, using a larger dataset from a collaborative research project.

Part III – Salvage surgery following rectal cancer resection

In **Chapter 6**, a systematic review of the available literature on redo anastomosis for all indications is displayed. **Chapter 7** describes the intra-operative and postoperative outcomes, as well as the long-term results including anastomotic healing and permanent stoma rates, after redo coloanal anastomosis for anastomotic leakage following LAR in two tertiary referral centres for redo surgery.

Transanal minimally invasive surgery (TAMIS) is gaining popularity for primary rectal cancer resection because of the facilitated dissection deep down in the pelvis, but might therefore also be particularly helpful in redo surgery for anastomotic leakage. In **Chapter 8,** procedural and short-term postoperative outcomes following TAMIS redo surgery, both TAMIS assisted redo anastomosis and TAMIS assisted ICP with colostomy and omentoplasty, are described and compared to outcomes following conventional redo surgery.

In patients' desire to avoid a permanent stoma in case of failure of minimally invasive treatment for anastomotic leakage, not only surgical outcomes following redo anastomosis should be assessed, but also ano-neorectal function. The last chapter of this thesis, **Chapter 9**, focusses on functional outcomes and quality of life after redo anastomosis, in a multicentre international comparative cohort study. Outcomes after redo anastomosis are compared to outcomes following primary healed anastomosis after TME for rectal cancer.

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PART ONE

Restorative rectal cancer resection

CHAPTER 1

Anastomotic leakage and chronic presacral sinus formation after low anterior resection

Results from a large cross-sectional study

Annals of Surgery. 2017 Nov;266(5):870-877.

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Dutch Snapshot Research Group

Abstract

Objectives
Little is known about late detected anastomotic leakage after low anterior resection for rectal cancer, and the proportion of leakages that develops into a chronic presacral sinus.

Methods
In this collaborative snapshot research project, data from registered rectal cancer resections in the Dutch Surgical Colorectal Audit in 2011 were extended with additional treatment and long-term outcome data. Independent predictors for anastomotic leakage were determined using a binary logistic model.

Results
A total of 71 out of the potential 94 hospitals participated. From the 2095 registered patients, 998 underwent a low anterior resection, of whom 88.8% received any form of neoadjuvant therapy. Median follow-up was 43 months (interquartile range 35–47). Anastomotic leakage was diagnosed in 13.4% within 30 days, which increased to 20.0% (200/998) beyond 30 days. Nonhealing of the leakage at 12 months was 48%, resulting in an overall proportion of chronic presacral sinus of 9.5%. Independent predictors for anastomotic leakage at any time during follow-up were neoadjuvant therapy (odds ratio 2.85; 95% confidence interval 1.00–8.11) and a distal (≤3cm from the anorectal junction on magnetic resonance imaging) tumor location (odds ratio 1.88; 95% confidence interval 1.02–3.46).

Conclusions
This cross-sectional study of low anterior resection for rectal cancer in the Netherlands in 2011, with almost routine use of neoadjuvant radiotherapy, shows that one third of anastomotic leakages is diagnosed beyond 30 days, and almost half of the leakages eventually do not heal. Chronic presacral sinus is a significant clinical problem that deserves more attention.

Anastomotic leakage after low anterior resection (LAR) is still one of the main contributors to morbidity of rectal cancer treatment, despite numerous attempts to decrease the incidence.[1–4] Reported incidences of symptomatic anastomotic leakage of colorectal and coloanal anastomoses remain approximately 9% to 15%.[5,6] Adjustable risk factors for leakage consist of smoking, obesity, neoadjuvant therapy, and nutritional status. Other risk factors such as male sex, age, American Society of Anesthesiologists (ASA)-classification, and distance of the tumor from the anal verge cannot be influenced.[7,8]

Although most of the anastomotic leaks are diagnosed within the initial postoperative period, subclinical leaks may only become overt by endoscopy or imaging of the anastomosis in preparation for diverting stoma closure.[9,10] Late symptoms of leakage might be nonspecific with slow progression, typically in those patients in whom a diverting stoma was closed because of false-negative imaging or endoscopy. Patients with a late leak or even chronic presacral sinus can present up to several years after initial surgery with a variety of symptoms, such as presacral pain, anemia, purulent discharge, fistulae, or even sepsis.[11,12]

Literature on late anastomotic leak and chronic sinus is scarce.[9,10,13] The available series are often monocentric and conducted in tertiary referral centers, not providing the overall picture.[10,12–15] A nationwide, cross-sectional study with long-term surgical outcomes would give more insight into this potentially underexposed complication. Therefore, the aim of this snapshot study was to determine the incidence of late anastomotic leakage and chronic sinus formation after LAR for rectal cancer and its predisposing factors, and to assess long-term related reinterventions.

Methods

Study Design

A retrospective, resident-led, collaborative research project with a cross-sectional study design was conducted in 71 hospitals in the Netherlands. The methodology of this project has been described earlier in the first publication of the Dutch Snapshot Research Group.[16] Short-term data of all patients in the Netherlands undergoing resection of colorectal cancer are prospectively collected in the Dutch Surgical Colorectal Audit (DSCA), which is obligatory by the Dutch Inspectorate of Healthcare. The DSCA dataset of the year 2011 was extended with additional procedural data and long-term surgical and oncological outcomes. Web-based data collection was performed by surgical residents under the supervision of 1 or 2 consultants during a 5-month period (from May 2015 to October 2015). For present analysis on anastomotic leak,

only patients who underwent a LAR with colorectal or coloanal anastomosis were included from the total cohort. The design of the study and the preparation of the manuscript was performed according to the Strengthening the Reporting of Observational Studies in Epidemiology statement.[17]

Ethics

The medical ethical committee of the Academic Medical Center in Amsterdam reviewed and approved the observational study design and decided that informed consent was not needed to be obtained as there was not an additional burden for the patient due to the observational design of the study.

Definitions

LAR was defined as a total mesorectal excision with the formation of a colorectal or coloanal anastomosis. The primary outcome was anastomotic leak diagnosed at any time during follow-up. This was defined as the presence of any of the following factors: contrast extravasation on imaging studies, presacral collection requiring surgical or radiological or endoscopic intervention, or a presacral collection that either led to delay in stoma reversal or led to resection or reconstruction of the anastomosis. A late anastomotic leak was defined as a leak that was diagnosed more than 30 days postoperatively. Secondary outcome parameter was chronic sinus, defined as a presacral abscess that was proven by imaging studies and was present more than a year after the initial resection. A leaking anastomosis was considered as "not-healed" if a chronic sinus was reported. In order to assess the type of intervention that was performed for anastomotic leak, participants were asked to classify each intervention into 1 out of 8 options: surgical drainage, radiological drainage, transanal closure of an anastomotic defect, endosponge treatment, resection of the anastomosis with construction of a permanent colostomy, anastomotic redo operation and diverting ileostomy. Other interventions were reported as "different".

Statistical Analysis

Categorical or dichotomous outcomes were presented as absolute numbers and percentages. The χ^2 test was used for intergroup variation. Descriptive outcomes were reported as median with interquartile range (IQR) or mean with standard deviation and in accordance to their distribution the Mann-Whitney U test was used for intergroup variation. For determining the incidence of chronic sinus, patients were censored who died or were lost to follow-up before 12 months needed for a presacral abscess to be considered a chronic sinus. Chi-square test was used for intergroup comparisons. Univariable and multivariable logistic regression analyses were performed using a

binary logistic model to identify predictors for anastomotic leak and chronic sinus. The results were expressed using odds ratios (ORs) and 95% confidence intervals (CIs). Variables with a P value of less than 0.1 were included in the multivariate analysis and a P value of less than 0.05 was considered to be statistically significant. All analyses were performed with IBM SPSS statistics, version 23.0 (IBM Corp, Armonk, NY).

Results

Included Patients

A total of 71 out of 94 invited hospitals participated in this Snapshot study. Long-term outcomes of 2095 patients who underwent resection for rectal cancer in 2011 were registered. Out of these 2095 patients, 998 underwent an LAR with anastomosis, with or without diverting stoma, and were included for the present analysis. Median completeness of data was 100.0% (IQR 96.7–100). Median follow-up was 43 (IQR 25–47) months. The patient and tumor characteristics are displayed in Table 1. Median distance from the lower border of the tumor to the anorectal junction on preoperative magnetic resonance imaging was 8 (IQR 6–10) cm. Any form of neoadjuvant therapy was given to 886 patients (88.8%), consisting of short-course radiotherapy in 481 patients and chemoradiotherapy in 273 patients (Table 2). A laparoscopic approach was applied in 510 patients (52.5%). The anastomosis was stapled in 96.3%, had a side-to-end configuration in 73.8%, and was diverted in 73.9%.

Anastomotic Leakage

Anastomotic leakage was diagnosed in 200 of 998 (20.0%) of the patients during complete follow-up. Median time to diagnosis of the leak was 15 (IQR 6–67) days. The reported postoperative anastomotic leakage rate in the original DSCA database was 82 of 998 (8.2%). Retrospective review of the files in the present Snapshot study revealed that the number of anastomotic leakages that were diagnosed within 30 days appeared to be 134 (13.4%). Beyond 30 days, another 66 patients were diagnosed with an anastomotic leakage (Figure 1).

The baseline characteristics of the patients with and without anastomotic leakage are presented in Table 1, and distribution of neoadjuvant therapy and surgical details among the 2 groups in Table 2. There was no difference in leak rate between open or laparoscopic surgery (21.2% and 19.0%; P = 0.39). Diverting stoma was not significantly related to overall leak rate: 19.4% with stoma versus 21.9% (P = 0.38) without stoma, but 30-day leak rate was significantly higher in patients without a diverting stoma

Table 1. Baseline characteristics

	LAR (n=998)	Anastomotic Leak (n=200, 20.1%)	No Anastomotic leak/sinus (n= 798, 79.9%)	P- value
Sex (male)[1]	631/997 (63.3%)	133/200 (66.5%)	498/797 (62.5%)	p= 0.29
< 60 yr	342/998 (34.3%)	71/200 (35.5%)	271/798 (34.0%)	P=0.06
61-70 yr	344/998 (34.5%)	79/200 (39.5%)	265/798 (33.2%)	
> 70-80 yr	271/998 (27.2%)	47/200 (23.5%)	224/798 (28.1%)	
> 80 yr	41/998 (4.1%)	3/200 (1.5%)	38/798 (4.8%)	
ASA I[2]	317/973 (32.6%)	68/195 (34.9%)	249/778 (32.0%)	P=0.86
ASA II	532/973 (54.7%)	103/195(52.8%)	429/778 (55.1%)	
ASA III	123/973 (12.6%)	24/195 (12.3%)	99/778 (12.7%)	
ASA IV	1/973 (0.1%)	0	1/778 (0.1%)	
BMI[3] < 25	395/939 (42.1%)	77/192 (40.1%)	318/747 (42.6%)	P=0.76
BMI 25-30	418/939 (44.5%)	90/192 (46.8%)	328/747 (43.9%)	
BMI > 30	126/939 (13.4%)	25/192 (13%)	101/747 (13.5%)	
Diabetic[4]	101/631 (16.0%)	23/125 (18.4%)	78/506 (15.4%)	P=0.42
Nondiabetic	530/631 (84%)	102/125 (81.6%)	428/506 (84.6%)	
Tumour characteristics: Distance to the anorectal junction[5]				
≤ 3cm	58/777 (7.5%)	18/163 (11%)	40/614 (6.5%)	P= 0.05
3.1-7.0 cm	284/777 (36.6%)	65/163 (39.9%)	219/614 (35.7%)	
> 7 cm	435/777 (56.0%)	80/163 (49.1%)	355/614 (57.8%)	
Pathological staging[6]				
pT0	72/969 (7.4%)	13/195 (6.7%)	59/774 (7.6%)	P=0.69
pT1	79/969 (8.2%)	16/195 (8.2%)	63/774 (8.1%)	
pT2	329/969 (34.0%)	58/195 (29.7%)	271/774 (35.0%)	
pT3	462/969 (47.7%)	102/195 (52.3%)	360/774 (46.5%)	
pT4	27/969 (2.8%)	6/195 (3.1%)	21/774 (2.7%)	
pN+[7]	349/961 (36.3%)	65/193 (33.7%)	284/768 (37%)	P=0.39
M1[8]	62/868 (7.1%)	13/180 (7.2%)	49/689 (7.1%)	P=0.96

[1] Gender was unknown in 1 patient. [2] ASA classification was unknown in 25 patients. [3] BMI was unknown in 59 patients. [4] The diabetic status was not reported/unknown in 367 patients. [5] Tumour distance was not reported in 221 patients. [6] T-stadium was unknown in 29 patients. [7] N-stadium was unknown in 37 patients. [8] M-stadium was unknown in 130 patients. BMI indicates body mass Index.

compared to those with a stoma (19.2% vs 11.4%; P < 0.01). Patients receiving any form of neoadjuvant therapy had a significantly higher overall leak rate compared to patients who did not receive neoadjuvant therapy: 21.6% versus 8.0% (P = 0.001), with OR of 3.15 (95% CI 1.56–6.33) in univariate analysis (Table 3). The 30-day leak rate was also significantly higher in patients receiving neoadjuvant therapy: 14.4% versus 5.4% (P = 0.008), respectively. There was no difference in 30-day and overall leak rate

Table 2. Perioperative characteristics

	LAR (n=998)	Anastomotic Leak (n=200, 20.1%)	No Anastomotic leak/sinus (n= 798, 79.5%)	p-value
Neoadjuvant therapy				
Any form	886/998 (88.8%)	191/200 (95.5%)	695/798 (87.1%)	P=0.001
SCRT (5x5 Gy)	481/998 (48.2%)	105/200(52.5%)	376/798 (47.1%)	P=0.03
CRT	273/998 (27.5%)	63/200 (31.5%)	210/798 (26.3%)	
Other RT schedule	22/998 (2.2%)	4/200 (2%)	18/798 (2.3%)	
Only chemotherapy	7/998 (0.7%)	2/200 (1%)	5/798 (0.6%)	
Neoadjuvant treatment regimen unknown	103/998 (10.3%)	17/200 (8.5%)	86/798 (10.8%)	
Surgical characteristics				
Laparoscopic approach[1]	510/973 (52.4%)	97/195 (49.7%)	413/778 (53.1%)	P=0.40
Elective[2]	958/974 (98.4%)	194/195 (99.5%)	764/778 (98.2%)	P=0.17
Diverting stoma	738/998 (73.9)	143/200 (71.5%)	595/798 (74.6%)	P=0.38
Unintentional permanent stoma[3]	151/915 (16.5%)	82/178 (46.1%)	67/793 (8.9%)	P<0.01
Type of anastomosis[4] Side to end End to end	 694/940 (73.8%) 243/940 (25.9%)	 139/190 (73.2%) 51/190 (26.8%)	 555/747 (74.3%) 192/747 (25.7%)	 P=0.75
Technique of anastomosis[5] Stapled Handsewn	 936/972 (96.3%) 36/972 (3.7%)	 193/198 (97.5%) 5/198 (2.5%	 743/774 (96.0%) 31/774 (4.0%)	 P=0.33

[1] Surgical approach was unknown in 24 patients. [2] Urgency of the operation was unknown in 14 patients. [3] A stoma was deemed permanent when present more than a year after the index operation, 83 patients were dead or lost to follow-up within the first year. [4] Type of anastomosis was unknown in 58 patients. [5] technique of anastomosis was unknown in 16 patients. CRT indicates chemoradiotherapy; RT, radiotherapy; SCRT, short-course radiotherapy.

between patients receiving short-course radiotherapy (5 x 5 Gy) or long-course chemoradiotherapy: 14.8% versus 16.8% (P = 0.45) within 30 days and 21.8% versus 23.1% (P = 0.69) at the end of follow-up, respectively. A tumor distance from the anorectal junction less than 3 cm was significantly associated with a higher risk of anastomotic leakage compared to more proximal tumors (OR 2.00, 95% CI 1.09–3.66). In multivariable analysis, tumor distance within 3 cm from the anorectal junction and neoadjuvant therapy were independent predictors for anastomotic leakage at any time during follow-up with an OR of 1.88 (95% CI 1.02–3.46, P = 0.04) and 2.85 (95% CI 1.00–8.11, P = 0.049), respectively (Table 3).

The 30-day mortality rate in patients with anastomotic leakage was 1.0%, and 1.5% (P = 0.58) in patients without anastomotic leakage. Corresponding 90-day mortality rates were 3.0% and 1.9% (P = 0.34), respectively.

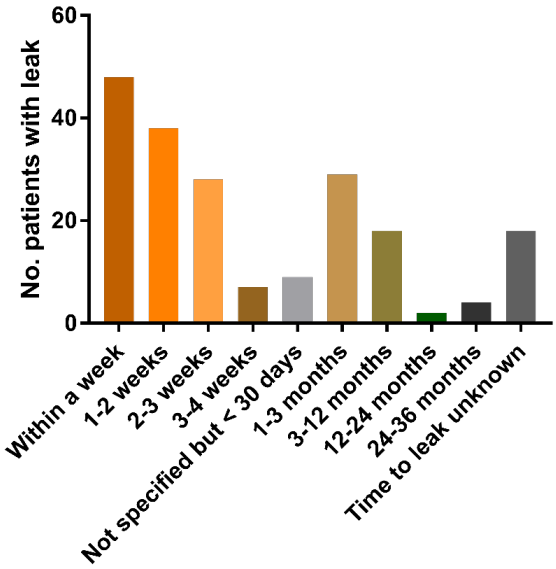

Figure 1. Time to diagnosis of anastomotic leak.

Chronic Sinus

A persistent presacral abscess was present in 85 of 893 evaluable patients (9.5%). Of 200 patients with an anastomotic leakage diagnosed at any time during follow-up, 22 patients died or were lost to follow-up within the first year after surgery and from 1 patient the data on chronic sinus was missing. Of the 177 remaining patients, 85 were diagnosed with a chronic sinus, which corresponds with a nonhealing rate of anastomotic leakage of 48.0% at 12 months.

There was no difference in the incidence of chronic sinus between open or laparoscopic surgery: (8.9% vs 9.9%; P = 0.59), stapled versus hand-sewn anastomosis (9.0% vs 3.1%; P = 0.25). A chronic sinus was observed less frequently after the early (<30 days) versus late (>30 days) diagnosed leak (39.5% vs 65.6%; P <0.01). Neoadjuvant therapy was administered in 81 (95.3%) of the 85 patients with a chronic presacral sinus. The chronic sinus rate was 81 of 796 (10.2%) for patients receiving neoadjuvant therapy compared to 4 of 97 (4.1%) for patients without neoadjuvant treatment (P = 0.07).

An unintentional permanent stoma was present in 82 (46.1%) of the patients with an anastomotic leak, compared to 67 (8.9%) in the patients without anastomotic leakage (P < 0.01).

Table 3. Univariable and multivariable analysis of predictors for anastomotic leak diagnosed at any time during median 43 months of follow-up

Variable	Univariable analysis		Multivariable analysis	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Male	1.92 (0.86-1.65)	0.29	-	
Age				
< 61	1 (reference)		1 (reference)	-
61-70	1.14 (0.79-1.64)	0.49	1.40 (0.93-2.11)	0.10
71-80	0.80 (0.54-1.21)	0.29	0.95 (0.60-1.51)	0.83
> 80	0.30 (0.09-1.01)	0.05	0.63 (0.18-2.20)	0.47
ASA physical status 3/4	0.95 (0.59-1.53)	0.84		
Any neoadjuvant treatment	3.15 (1.56-6.33)	0.001	2.85 (1.00-8.11)	0.049
BMI >30	0.96 (0.60-1.53)	0.87	-	
Diverting stoma	0.87 (0.61-1.21)	0.38	-	
Laparoscopic approach	0.88 (0.64-1.20)	0.40	-	
Distance to the anorectal junction				
≤ 3cm	2.00 (1.09-3.66)	0.03	1.88 (1.02-3.46)	0.04
3.1 – 7 cm	1.32 (0.91-1.90)	0.14	1.28 (0.88-1.85)	0.20
>7 cm	1 (reference)		1 (reference)	

BMI indicates body mass index.

Interventions for Anastomotic Leakage

At least 1 intervention for anastomotic leakage was reported in 144 of 200 (72.0%) patients. The total number of interventions was 186. Figure 2 presents the different types of interventions being performed in 5 different time periods. For each time period, the interventions were classified based on whether it was the first procedure, a second intervention, or the third (or more) intervention for a particular patient. Within 30 days, 116 (63%) interventions were carried out, of which 106 (91%) were first interventions. Initial 30-day interventions were take down of the anastomosis with end colostomy in 28 (26.4%) patients, followed by surgical drainage in 25 (23.6%) and construction of a diverting ileostomy in 15 (14.2%) patients. If the first intervention was performed after 30 days, surgical drainage was the most frequently applied procedure in 12 of 38 (31.6%). If no intervention for anastomotic leakage was performed, 24 (47.1%) of 51 evaluable patients developed a chronic sinus at 12 months. In patients who underwent any type of intervention for anastomotic leakage and who were still alive at 12 months, 60 of 127 (47.2%) had a chronic presacral sinus.

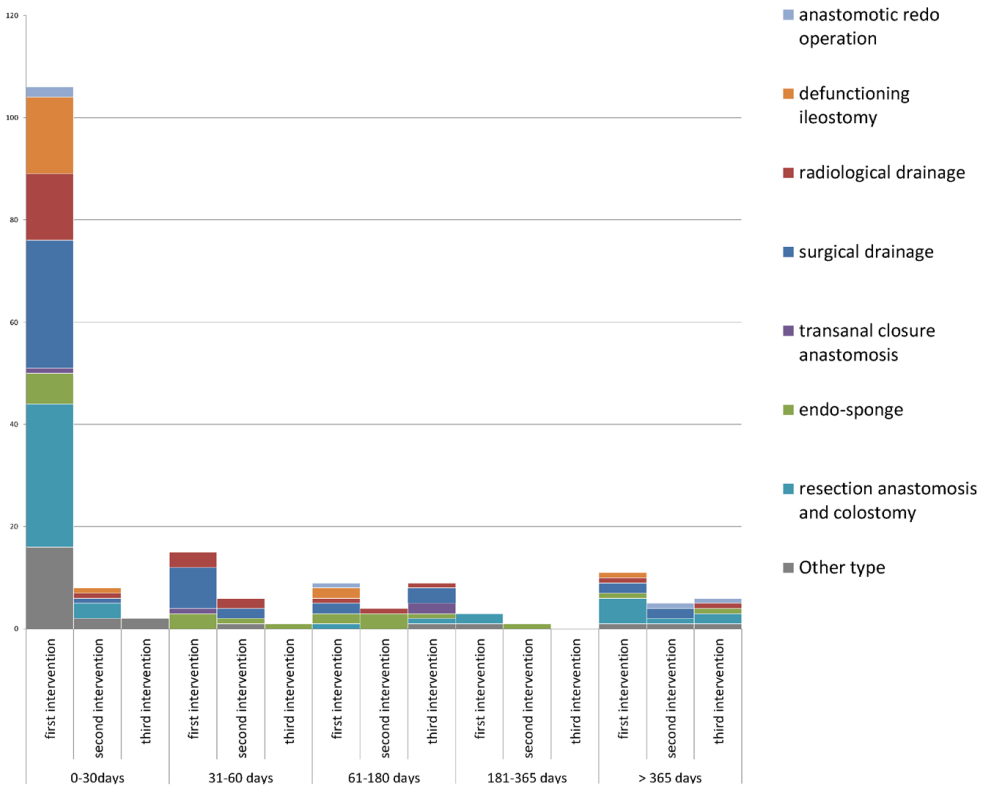

Figure 2. Type of intervention and timing of intervention for anastomotic leak.

Discussion

This large cross-sectional study of 998 rectal cancer patients who underwent LAR with primary anastomosis in 2011 showed that approximately one third of the anastomotic leaks were being diagnosed beyond 30 days postoperatively. Almost half of the anastomotic leaks eventually developed into a chronic sinus after 12 months. Neoadjuvant therapy and a distal tumor location (<3 cm) were independent risk factors for being diagnosed with anastomotic leakage at any time during 43 months of follow-up. Several leak-related reinterventions were performed in 72% of the patients, with a similar incidence of chronic sinus compared to those not undergoing any reintervention.

The observed anastomotic leak rate during complete follow-up is high in comparison to the literature.[10,12,15,18] One of the explanations is the fact that the present study also

included late diagnosed anastomotic leaks. Leakage rates are often reported until 30 days or in hospital.[7,19–21] One can question whether surgical complications can be adequately assessed during the often cited 30-day timespan as a substantial proportion of complications may be diagnosed outside this immediate postoperative period. This is also being underlined by our observed mortality rates in patients with anastomotic leakage, which increased from 1% at 30 days to 3% at 90 days. Another explanation is that some atypical leakages are not always included in the definition, for example, those presenting as rectovaginal fistula, or presacral abscesses without identified anastomotic defect.

Randomized trials on the role of diverting ileostomy include relevant data, because of detailed prospective data collection specifically focused on anastomotic leakage. The landmark study by Matthiessen et al[22] reported a similar overall leakage rate of 19.2% (45/234) compared to our study. Interestingly, the difference in 30-day leak rate in favor of patients with a diverting stoma, diminished after a longer follow-up period. This strengthens our hypothesis that anastomotic leakage will occur irrespective of fecal diversion, but that diagnosis of the leak is delayed if a diverting stoma is present. Preoperative radiotherapy was applied in 79.1% of the patients, with a 20.7% leak rate in irradiated patients and 13.3% in the no-radiotherapy group, which was not significantly different due to sample size. The initial diverting stoma appeared to be permanent in 13.8%, and the permanent stoma rate in the nondiverting arm of the study was 16.9%. Our 16.5% overall permanent stoma rate was slightly higher (Table 2).

The almost routine use of radiotherapy in the Netherlands in 2011 as a result of the former Dutch guideline, is likely to be one of the main contributors to the high observed leakage rate and the impaired secondary healing of the anastomosis as presented by the 48% nonhealing rate.[23] Interestingly, previous prospective cohort series, randomized controlled trials and systematic reviews all have contradicted the correlation between neoadjuvant radiotherapy and an increased risk of anastomotic leakage.[7,19–21,24–26] However, in a post-hoc analysis of the Dutch TME trial, preoperative radiotherapy was an independent predictor of nonreversal of a secondary stoma.[27] Anastomotic leakage was the reported reason for secondary stoma formation in 66%. But actually this proportion seemed to be almost 100% since anastomotic leakage–related complications such as abscess, sepsis, peritonitis, or fistula were reported in an additional 25% of the patients. Remaining causes were bleeding (1%), stenosis (2%), and other/unknown factors (5%). After 7.1 years of follow-up, 51% of the secondary stomas were not reversed, which is comparable to the 46.1% permanent stomas after anastomotic leakage found in the present study. The nonreversal of intentionally temporary stoma's in patients who underwent LAR indicates that there is a substantial problem of nonhealing of anastomotic leaks with a significant impact of radiotherapy.[27]

Late diagnosed anastomotic leaks, both symptomatic and asymptomatic, constitute a treatment dilemma. It is unclear whether a long existing leakage with delayed onset of symptoms can appropriately be treated with a diverting ileostomy alone or whether major salvage surgery is necessary. Extensive follow-up is required to answer this question, because secondary fistula originating from a chronic presacral sinus can develop even after more than 20 years, with a fistula tract following a route of less resistance than the anal sphincter (ie, along the piriformis muscle or the trochanteric region).[14] For patients, it often means impaired quality of life related to an unintentional permanent stoma, secondary complications of persisting leakage or need for major salvage surgery.[11,27–30] The overall proportion of chronic sinus of 9.5% in this large multicenter cohort indicates that this is a significant clinical condition that requires more evaluation to determine the long-term implications and the optimal treatment strategy.

The literature on chronic sinus is scarce, but available series show the clinical impact it might have.[12,14,28] A chronic sinus can present with a variety of symptoms and, if not or inadequately treated, may lead to severe problems such as hydronephrosis related to stricturing fibrosis of the ureter at the level of the sinus, osteomyelitis, and even necrotizing fasciitis.[14,28] Patients with a chronic sinus are often subject to multiple interventions in an attempt to control the infectious problems in the pelvis with associated morbidity, hospital stay, and costs.[15,28,29]

A possible limitation of this study is the fact that it was decided not to include clinical symptoms in the definition of anastomotic leak as clinical symptoms are difficult to retrieve from electronic patient files and, consequently, are multi-interpretable. Therefore it was not possible to make a distinction between symptomatic and asymptomatic anastomotic leaks. Nevertheless, the high nonhealing rate and potential risks of a chronic sinus suggests that even the “asymptomatic leaks” are of clinical importance in the end. Furthermore, some of the data were lacking related to the retrospective study design.

In conclusion, this large cross-sectional study showed that a high percentage of rectal cancer patients undergoing LAR are eventually being diagnosed with an anastomotic leak, and that almost half of the anastomotic leaks developed into a chronic sinus. This was significantly associated with radiotherapy. Even though the literature on chronic sinus is scarce, it appears to be a substantial clinical problem that deserves a higher awareness.

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CHAPTER 2

Impact of an institutional change from routine to highly selective diversion of a low anastomosis after TME for rectal cancer

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Abstract

Introduction

The need for routine diverting ileostomy following restorative total mesorectal excision (TME) is increasingly debated as the benefits might not outweigh the disadvantages. This study evaluated an institutional shift from routine (RD) to highly selective diversion (HSD) after TME surgery for rectal cancer.

Materials and methods

Patients having TME with primary anastomosis and HSD for low or mid rectal cancer between December 2014 and March 2017 were compared with a historical control group with RD in the preceding period since January 2011. HSD was introduced in conjunction with uptake of transanal TME.

Results

In the RD group, 45/50 patients (90%) had a primary diverting stoma, and 3/40 patients (8%) in the HSD group. Anastomotic leakage occurred in 10 (20%) and three (8%) cases after a median follow-up of 36 and 19 months after RD and HSD, respectively. There was no postoperative mortality. An unintentional stoma beyond 1 year postoperative was present in six and two patients, respectively. One-year stoma-related readmission and reoperation rate (including reversal) after RD were 84% and 86%, respectively. Corresponding percentages were significantly lower after HSD (17% and 17%; $P < 0.001$). Total hospital stay within one year was median 11 days (IQR 8-19) versus 5 days (IQR 4-11), respectively ($P < 0.001$).

Conclusion

This single institutional comparative cohort study shows that highly selective defunctioning of a low anastomosis in rectal cancer patients did not adversely affect incidence or consequences of anastomotic leakage with a substantial decrease in 1-year readmission and reintervention rate, leading to an overall significantly reduced hospital stay.

Introduction

Anastomotic leakage following restoration of continuity is still a feared complication. The incidence is related to several patient and procedural factors, with a reported proportion of patients developing anastomotic failure after total mesorectal excision (TME) as high as 28%.[1-3] This still poses a major challenge with a significant impact on oncological outcome, quality of life and socioeconomic costs.[4-7]

The routine construction of a diverting ileostomy to protect the anastomosis is common practice after TME surgery. This is based on a meta-analysis of randomized trials showing lower anastomotic leakage rates and less urgent re-operations after a diverting stoma.[8] However, a recent Dutch population based study revealed that the long term anastomotic failure rate with or without diverting stoma is similar, that the diagnosis is delayed in the defunctioned patients, and the possibilities to salvage the anastomosis are reduced.[9,10] Furthermore, a diverting stoma itself significantly adds to the morbidity of rectal cancer surgery.[11] A substantial proportion of patients will endure complications such as peristomal dermatitis or infection, or require admission due to stoma dysfunction (e.g. obstruction at the stoma site or dehydration caused by high output stoma). Eventual stoma closure requires another readmission and intervention with associated morbidity.[12]

In the Netherlands, the use of routine diversion is increasingly debated, and selective omission of a diverting stoma by some centres has shown to be safe.[13] At the Academic Medical Centre, we decided to change our practice regarding routine diverting ileostomies in December 2014, at the time that transanal TME (TaTME) was introduced at our unit. Abandoning the routine use of diverting ileostomy after TME was in line with our longstanding policy of no routine diversion after restorative proctocolectomy with ileo-anal pouch anastomosis.[14] Furthermore, this was embedded in a protocol of day 4 CRP measurements with CT imaging for any suspicion of leakage, and based on the anticipated better healing of the double pursestring single stapled anastomosis after TaTME.

The aim of this study was to evaluate the institutional shift from routine defunctioning (RD) to highly selective defunctioning (HSD), with respect to management of anastomotic leakage and stoma-related outcome in TME surgery for rectal cancer.

Material and methods

Study design and patients

All consecutive patients having TME with primary stapled anastomosis for adenocarcinoma of the lower and middle rectum at our university hospital between January 2011 and March 2017 were retrospectively identified from a prospectively maintained database. The institutional shift from RD to HSD in December 2014 divided the cohort into two groups of patients. This institutional shift was paralleled with a shift from conventional laparoscopic TME (LaTME) to transanal TME (TaTME). Exclusion criteria were other diagnosis than primary rectal cancer, partial mesorectal excision, a primary open approach of the abdominal phase, and a handsewn anastomosis.

The Institutional Review Board of the Academic Medical Centre in Amsterdam, the Netherlands, concluded that written informed consent was not required for the present study since the data were retrospectively collected and analysed anonymously.

Procedure

All procedures were performed or supervised by at least one of two specialised colorectal surgeons (WAB and PJT). Preoperative measures included mechanical bowel preparation and intravenous antibiotics just before incision. The splenic flexure was completely mobilised with high ligation of the inferior mesenteric vein in all procedures. Preferably the superior rectal artery was transected with preservation of the left colic artery, and a high ligation of the inferior mesenteric artery was only performed for oncological reasons (suspected central lymph nodes) or to gain additional bowel length. No specific tests were used to check the blood supply of the new colonic conduit. In the LaTME group, all patients had a double stapled anastomosis and construction of a diverting ileostomy as a rule with exceptions according to the surgeons' intraoperative judgement in combination with age and/or explicit wish of the patient. An air leak test was not performed as a routine, while the pelvis was routinely drained for 48 h. In the TaTME group, a double purse string, single stapled anastomosis was constructed after which the staple line was reinforced transanally with a continuous transmural MonoPlus® 3-0 suture (B. Braun Medical Inc.). Configuration of the anastomosis was preferably side-to-end. Postoperative management was according to enhanced recovery after surgery (ERAS) protocols, that were already implemented before the study period.[15] At day 4 postoperatively, CRP measurements were performed as a routine, and in case of any suspicion for anastomotic leakage, a CT scan with intraluminal contrast was performed to assess the anastomosis.

Outcome measures

Data collection included baseline characteristics, operative details, early postoperative outcome and follow-up until 12 months postoperatively. Primary endpoint was anastomotic leak rate at one year. Secondary endpoints were length of postoperative stay following the index procedure, overall complication and mortality rate within 30 days, unintentional stoma rate beyond one year postoperatively, stoma-related morbidity, readmission and reoperation rate within one year, and total hospital stay within one year postoperatively.

Definitions

In case of clinical suspicion of anastomotic leak, CT imaging with rectal contrast was performed. Anastomotic leakage was defined as the presence of either an early (<30 days) or late (>30 days) leak, including anastomotic fistula, abscess at the level of anastomosis (regardless of contrast extravasation), or any anastomotic contrast extravasation on imaging studies (including patients without symptoms) within one year postoperatively.

Overall complications were defined using the Clavien-Dindo classification of surgical complications[16], and only complications related to the index procedure were registered. If patients underwent multiple reinterventions within 30 days, each separate category was scored (e.g. if a patient underwent both a percutaneous reintervention and a relaparoscopy, both radiological and surgical procedures were scored). With respect to stoma-related morbidity; each separate stoma-related complication, readmission or reoperation was counted. An ileus was scored as 'stoma-related', when it occurred while having a stoma or directly postoperative following stoma closure. Unintentional stoma rate beyond one year postoperatively included presence of the primary diverting stoma, permanent colostomy after take down of initial colorectal/coloanal anastomosis, and patients who got another diverting stoma for missed leakage after initial stoma closure.

Statistical analysis

Data were presented according to distribution with means ± standard deviation (SD) or medians with interquartile range (IQR). Numerical data were compared according to normality with either a T-test or Mann-Whitney U test, and categorical data with the Chi square or Fischer's exact test. Kaplan-Meier analyses were used to calculate time to anastomotic failure and stoma-free survival. If a patient underwent primary stoma reversal, but subsequently received a secondary stoma due to anastomotic leakage, the patient was analysed as still having a stoma. Significance was set at $P < 0.05$. All analyses were performed with IBM SPSS statistics, version 24.0.0 (IBM Corp., Armonk, NY, United States). The STROBE guidelines for observational studies were adhered to.[17]

Results

A total of 124 patients underwent TME with primary anastomosis between January 2011 and March 2017. After exclusion of patients with an underlying pathology other than primary rectal cancer (n = 12), partial mesorectal excision (n = 13), primary open approach of the abdominal phase (n = 1), handsewn anastomosis (n = 6), or missing operation report (n = 2), a total of 90 cases remained in the analysis. Of the included patients, 50 patients (56%) underwent LaTME with RD, and 40 (44%) underwent TaTME with HSD. A primary diverting stoma was performed in 45 of 50 (90%) in the RD group, and in 3 out of 40 (8%) in the HSD group. Patients' demographics are described in Table 1. Overall, patients were predominantly male (72%) and mean age was 61 (±11) years. Patient characteristics were comparable among the two groups, except for a higher proportion of neoadjuvant chemoradiotherapy in the RD group (P = 0.016) and more distal tumours in the HSD group (P = 0.014). Operative details are displayed in Table 2.

Incidence and management of anastomotic leakage

Median follow-up was 36 and 19 months after TME with RD and HSD, respectively. There were no significant differences in anastomotic leak rate between the groups. Anastomotic leakage rate at one year postoperatively was 20% (10 of 50) after RD and 8% (3 of 40) after HSD (P = 0.094). At 30 days, corresponding leak rates were 12% (6 of 50) and 8% (3 of 40) (P = 0.726). After RD, anastomotic leakage was managed by radiological drainage (n = 2), endoclip closure (n = 1), endo-sponge® treatment followed by transanal closure (n = 3), or at least one surgical reintervention (n = 4). At one year postoperatively, out of ten patients that developed an anastomotic leak two still had a primary diverting ileostomy due to a chronic sinus, two needed another stoma after initial closure due to a missed anastomotic leak, and one required a permanent colostomy.

After HSD, anastomotic leakage occurred in three patients of which two were managed by antibiotics alone. Of the latter two patients, one had primary diversion based on anticipated high risk of leakage intra-operatively, and the other patient did not need secondary diversion. Both were free from stoma at one year. The remaining patient had faecal diversion prior to the index procedure for primary obstructing tumour, and was treated by multiple endosponge ® changes followed by transanal closure of the anastomotic defect. However, the patient developed an anastomotic fistula to the urethra following stoma closure, which did not heal. Eventually, intersphincteric resection of the anastomosis with omentoplasty and permanent colostomy was performed.

The median duration between TME and clinical diagnosis of anastomotic leakage was 14 days (range 5-142) after RD, and 4 days (range 1-5) after HSD (P = 0.014). In the RD

Table 1. Baseline characteristics

		Group A	Group B	
		RD[a] *(n=50)*	HSD[b] *(n=40)*	P-value
Gender	Male	37 (74)	28 (70)	0.674
Age	Years ± SD	61 ± 12	62 ± 9	0.550
Body-mass index	Kg/m^2 ± SD	26 ± 4	26 ± 3	0.960
ASA-classification	ASA 1	21 (42)	15 (38)	0.665
	ASA 2	27 (54)	23 (58)	0.740
	ASA 3	2 (4)	2 (5)	1.000
Comorbidity	Diabetes	6 (12)	6 (15)	0.677
Cigarette smoking	Current smokers	9 (19)	12 (31)	0.212
Tumour distance[c]	< 3 cm	3 (6)	10 (25)	0.014
	3-7 cm	45 (94)	30 (75)	0.014
Neoadjuvant therapy	Short course radiotherapy	13 (26)	8 (20)	0.504
	Chemoradiotherapy	25 (50)	10 (25)	0.016
Adjuvant chemotherapy	Total	3 (6)	1 (3)	0.626
Pathological tumor stage	Stage I	18 (36)	10 (25)	0.263
	Stage II	14 (28)	11 (28)	0.958
	Stage III	15 (30)	14 (35)	0.614
	Stage IV	3 (6)	5 (13)	0.458
Follow-up duration	Months (IQR)	36 (24-47)	19 (13-27)	<0.001

N=number of patients; ASA-classification= American Society of Anesthesiologists classification; categorical data presented in number with percentages and continuous data are presented according to distribution in means with standard deviation (SD) or in medians with interquartile range (IQR).
[a] Routine defunctioning.
[b] Highly selective defunctioning.
[c] Distance from lower border of the tumour to the anorectal junction on sagittal MRI.

group, anastomotic leakages continued to develop until 6 months, while in the HSD group the incidence of anastomotic leakage stabilised after one week, (Figure 1A; P = 0.115 (log-rank test)). Of evaluable patients with a postoperative day four CRP level of 150 mg/L or more, 19% had anastomotic leakage, versus 8% of patients with a postoperative day four CRP level below 150 mg/L (P = 0.342).

Surgical outcome

Median length of postoperative stay after the index procedure was significantly longer after RD (6 days (IQR 5-11)) compared to HSD (5 days (IQR 4-6); P < 0.001). Within 30 days after surgery, neither overall postoperative complication, readmission, reintervention nor mortality rates differed significantly between RD and HSD (Table 3).

Table 2. Operative details

		Group A	Group B	
		RD[a] *(n=50)*	**HSD**[b] *(n=40)*	**P-value**
Type of surgery	LaTME[c]	50 (100)	0 (0)	-
	TaTME[d]	0 (0)	40 (100)	-
Surgical approach	Laparoscopic	50 (100)	40 (100)	-
Conversion	Total	1 (2)	0 (0)	1.000
Additional resection	Total	6 (12)	4 (10)	1.000
Specimen extraction	Transanally	0 (0)	31 (80)	<0.001
	Pfannenstiel	49 (98)	9 (23)	<0.001
	Laparotomy	1 (2)	0 (0)	1.000
Diverting stoma	None	4 (8)	32 (80)	<0.001
	Primary	45 (90)	3 (8)	<0.001
	Secondary	0 (0)	2 (5)	0.195
	Preexistent[e]	1 (2)	3 (8)	0.319
Type of diverting stoma	Ileostomy	44 (88)	5 (13)	<0.001
	Colostomy	2 (4)	3 (8)	0.652
Anastomotic configuration	Side-to-end	41 (87)	32 (87)	1.000
	End-to-end	2 (4)	5 (14)	0.232
	Side-to-side	1 (2)	0 (0)	1.000
	J-pouch	3 (6)	0 (0)	0.252
Intraoperative complication	Total	1 (2)[f]	2 (5)[g]	0.583
Operative time	Minutes (IQR)	240 (210-290)	262 (243-312)	0.012

N=number of patients; categorical data presented in number with percentages and continuous data are presented according to distribution in means with standard deviation (SD) or in medians with interquartile range (IQR).
[a] Routine defunctionin.
[b] Highly selective defunctioning.
[c] Laparoscopic total mesorectal excision.
[d] Transanal total mesorectal excision.
[e] Prior to the index procedure for obstructing primary tumour.
[f] Wrongly inserted stoma.
[g] Included damage to arterial arcade and urethra damage

At one year postoperatively, 8% (4 of 50) of the patients after RD never had a stoma, compared to 80% (32 of 40) after HSD (P < 0.001). Although it was standard practice to construct a stoma in the RD group, four patients did not have a diverting stoma constructed, which was related to a combination of factors, such as young age, explicit wish of the patient, and intraoperative judgement of sufficient quality of the anastomosis by the surgeon. In HSD, three patients had defunctioning stoma prior to surgery for obstructing tumour, three had primary diversion due to suspected high

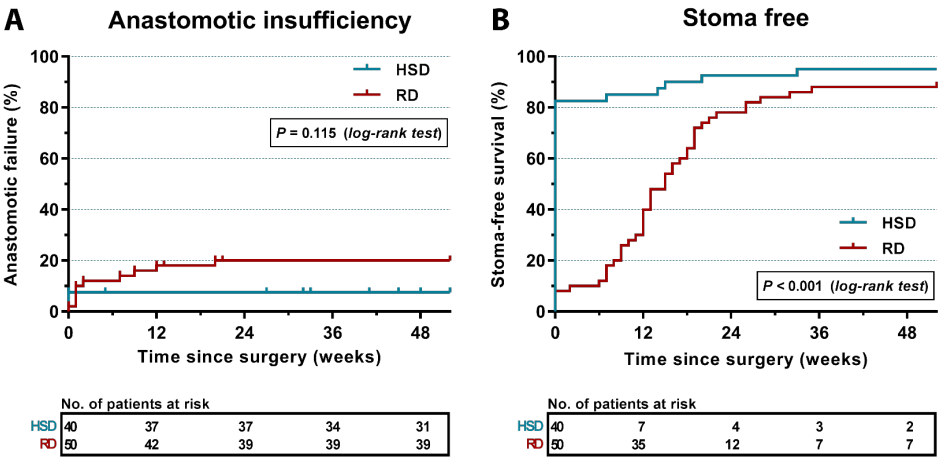

Figure 1. Kaplan-Meier curves showing anastomotic failure (Figure 1A) and stoma-free survival (Figure 1B) over time after routine (RD) and highly selective diversion (HSD).

Table 3. Postoperative outcome within 30 days

		Group A	Group B	
		RD[a] *(n=50)*	HSD[b] *(n=40)*	P-value
Hospital stay[c]	Days (IQR)	6 (5-11)	5 (4-6)	<0.001
Complication	Overall	19 (38)	11 (28)	0.294
	Surgical	16 (32)	8 (20)	0.201
Clavien-Dindo	Grade 1	7 (14)	1 (3)	0.071
	Grade 2	4 (8)	6 (15)	0.330
	Grade 3	7 (14)	3 (8)	0.502
	Grade 4	1 (2)	1 (3)	1.000
	Grade 5	0 (0)	0 (0)	-
	Grade ≥ 3	8 (16)	4 (10)	0.405
Readmission	Total	3 (6)	1 (3)	0.626
Reintervention	Total	16 (32)	9 (23)	0.317
	Surgical	2 (4)	3 (8)	0.652
	Radiological	4 (8)	2 (5)	0.689
	Endoscopic	4 (8)	0 (0)	0.126

N=number of patients; categorical data presented in number with percentages and continuous data are presented according to distribution in means with standard deviation (SD) or in medians with interquartile range (IQR).
[a] Routine defunctioning.
[b] Highly selective defunctioning.
[c] Postoperative hospital stay duration.

risk of anastomotic failure, and two had stoma formation during follow-up: one for local recurrence requiring abdominoperineal resection (APR) and one due to postoperative purulent peritonitis with proven integrity of the anastomosis. At one year follow-up, bowel continuity in the HSD group was restored in all but two patients, compared to six patients in the RD group (Figure 1B).

Stoma-related complications occurred more frequently after RD (24 of 50 (49%)) than after HSD (5 of 40 (13%); Table 4). The overall stoma-related readmission rate within one year postoperatively was 84% in the RD group and 15% in the HSD group ($P < 0.001$). After RD, 86% of the patients had returned to theatre for a stoma-related problem including stoma closure, compared to 15% after HSD ($P < 0.001$). Total in-hospital stay within one year was median 11 days (IQR 8-19) after RD versus median 5 days (IQR 4-10) after HSD ($P < 0.001$).

Discussion

The present single institutional comparative cohort study evaluated the omission of routine faecal diversion during TME for rectal cancer. HSD appeared to be safe compared to RD with respect to anastomotic leakage rate, its clinical consequences and management, and unintentional stoma rate. Additionally, a significant reduction in stoma-related morbidity, and a considerably shorter hospitalisation period were observed after HSD.

It still is routine practice to construct a diverting stoma during TME surgery in most centres worldwide. However, the diverting stoma itself is substantially adding morbidity to TME surgery, related to its construction, its presence during several months, and reversal.[12,18-22] We observed stoma-related morbidity in 24 patients (49%) after RD, which is comparable to reported literature.[23] In the Netherlands, it is increasingly debated whether the advantages of a diverting stoma outweigh the disadvantages. If proven to be safe, omission of a diverting stoma in TME surgery would mean a significant reduction in treatment associated morbidity for rectal cancer patients. By abandoning routine defunctioning, we were able to reduce stoma related complications and to cut total one year in-hospital stay in half. This difference can mainly be attributed to the extra hospitalisations required for stoma closure.

It is believed that a covering stoma decreases anastomotic leak rate and mitigates the consequences of anastomotic failure. Moreover, many fear that patients who develop anastomotic leakage and did not have their anastomosis defunctioned, are more likely to lose their anastomosis permanently. In the current study, all patients in the HSD group who were not defunctioned prior to surgery or during surgery were

free from stoma at end of follow-up. Only two patients eventually had a permanent colostomy; one after APR for local recurrence, and one patient with a persisting anastomotic fistula to the urethra. Uncontrollable pelvic sepsis was not observed and there was no postoperative mortality. Although patient numbers are relatively small, this single institutional experience suggests that a diverting stoma can safely be omitted in a setting of close postoperative monitoring, without loss of continuity in case of leakage.

A recent publication from the international TaTME registry analysing 1594 patients found an anastomotic failure rate of 15.7% including early and delayed leak, pelvic abscess, anastomotic fistula, chronic sinus and anastomotic stricture.[24] The discrepancy with the 8% leakage rate of the current study may be related to several differences in study population (e.g. underlying disease, rate of neoadjuvant therapy, tumour height), or anastomotic leak definition and detection, but is more likely to be caused by the small numbers in the current study. Our overall anastomotic leak rate of 20% after LaTME is identical to the leakage rate as found in a recent collaborative snapshot study on rectal cancer surgery in 998 patients from 71 Dutch hospitals.[9] Rate of diverting stoma was 73.9%, chronic sinus 9.5%, and unintentional permanent stoma 16.5%. Neoadjuvant radiotherapy was revealed to be an important risk factor for developing anastomotic leakage and chronic sinus, and its application has since been substantially reduced following revision of the Dutch guidelines. This explains the baseline difference in radiotherapy between the RD and HSD group. The historical comparison with some important differences in baseline characteristics do not allow for any meaningful comparison between the leak rates of LaTME and TaTME, based on the present study. Hypothetically, the anastomosis might be improved after TaTME. First, the rectal stump is closed with a purse string suture, instead of cross stapling as performed in LaTME, which often needs multiple staple firings with increased risk of leakage.[25] Second, the use of a double purse string and single stapled anastomosis during TaTME avoids the typical 'dog ears' which occur after the double stapling anastomosis in LaTME. Potential superiority of TaTME versus LaTME needs to be evaluated in a randomized study such as the COLOR III.[26]

There are some limitations to this study. For one, a limitation may be the low numbers. Second, length of follow-up in the HSD group was only a median of 19 months. Also, we implemented TaTME at the same time as changing our primary diverting strategy, making it difficult to interpret actual risk of anastomotic leakage. On the other hand, regardless of the confounded comparison with respect to anastomotic leakage, we were able to show an important reduction in construction of diverting stomas and related need for reinterventions and hospital stay, without seeming to risk preservation of bowel continuity despite a learning curve effect in our

first series of TaTME's. Another limitation may be related to potential sampling bias. This population is a convenience cohort of rectal cancer patients treated between 2011 and March 2017 in one academic centre, and therefore the results may not be generalisable to all rectal cancer patients and other centres. The findings of this study need to be confirmed in larger prospective studies in different clinical settings.

Conclusion

In this single institutional comparative cohort study it appeared that the omission of routine diversion after TME did not increase anastomotic leak rate or unintentional stoma rate, although this finding should be confirmed in other studies. But if proven and widely implemented, this will substantially improve patient outcomes by significantly reducing the need for a temporary diverting stoma, resulting in a markedly lower hospitalisation duration and return to theatre. Not only could this translate into a better quality of life, but also in lower costs.[27]

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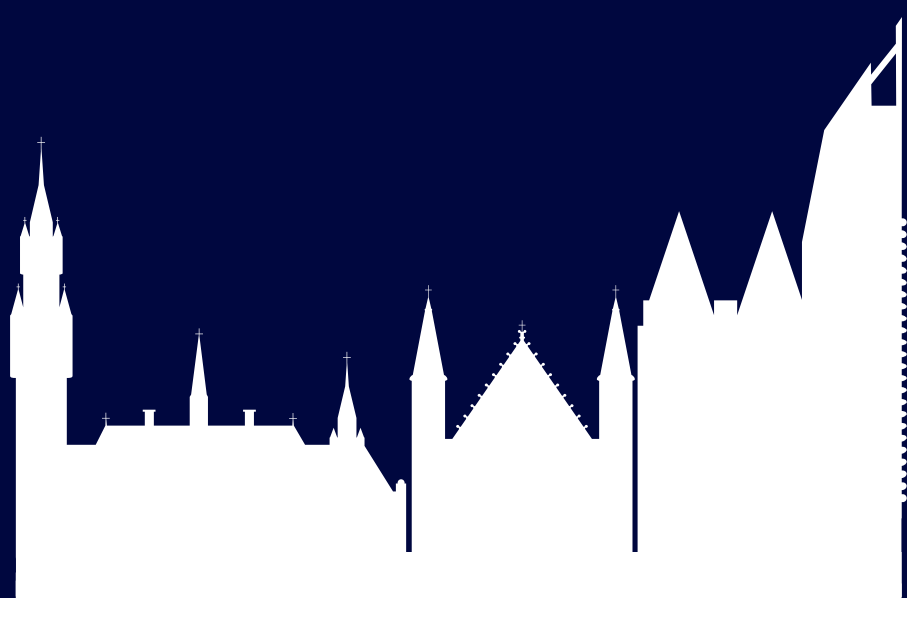

PART TWO

Non-restorative rectal cancer resection

CHAPTER 3

Low Hartmann's procedure or intersphincteric abdominoperineal resection in the primary treatment of low rectal cancer; a survey among surgeons evaluating current practice

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Abstract

Background

Low Hartmann's procedure (LHP) and intersphincteric abdominoperineal resection (iAPR) are both surgical options in the treatment of distal rectal cancer when there is no intention to restore bowel continuity. This study aimed to evaluate current practice among members of the Dutch Association of Coloproctology (WCP).

Methods

An online survey among members of the WCP who represent 66 Dutch hospitals was conducted. The survey consisted of 15 questions addressing indications for surgical procedures and complications.

Results

Surgeons from 37 hospitals (56%) responded. Thirty-six percent does not distinguish low from high Hartmann's procedures based on estimated length of the rectal remnant. Overall, iAPR was the preferred technique in 86%. If asking whether operative approach would be different in tumours at 1 cm from the pelvic floor compared to 5 cm distance, 62% stated that they would consider a different technique. The incidence of pelvic abscess after LHP was thought to be higher, equal or lower than iAPR in 36%, 36% and 21%, respectively, with the remaining respondents not answering this question.

Conclusions

The vast majority of the respondents considers iAPR as the preferred non-restorative procedure for rectal cancer not invading the sphincter complex, which contradicts with population based data from 2011.

Introduction

Colorectal cancer (CRC) is one of the top three most commonly diagnosed cancers worldwide in both males and females.[1] In the Netherlands, 15,000 new cases of CRC have been diagnosed in 2016, of which 4000 new cases of rectal cancer.[2] In rectal cancer, we primarily focus on resection of the tumour followed by restoration of bowel continuity, but frequently encountered problems after restorative surgery, such as anastomotic leakage and poor functional outcome have to be taken into account. Anastomotic leakage of a colorectal or coloanal anastomosis has been reported to occur in up to 21%[3,4], and recent studies focussing on the low anterior resection syndrome score (LARS score) show incidences of major LARS of 33 and 56%.[5,6] Considering these high incidences of anastomotic leakage and poor functional outcome, restoring bowel continuity might not always be the best option in specific patient populations, despite this is technically achievable and oncologically safe. Such patients are, for example, frail elderly patients or those with multiple comorbidities irrespective of age. Low Hartmann's procedure (LHP) and intersphincteric abdominoperineal resection (iAPR), both with the creation of a definitive colostomy, have been described as surgical procedures for resection of distal rectal cancer without invasion of the sphincter complex when bowel continuity is not desired. LHP has been associated with high rates of pelvic abscesses, but literature is inconsistent.[7-10] Data on the risk of pelvic abscess after iAPR are even more scarce.[10-12] This lack of evidence forces colorectal surgeons to base their choice for either LHP or iAPR as non-restorative treatment for distal rectal cancer on mere experience.

The aim of this study was to gain insight into current preferences regarding indication and surgical technique, as well as opinions on infectious complications considering its incidence and preferred treatment following LHP and iAPR. This survey among Dutch colorectal surgeons was intended to be a first step towards guidelines for the treatment of rectal cancer not invading the sphincter complex, and without the intention to restore continuity.

Materials and methods

Survey

An online survey consisting of 15 questions regarding LHP and iAPR as primary treatment for rectal cancer was sent to members of the Dutch Association of Coloproctology (WCP) in October 2016, representing 66 Dutch hospitals. The WCP aspires to ensure at least one representative from every Dutch hospital. A reminder

was sent by email in December 2016 to all representatives who did not respond after the first email. The survey contained questions about the definition of the LHP, choices in operative technique in ultralow tumours (<1 cm from the pelvic floor) and more proximal tumours (<5 cm), the choice for LHP or iAPR as primary treatment strategy, the use of omentoplasty in iAPR, estimated incidence of pelvic abscesses subsequent to both LHP and iAPR and the treatment of pelvic abscesses after LHP. The complete survey can be found in Appendix 1.

Operative techniques

In order to clearly outline the procedures being discussed in this survey, a description was included. In LHP, a rectal resection according to TME principle is performed, with transection and closure of the rectum below the tumour, and creating an end colostomy.[13] In iAPR, the anoderm is incised by a perineal approach, continuing the TME dissection in the intersphincteric plane, with preservation of the external sphincter, levator muscles and puborectal muscle. No rectal remnant is left behind and an end colostomy is created.[11]

Data extraction and statistical analysis

Data were collected using an online survey tool. All data were collected anonymously and processed using IBM SPSS Statistics for Windows (Version 24.0. Armonk, NY: IBM Corp). According to distribution, numerical data were reported as median with range or interquartile range (IQR) or mean with standard deviation (SD). Categorical variables were presented as number and proportion in percentages.

Results

Response rate at hospital level was 37 out of 66 (56%). Of four hospitals with multiple locations, multiple surgeons representing each location responded, resulting in a total number of responding surgeons of 42. Representatives of six out of eight Dutch academic hospitals responded, 23 teaching hospitals and eight non-teaching hospitals. An overview of the respondents' characteristics is shown in Table 1.

LHP and iAPR

In total, 36% of the respondents (n=15/42) stated not to distinguish between a high or low Hartmann's procedure. Figure 1 shows the distribution of the definition of a low Hartmann's procedure as reported by all responding surgeons. When there is no oncological indication to perform a conventional or extralevator APR, 86% (n=36/42)

Table 1. Respondents' characteristics.

Responding hospitals	**Total, n (%)**	**37/66 (56)**
Type of hospital	Academic hospital, n (%)	6/37 (16)
	Teaching hospital, n (%)	23/37 (62)
	Non-teaching hospital, n (%)	8/37 (22)
Number of responding surgeons	Total, n	42
Experience of responding surgeons	1-10 years, n (%)	20/42 (48)
	11-20 years, n (%)	18/42 (43)
	21+ years, n (%)	3/42 (7)
	Unknown, n (%)	1/42 (2)
Patients operated for rectal cancer per hospital	Annually, median (IQR)	50 (38-72)
Operations for rectal cancer per surgeon	Annually, median (IQR)	25 (20-30)
Surgeons performing Hartmann procedures for rectal cancer	Total, n (%)	35/42 (83)

of the responding surgeons consider an iAPR as the preferred procedure in low rectal cancer when there is no intention to restore bowel continuity. Twenty-six respondents (62%) indicated that they would consider a different operative technique in a tumour located at one centimetre (cm) from the pelvic floor than in a tumour located at 5 cm. Not all choices were clarified, but the most frequently stated reason was that in ultralow tumours (one cm from the pelvic floor) an iAPR is more frequently considered than in more proximal tumours. Regarding the definitions of a low Hartmann's procedure and the choice for operative technique in tumours at 1 and 5 cm from the pelvic floor, 21% (n=9/42) reported that there is no consensus within their hospital.

Omentoplasty in iAPR is always performed by 45% (n=19/42) of the surgeons, 36% (n=15/42) performs an omentoplasty selectively and 19% (n=8/42) never performs an omentoplasty in iAPR. Thirty-two surgeons (76%) reported consensus in their hospital regarding the creation of an omentoplasty.

Pelvic abscess

Of all responding surgeons, 36% (n=15/42) believes that a pelvic abscess occurs more frequently after LHP than after iAPR, 36% (n=15/42) believes that pelvic abscesses occur in a similar rate after both LHP and iAPR and 21% (n=9/42) thinks that iAPR results in more pelvic abscesses than LHP. Three correspondents did not answer this question. The majority of the respondents (27/42, 64%) use transanal drainage as preferred treatment for pelvic abscesses after LHP with percutaneous drainage on indication, while 14% (n=6/42) always use transanal drainage and 14% (n=6/42) prefer percutaneous drainage and transanal drainage on indication. Three respondents did

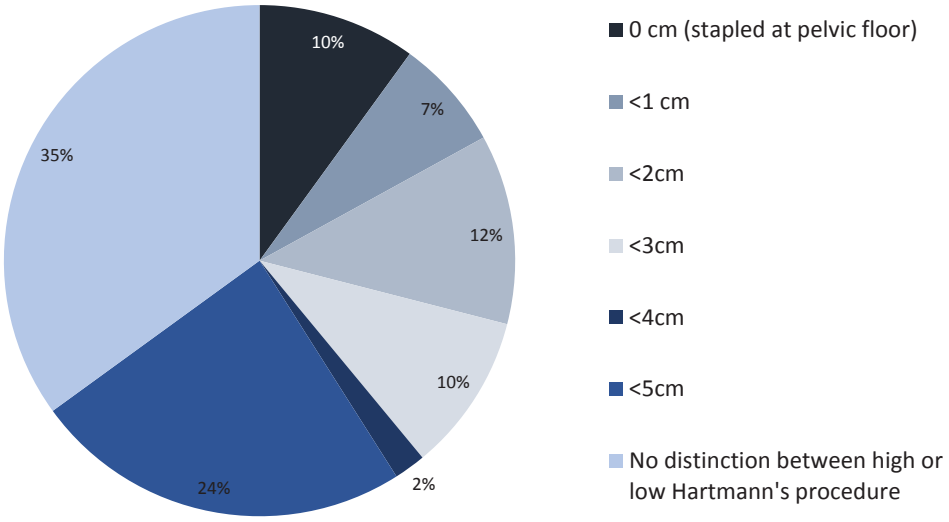

Figure 1. At what expected length of the rectal remnant do you consider a Hartmann's procedure as a *low* Hartmann's procedure?

not answer this question. In total, 29/42 surgeons (69%) indicated that there was a consensus in their unit regarding the treatment of pelvic abscesses subsequent to LHP, 11/42 (26%) reported no consensus regarding this topic and two respondents (5%) did not answer this question.

Discussion

This study shows that there is no consensus regarding operative technique for non-restorative surgery in the primary treatment of rectal cancer within the community of Dutch colorectal surgeons. It shows that 86% of the surgeons consider iAPR as the preferred procedure, but 21% indicates that there is no consensus within their hospital regarding the specific use of LHP or iAPR if considering tumours at 1 or 5 cm distance from the pelvic floor. Omentoplasty following iAPR is used in 81% of the respondents, either as a routine or on indication. Abscesses after LHP are preferably drained through the rectal stump, with 14% preference for percutaneous drainage, but 26% of respondents indicate absence of consensus on this topic within their units.

The high rate of 86% of surgeons who consider iAPR as the preferred technique in this specific group of rectal cancer patients is noteworthy. A recent publication by the Dutch Snapshot Research Group, reporting on cross-sectional data on the treatment

of rectal cancer in the Netherlands in 2011, shows that non-restorative surgery consisted of 25% iAPR and 75% LHP [12]. Possible explanations for this discrepancy might be related to the relatively low response rate with limited representativity, the restricted intra-hospital consensus, and historical changes in decision making (between 2011 and 2016). The iAPR technique has gained popularity over the last years as an alternative to LHP, probably related to some literature reports on relatively high abscess rates after LHP.[7-9]

The lack of consensus on preferred operative technique might be explained by the differences in expected complications. This survey shows that there is a difference in expectations among surgeons regarding the pelvic abscess rate after both iAPR and LHP. Probably, surgeons who expect a higher rate of pelvic abscesses after LHP will prefer an iAPR and vice versa. The variety in opinions regarding the risk of pelvic abscess subsequent to both techniques is not surprising, since literature on this topic is also inconclusive. There are only few small and retrospective studies which report on pelvic abscess rate after Hartmann's procedure, with varying rates between 3 and 33%.[7-10,14] Tøttrup and Frost[9] reported an incidence of pelvic abscesses of 33%, when in the Hartmann's procedure the rectum was transected within 2 cm of the pelvic floor. In contrast, Sverrisson et al. reported an incidence of only 3% in patients who had a Hartmann's procedure of which 90% was stapled just above or at the pelvic floor. Therefore, it is still unclear if the length of the rectal remnant influences the risk of pelvic abscess formation.[9,14] Pelvic sepsis has been reported between 6 and 17% following iAPR with end colostomy.[10-12] Also, a 30% rate of perineal wound problems after iAPR has been described.[15] This finding might also influence surgeons in choosing between LHP and iAPR, but this aspect was not included in the survey.

The HAPIrect trial is an ongoing randomized multicentre trial comparing Hartmann's procedure and iAPR as primary treatment for rectal cancer, also including patients with rectal cancer with tumours up to 5 cm from the anal verge.[16] The lowest of these tumours are of specific interest, since it can be hypothesized that a shorter rectal remnant is more likely to break down and cause pelvic sepsis, possibly favouring the iAPR in this group. Since the *(ultra)low* Hartmann's procedure might be more prone to complications than the more proximal procedure, it is of importance to distinguish between the two. Of all surgeons, 36% does not distinguish between high or low Hartmann's procedure, and within the remaining 64% there is no consensus on the definition of a low procedure. Similar to the respondents of this survey, literature is not consistent on the definition of a low Hartmann's procedure.

Performing an omentoplasty can potentially reduce the incidence of pelvic abscess by filling the pelvic cavity and because of its physiological properties such as the promotion of angiogenesis and immunological effects. This was confirmed in a recent

review showing a reduction of perineal wound morbidity after APR when an omentoplasty is created.[17] A large cross-sectional study in the Netherlands, however, revealed no reduction of pelvic abscesses after APR with primary closure of the perineal wound and omentoplasty compared to primary closure without omentoplasty.[18] The present survey found that only 19% of respondents never perform an omentoplasty in iAPR, despite conclusive evidence on the additional value and the need for additional dissection and increase in operating time.

Limitation of this study is the low response rate of 56%, which could lead to nonresponse errors. However, it has been demonstrated that a low response rate does not necessarily influence the outcome and the representativeness of the respondents is more important than the actual response rate.[19,20] We do believe to have reached a representative sample of Dutch colorectal surgeons by contacting members of the WCP from each hospital throughout all the Netherlands, with respondents from academic, teaching as well as non-teaching hospitals.

Clearly, there is a need for more high-quality studies and guidelines regarding the primary treatment of rectal cancer without restoration of bowel continuity, especially since the frail elderly patients with multiple comorbidities are a growing population; a population wherein the surgeon and patient might choose to avoid the risks of a leaking anastomosis or poor functional outcome after restoration of bowel continuity by creating a definitive colostomy.

Conclusions

There is no consensus among colorectal surgeons in the Netherlands regarding the choice for LHP or iAPR as primary treatment for patients with distal rectal cancer without the intention to restore bowel continuity. The majority prefers iAPR, which is in contradiction to published Dutch daily practice 5 years earlier. The lack of consensus on the definition of LHP and the varying thoughts on pelvic abscess formation following the two procedures reflects the ambiguity on this topic in current literature.

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Appendix 1. Survey

Survey: resection without a primary anastomosis for distal rectal cancer: which operative technique do you prefer?

This survey contains 15 open and multiple choice questions and will take 2-3 minutes to fill out.

The survey addresses patients with distal rectal cancer in whom a resection with distal stapling of the rectum is feasible in order to achieve an oncological safe resection margin and in whom an anastomosis is deemed undesirable, either preoperatively or intraoperatively and an definitive end colostomy is created. In these patients three different operative techniques remain possible: low Hartmann's procedure (LHP), abdominoperineal resection (APR) and the intersphincteric resection (ISR).

* Mandatory question

1. What is the name of your hospital? *
Obtained results will not be able to be traced back to individual hospitals.

2. How many years have you been working as a gastrointestinal surgeon?*

3. How many patients with rectal cancer do you operate on annually?*

4. How many patients with rectal cancer are operated annually in your hospital?*

5. Do you perform Hartmann's procedures for rectal cancer?
- o Yes
- o No
- o Not me, but other surgeons in my hospital do.

6. Until what length of the rectal remnant do you consider a procedure a LOW Hartmann's procedure?*
- o A rectal remnant of 0 cm (stapled at the pelvic floor)
- o A rectal remnant of ≤1cm
- o A rectal remnant of ≤2cm
- o A rectal remnant of ≤3cm
- o A rectal remnant of ≤4cm

- o A rectal remnant of ≤5cm
- o I do not distinguish between high or low Hartmann's procedures.

7. Is your choice of treatment (considering operative technique) different in tumours located at 1cm from the pelvic floor than in tumours at 5cm from the pelvic floor? *

If selected "yes", please specify the differences in treatment and your considerations under "other".

- o Yes
- o No
- o Other:

8. Regarding question 6 and 7: is there consensus in your hospital? *

Please specify under "other".

- o Yes
- o No
- o Other:

9. If there is NO oncological indication to perform an APR, do you consider an intersphincteric resection (ISR)?

Please specify under "other".

- o Yes
- o No
- o Not me, but other surgeons in my hospital do.
- o Other:

10. Do you perform an omentoplasty in APR or ISR? *

If selected "always", please specify the technique you use for the omentoplasty under "other".

- o Never
- o Always
- o If indicated
- o Other:

11. Regarding question 10: is there consensus in your hospital? *

Please specify under "other".

- o Yes
- o No
- o Other:

12. Which statement do you believe is correct? *

- o The low Hartmann's procedure causes MORE pelvic abscesses than the APR or ISR.
- o The low Hartmann's procedure causes SIMILAR rates of pelvic abscesses as the APR or ISR.
- o The low Hartmann's procedure causes LESS pelvic abscesses than the APR or ISR.
- o Other:

13. When a pelvic abscess occurs after a Hartmann's procedure my preferred treatment is: *

- o Always transrectal drainage (through the rectal remnant)
- o Always percutaneous drainage (mostly transgluteal approach)
- o Mostly transrectal drainage, percutaneous drainage when indicated
- o Mostly percutaneous drainage, transrectal drainage when indicated
- o Other:

14. Regarding question 13: is there consensus in your hospital? *

Please specify under "other".

- o Yes
- o No
- o Other:

15. Comments:

CHAPTER 4

Low Hartmann's procedure or intersphincteric proctectomy for distal rectal cancer: a retrospective comparative cohort study

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Abstract

Purpose

Two non-restorative options for low rectal cancer not invading the sphincter are the low Hartmann's procedure (LH) or intersphincteric proctectomy (IP). The aim of this study was to compare postoperative morbidity with emphasis on pelvic abscesses after LH and IP.

Methods

All patients that had LH or IP for low rectal cancer were included in three centres between 2008 and 2014 in this retrospective cohort study. Follow-up was performed for at least 12 months.

Results

A total of 52 patients were included: 40 LH and 12 IP. Median follow-up was 29 months (IQR 23). There were no differences between groups in gender, age and ASA classification. Seven patients in the LH group (18%) and four patients in the IP group (33%) developed a complication within 30-day postoperative with a Clavien-Dindo classification grade III or higher (P = 0.253). Four out of 40 patients (10%) in the LH group and two out of 12 patients (17%) in the IP group developed a pelvic abscess (P = 0.612). Reinterventions were performed in 11 (28%) patients in the LH group and five (42%) patients in the IP group (P = 0.478), with a total number of reinterventions of 13 and 20, respectively. Six and 15 interventions were related to pelvic abscesses, respectively.

Conclusion

Pelvic abscesses seem to occur in a similar rate after both LH and IP. Previous reports from the literature suggesting that IP might be associated with less infectious pelvic complications compared to LH are not supported by this study, although numbers are small.

Introduction

The surgical treatment of distal rectal cancer which does not involve the sphincter complex or pelvic floor is total mesorectal excision (TME) with or without restoration of continuity. To avoid the risks or poor function of a low anastomosis in frail elderly patients, a low Hartmann's procedure (LH) can be performed, creating a small rectal stump and an end colostomy. Alternatively, an intersphincteric proctectomy (IP) with resection of the rectal stump and end colostomy has been proposed in these specific patients.[1,2]

If compared to IP, LH has no risk of perineal wound complications. However, LH has been associated with high rates of pelvic abscesses, especially in case of a short rectal stump (< 2 cm).[1-3] Leaving a rectal stump could lead to stasis of rectal contents above the internal sphincter with the risk of staple line rupture and pelvic abscess formation. Persisting mucus production and diversion proctitis might result in long-term complaints of pain and discharge.

After IP, the rectum is completely resected with preservation of the pelvic floor and the perineal wound is limited. IP has been proposed to be a better solution than LH in patients who are no candidate for a coloanal anastomosis based on a high operative risk or expected poor bowel function. However, there is only little data available to conclude on the best surgical approach. Therefore, the aim of this study was to compare postoperative morbidity with emphasis on pelvic abscesses after LH and IP with a minimum follow-up of 12 months.

Methods

Patients

All patients from one academic medical centre (Academic Medical Centre Amsterdam) and two teaching hospitals (Tergooi Hospital Hilversum and Maasstad hospital Rotterdam) in the Netherlands who underwent a LH or IP with a permanent colostomy for primary distal rectal cancer between 2008 and 2014 were identified. Distal rectal cancer was defined as when the lower border of the tumour was within 5 cm from the anorectal junction, indicated by the upper margin of the puborectal muscle on MRI. LH or IP was considered oncologically safe by the multidisciplinary team, when considering the lower margin of the tumour. Inclusion of patients was restricted to any form of preoperative radiotherapy, the procedure being performed or supervised by a colorectal surgeon, and curative intent in order to reduce heterogeneity.

Surgical procedures

LH consisted of an oncological rectal resection according to the TME principle, thereby creating an end colostomy and a stapled rectal remnant.[5,6] LH could have been performed both open or laparoscopically. IP was performed using open or laparoscopic approach for the abdominal phase and with the patient either in prone position or lithotomy position for the perineal phase. Following an incision of the anoderm, the dissection was continued in the intersphincteric plane, preserving the external sphincter, levator muscles and puborectal muscle. Perineal closure was performed by layered suturing of the external sphincter and perineal skin in the midline.[7,8]

Data extraction

Patient and treatment characteristics were retrospectively collected from patient records. Patient charts, radiology reports and operative reports were searched for patient demographics, tumour location and primary treatment characteristics. Tumour stage, circumferential resection margin (CRM), tumour perforation and lymphatic and extramural vascular invasion were extracted from the pathology report. Patient files were further searched for hospital stay, complications, reinterventions, readmissions, local recurrence, distant metastases and mortality.

Outcome

Major postoperative complications within 30 days were defined as Clavien-Dindo grade three or higher. This includes all complications requiring surgical, endoscopic or radiological intervention (grade three), life-threatening complications requiring intensive care management (grade four) or death (grade five).[9,10] Pelvic abscesses and reinterventions and readmissions related to the primary surgical intervention were recorded until end of follow-up. It was decided that at least 1 year of follow-up was needed to ensure complete reporting of outcomes. If 1 year follow-up was not available in the patient files, the general practitioner or other hospitals if applicable were contacted to obtain further information regarding outcome measures. Surgical and oncological follow-up was conducted according to Dutch guidelines for rectal cancer or more frequent if necessary.[4]

Definitions

A pelvic abscess was defined as a fluid collection in the pelvic cavity as demonstrated on computed tomography (CT). Reinterventions were defined as surgical, endoscopic or radiological intervention either without anaesthesia or under local or general anaesthesia. Postoperative outcome was defined as events occurring within 30 days of surgery. Chronic presacral sinus was defined as a persistent pelvic abscess at least 1 year after surgery.

Statistical analysis

According to distribution, numerical data were reported as median with range or interquartile range (IQR) or mean with standard deviation (SD). Categorical variables were presented as number and proportion in percentages. Comparison between groups for discrete variables was made by the Chi-square test, the Chi-square test for trend or the Fischer exact test when appropriate. The independent t test was used to compare normally distributed continuous variables and the Mann-Whitney U test was used to compare continuous variables not normally distributed. Survival rates were calculated using the Kaplan-Meier method and compared between groups using the log-rank test. $P \leq 0.05$ was considered statistical significant. Analyses were performed using IBM SPSS Statistics for Windows (Version 23.0. Armonk, NY: IBM Corp).

Results

A total of 52 patients were included, 34 patients from Tergooi hospital, 11 from the Maasstad Hospital and seven from the Academic Medical Centre. Forty patients were treated with LH and 12 patients with IP, all in elective setting. A total of seven different surgeons performed all procedures. Baseline characteristics are described in Table 1. A non-restorative procedure was based on a patient-based expected high risk of anastomotic leakage or poor function. In the IP group, there were significantly more low tumours than in the LH group ($P = 0.046$). The intraoperative characteristics are displayed in Table 2. The median duration of surgery was 145 min (IQR 61) in the LH group and 297 min (IQR 138) in the IP group ($P < 0.001$). There were no multivisceral resections, but three patients underwent a simultaneous procedure: hysterectomy because of uterine leiomyomas with suspicion of cancer, right hemicolectomy because of synchronous colon cancer and left adnexectomy for varicocele. Two patients with stage 4 disease underwent a synchronous resection of metastases; one patient underwent a lobectomy of the left lower lobe because of a metastasis in the lung and one patient had a metastasectomy of the liver. Pelvic drains were placed during the index procedure in 35 patients (88%) in the LH group and in eight patients (67%) in the IP group ($P = 0.076$). Significantly, more patients in the IP group underwent omentoplasty (50 vs. 13%; $P = 0.011$). Three patients had intra-operative complications. There was one patient with tumour perforation at pathological examination in the LH group. The circumferential resection margin (CRM) was at least 1 mm in all patients (Table 3).

Table 1. Baseline characteristics

	LHP (n=40)	**IP** (n=12)	**P value**
Sex			1.000
Male	24 (60%)	7 (58%)	
Female	16 (40%)	5 (42%)	
Age (years), *mean (± SD)*	74 (± 10.2)	73 (± 7.0)	0.904
BMI, *median (IQR)*	25.0 (8.7)	25.9 (4.5)	0.585
ASA classification			0.264
1	3 (8%)	1 (8%)	
2	22 (55%)	9 (75%)	
3	15 (38%)	2 (17%)	
Height of tumour on MRI			0.046
1 cm	1 (3%)	5 (42%)	
2 cm	9 (23%)	2 (17%)	
3 cm	11 (28%)	0	
4 cm	8 (20%)	3 (25%)	
5 cm	11 (28%)	2 (17%)	
Preoperative treatment			
Short course radiotherapy	31 (78%)	7 (58%)	0.267
Long course chemo radiotherapy	9 (23%)	5 (42%)	0.189
Indication primary colostomy			0.777
Expected high risk of leakage considering patient related risk factors	29 (73%)	9 (75%)	
Expected poor functional outcome of ultra-low anastomosis	7 (18%)	1 (8%)	
Expected high risk of leakage related to quality of tissue	3 (8%)	1 (8%)	
Missing	1 (3%)	1 (8%)	
Timing of decision for permanent colostomy			0.287
Preoperative	23 (58%)	9 (75%)	
Intra-operative	16 (40%)	2 (17%)	
Missing	1 (3%)	1 (8%)	

BMI body mass index, *ASA* American Society of Anaesthesiology, *cm* centimetres

Postoperative outcome

Thirty-day postoperative major complications were observed in seven out of 40 patients (18%) in the LH group. Three patients developed a pelvic abscess within 30 days, treated by percutaneous drainage in one and transanal drainage under general anaesthesia in the two other patients. One patient had a fascial dehiscence which was operatively closed, and one patient had a bleeding from the rectal stump which was coiled. Two patients died within 30 days. Both patients developed peritonitis for which a relaparotomy was performed. One patient had a bowel perforation just below the stoma site, and one patient had a gastric perforation.

Table 2. Intra-operative characteristics

	LHP (n=40)	**IP** (n=12)	**P value**
Duration of surgery *Minutes, median (IQR)*	145 (61)	297 (138)	<0.001
Technique *Open* *Laparoscopic*	16 (40%) 24 (60%)	6 (50%)[a] 6 (50%)	0.740
Multivisceral resection	0	0	1.000
Omentoplasty	5 (13%)	6 (50%)	0.011
Tumour perforation	0	0	-
Pelvic drains *No* *Yes, 1 drain* *Yes, 2 drains* *Missing*	4 (10%) 33 (83%) 2 (5%) 1 (3%)	4 (33%) 8 (67%) 0 0	0.129
Duration pelvic drainage *Days, median (IQR)*	2 (2)	9 (9)	0.006
Intra-operative complications *Bleeding* *Bowel injury* *Subcutaneous emphysema*	1 (3%) 1 0 0	2 (17%) 0 1 1	0.129

[a] In one patient laparoscopic approach was converted to an open approach because of haemodynamic instability after subcutaneous emphysema

Table 3. Pathology

	LHP (n=40)	**IP** (n=12)	**P value**
ypTNM tumour stage *Stage 0* *Stage I* *Stage II* *Stage III* *Stage IV*	4 (10%) 13 (33%) 9 (23%) 13 (33%) 1 (3%)	2 (17%) 2 (17%) 5 (42%) 2 (17%) 1 (8%)	0.804
Tumour perforation at pathological examination	1 (3%)	0	1.000
Positive CRM	0	0	-
Lymphatic invasion	4 (10%)	1 (8%)	1.000
Extramural vascular invasion	3 (8%)	0	1.000

In the IP group, four out of 12 patients (33%) developed major complications, which was not significantly different from the LH group (P = 0.253). Transvaginal drainage of a pelvic abscess was performed under general anaesthesia in one patient and revision of a necrotic colostomy in another patient. One patient had a herniation of the appendix through a former drain opening, treated by open appendectomy. The fourth patient underwent relaparotomy for postoperative haemodynamic instability, but without the need for any intervention. There was no postoperative mortality in the IP group.

Long-term surgical outcome

Patients were followed for a median duration of 29 months (IQR 23); 26 months (IQR 26) in the LH group and 32 months (IQR 21) in the IP group (P = 0.957). The proportion of patients that developed a pelvic abscess at any time until end of follow-up, including short-term postoperative outcome, was four out of 40 (10%) in the LH group and two out of 12 (17%) in the IP group (P = 0.612).

Overall, five patients with a drain developed a pelvic abscess, compared to one patient without drain (P = 1.000). All patients in the LH group who developed a pelvic abscess were drained. Date of removal of the drain was reported in one patient, and the pelvic abscess was diagnosed 12 days after drain removal. Of both patients with a pelvic abscess in the IP group, one patient received intra-operative drainage and one did not. Date of removal of the drain was reported in one patient, who developed a pelvic abscess in the presence of a pelvic drain. Duration of drainage was significantly longer in the IP group compared to the LH group (P = 0.006), but duration of drainage was not associated with the risk of developing a pelvic abscess (P = 0.539).

Of the total of four patients with a pelvic abscess in the LH group, as partially described above, one patient was treated by percutaneous drainage and three patients were treated by transanal drainage. Two of the latter underwent a second transanal drainage. In the IP group, the second patient with a pelvic abscess underwent a total of 13 endo-sponge® (B. Braun Medical B.V., Melsungen, Germany) treatments with final closure of the perineum. All abscesses were treated successfully, and none of the patients developed a chronic presacral sinus.

Complications that required reintervention occurred in 11 patients (28%) in the LH group and five (42%) in the IP group (P = 0.478). A total of 13 patients were readmitted at any time until end of follow-up: nine out of 40 patients (23%) in the LH group and four out of 12 (33%) in the IP group (P = 0.466). An overview of all reinterventions and readmissions at any time during follow-up is presented in Table 4.

Table 4. Postoperative outcome

	LHP (n=40)	**IP** (n=12)	**P value**
Duration of admittance *Days, median (IQR)*	 15 (14)	 18 (28)	 0.170
Major complications within 30 days *Clavien-Dindo grade III*	7 (18%) 5 (13%)[b]	4 (33%) 4 (33%)[c]	0.253 0.185
Clavien-Dindo grade IV	0	0	-
Clavien-Dindo grade V	2 (5%)	0	1.000
Pelvic abscess[a]	4 (10%)	2 (17%)	0.612
Time between surgery and diagnosis pelvic abscess *Days, median (range)*	 20 (14-65)	 44 (7-81)	 1.000
Reintervention[a]	11 (28%)	5 (42%)	0.478
Two or more reinterventions[a]	2 (5%)	1 (8%)	0.553
Total number of reinterventions at any time during follow-up *Drainage of pelvic abscess* *Endo-sponge® treatment of pelvic abscess* *Closure of perineum* *Relaparotomy* *Correction of parastomal herniation* *Closure of fascial dehiscence* *Coiling of bleeding rectal stump* *Appendectomy* *Revision of necrotic colostomy*	13 6 0 0 3 2 1 1 0 0	20 1 13 1 1 2 0 0 1 1	-
Readmission[a]	9 (23%)	4 (33%)	0.466
Total number of readmissions *Pelvic abscess* *Stoma complications* *Fever* *Ileus* *Anaemia* *Herniation of appendix through drain opening*	12 5 3 3 1 0 0	7 3 2 0 0 1 1	-
Two or more readmissions[a]	3 (8%)	1 (8%)	1.000
Time between surgery and first readmission *Days, median (IQR)*	 18 (669)	 31 (88)	 0.643
Total duration of readmissions until end of follow-up *Days, median (IQR)*	 20 (15)	 5 (15)	 0.061
Total duration of readmissions due to pelvic abscess *Days, median (range)*	 15 (10-29)	 12 (7-16)	 0.639

[a] Number of patients, at any time during follow-up
[b] Including three patients with a pelvic abscess
[c] Including one patient with a pelvic abscess

Long-term oncological outcome

There were no local recurrences in both groups. Distant metastases were detected in six patients, all in the LH group (P = 0.316). The 3-year overall survival rate was 84% in the LH group and 92% in the IP group (log-rank test; P = 0.569).

Discussion

This multicentre retrospective cohort study showed that there is no significant difference in major complications (Clavien-Dindo grade III or higher) or overall pelvic abscess rate between LH group and IP.

There is a great variability in literature with respect to the rate of pelvic sepsis after IP and LH. Tøttrup et al. reported that LH was associated with a 19% pelvic abscess rate, which was even 33% in the subgroup of patients with a short Hartmann stump (less than 2 cm from the pelvic floor).[2] Sverrisson et al. reported a pelvic abscess rate of only 3% in patients undergoing LH.[11] Two other studies found a 12 and 17% pelvic abscess rate after LH, without clarification of the length of the stump.[1,3] The variability in the rate of pelvic sepsis might be explained by a different length of the rectum stump. Possibly, the ultrashort stumps are more likely to break down. Unfortunately, in the current study, the exact length of the rectal stump in the LH group could not be reliably assessed. The distal resection margin was too inconsistently reported on by the pathologist to be able to calculate an exact length. One may assume that lower tumours will result in a shorter rectal stump, but this study did not find a difference between the height of the tumour on MRI and the development of pelvic abscesses in the LH group (P = 0.965).

Abdominoperineal resection (APR) has been proposed as an alternative to LH, avoiding the risk of leakage of the rectal stump. However, studies comparing LH and APR show high incidences of infectious pelvic complications for both techniques and do not conclude on superiority of any technique.[1,3,12] IP has the potential to reduce the perineal wound complications compared to APR by preserving the external sphincter and pelvic floor. Eriksen et al. is one of the few authors who assessed the outcome after IP with permanent colostomy as primary treatment for rectal cancer in 50 patients.[7] They reported pelvic abscesses in three patients (6%), compared to two out of 12 (17%) in the IP group of the present study.

Apart from the length of the stump, the presence of an omentoplasty could affect the incidence of pelvic abscesses. Theoretically, the omentum fills up the dead space and the well-vascularized tissue with specific immunological capacities might have a positive influence on the risk of infectious pelvic complications. Even though an omentoplasty was performed significantly more often in IP compared to LH, this did not translate into a lower pelvic abscess rate. Posthoc analysis of the BIOPEX study on pelvic closure techniques after APR did not show any impact of an omentoplasty on perineal wound healing.[13] This study neither could find any impact of placement of a pelvic drain during the index surgery on the risk of pelvic abscess formation. The expected risk of blowout or leakage of the rectal stump may be a reason for the higher number of drainages in the LH group.

A long period of follow-up beyond 30 days postoperatively is a necessity when assessing complications of pelvic surgery, since they have extensive clinical consequences resulting in multiple reinterventions and readmissions over a prolonged period of time. This especially applies to patients who received neoadjuvant radiotherapy, resembling the patients in the current series. Not only does recent literature show that these patients are at higher risk of the formation of pelvic abscesses, they are also prone to delayed healing of the abscesses with even the risk of developing a chronic pelvic sinus.[14-16] The chronic pelvic sinus is a condition which is difficult to manage with a high impact on quality of life of the patient. Chronic purulent anal or perineal discharge, pain and drains cause considerable discomfort. Abscess drainage with rinsing of the sinus sometimes requires hospital admission or specialized care at home.

The LH group had a significantly shorter duration of surgery ($P < 0.001$). The possible explanation for this difference is multifactorial. Firstly, IP is a more elaborate technique with both an abdominal and a perineal phase, whereas LH only has an abdominal phase. Secondly, when the surgeon prefers the patient to be in prone position for the perineal phase, additional time is needed to turn the patient.

Limiting factor of this study is its retrospective design, which may have resulted in incomplete data. The small sample size and few events reduce the power to find significant differences between the groups and may also lead to a type II error in the findings of similar complication rates between groups in this study. Thirdly, we have not been able to assess the correlation between the length of the rectal stump and pelvic abscess formation. Despite these limitations, we do think that our data contribute to the scarce available data on this subject. The HAPIrect collaborative study group started a randomised trial comparing LH with IP, which will hopefully bring the final answer.[8]

Conclusion

Pelvic abscesses are a significant cause for reintervention and readmissions, and this study suggests that this complication occurs in a similar rate in patients with distal rectal cancer managed by LH or IP, although numbers are small.

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CHAPTER 5

What to do with the rectal stump during sphincter preserving rectal cancer resection with end colostomy: a collaborative snapshot study

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Abstract

Aim

Low Hartmann's resection (LHR) and intersphincteric abdominoperineal excision (iAPR) are both feasible options in the treatment of rectal cancer when restoration of bowel continuity is not desired. The aim of this study was to compare the incidence of pelvic abscess and associated need for re-intervention and readmission after LHR and iAPR.

Method

From a snapshot research project in which all rectal cancer resections from 71 Dutch hospitals in 2011 were evaluated, patients who underwent LHR or iAPR were selected.

Results

A total of 185 patients were included: 139 LHR and 46 iAPR. No differences in baseline characteristics were found except for more multivisceral resections in the iAPR group (22% vs 10%; P = 0.041). Pelvic abscesses were diagnosed in 17% of the LHR group after a median of 21 days (interquartile range 10–151 days), compared to 11% in the iAPR group (P = 0.352) after a median of 90 days (interquartile range 44–269 days; P = 0.102). All 28 patients with a pelvic abscess underwent at least one re-intervention. Four patients (9%) in the iAPR group and nine (7%) after LHR were readmitted because of a pelvic abscess over a median 39 months of follow-up.

Conclusion

This cross-sectional multicentre study suggests that cross-stapling and intersphincteric resection of the rectal stump, during non-restorative rectal cancer resection, are associated with an equal risk of pelvic abscess formation and have a similar need for re-intervention and readmission.

What does this paper add to the literature?

This study is one of the first to compare low Hartmann's resection and intersphincteric abdominoperineal resection with end colostomy as a primary treatment for rectal cancer. Both procedures are valid non-restorative surgical options used in times when there is an increased need for tailored surgery in high risk patients.

Introduction

Substantial comorbidity, old age and poor sphincter function are valid reasons to abort sphincter saving surgery in patients with rectal cancer. Restoring continuity in such patients might be fatal in case of an anastomotic leak. When it is not necessary to resect the anus and the pelvic floor for oncological reasons, these patients can be treated with sphincter preserving but non-restorative resection of the rectum. Options are either to cross-staple the distal rectum or to perform an intersphincteric excision of the rectal stump. The former is often referred to as a low Hartmann's resection (LHR) and the latter as an intersphincteric abdominoperineal excision (iAPR).

Some studies have reported high pelvic abscess rates after LHR, with a short rectal stump (≤ 2 cm) being a risk factor, suggesting that it is better to excise the remaining short rectal stump.[1] However, APR is also associated with a risk of pelvic abscess and perineal wound complications in up to 50% of patients.[2,3] Preserving the pelvic floor and external sphincter, using iAPR, has been suggested as an alternative technique to both LHR and conventional APR. Such a procedure will leave a less significant perineal wound and no rectal stump.[1,2,4] There are only a few studies regarding iAPR as primary treatment for rectal cancer and, to our knowledge, only one small study comparing iAPR with LHR.[5,6] Therefore, the aim of this study was to compare LHR and iAPR with respect to abscess formation and the associated need for re-intervention and readmission using a dataset from a collaborative research project involving 71 Dutch hospitals.

Methods

Snapshot design

A resident-led, retrospective cross-sectional snapshot study was performed, a method first described by Pinkney and colleagues.[7,8] A total of 71 hospitals in the Netherlands participated, including all consecutive patients who underwent surgery for rectal cancer from January to December 2011. It was executed as collaborative research under the name of the Dutch Snapshot Research Group (DSRG), in collaboration with the Dutch Colorectal Audit (DCRA).

The Medical Ethical Committee of the Academic Medical Centre in Amsterdam, the Netherlands, reviewed and approved the study design and judged that no informed consent from the included patients was necessary considering the observational study design with no additional burden for the patient.

Data extraction

The methodology of this snapshot study has been described elaborately in the first publication of the DSRG.[9] Briefly, from the DCRA, all patients who had a resection for rectal cancer in 2011 were identified. Existing data from the DCRA was completed by the snapshot study, including additional data on diagnostic and treatment characteristics and long-term surgical and oncological outcomes. Every participating hospital had one or two surgical residents who were supervised by a surgeon and were responsible for collection of the additional data in a web-based tool which was specifically developed and controlled for privacy regulations.

Patients

All patients from the snapshot database who underwent an elective LHR or iAPR as primary treatment for rectal cancer with curative intent were selected. For the LHR group, only patients with a distance of ≤ 6 cm between the lower border of the tumour and the anorectal junction on preoperative sagittal MRI were included to ensure that all Hartmann's resections could be considered low. Patients in whom no preoperative MRI was performed or in whom the height was not calculated were excluded. All patients who underwent iAPR were included, irrespective of the height of the tumour, since this would not influence the height of the resection. Patients were excluded if the indication for surgery was local recurrence, additional resection following previous (recto)sigmoid resection, or salvage surgery after the occurrence of persistent anastomotic leakage or pelvic abscess.

End-points and definitions

Primary end-points were the incidence of pelvic abscess and abscess related need for re-intervention and readmission during long-term follow-up. Secondary end-points were intra-operative complications, overall complications requiring surgical re-interventions, overall readmissions and postoperative mortality. Event rates were separately determined for the periods within 30 days of primary surgery and beyond. A pelvic abscess was defined as either an abscess on the rectal stump or a presacral abscess.

Statistical analysis

Descriptive data were reported as median with interquartile range (IQR) or mean with standard deviation (SD) where appropriate. Categorical variables were presented as number and percentage. Comparison between groups for discrete variables was made by the chi-squared test, the chi-squared test for trend or the Fischer exact test when appropriate. The independent *t* test was used to compare normally distributed

continuous variables and the Mann–Whitney *U* test was used to compare continuous variables not normally distributed. $P < 0.05$ was considered statistically significant. For the primary end-point, time-to-event analysis was performed, censoring for death or loss to follow-up, using the Kaplan–Meier method. Comparison between groups was made using the log-rank test. Analyses were performed using IBM SPSS Statistics for Windows (Version 24.0: IBM Corp., Armonk, New York, USA).

Results

Patients

From the total dataset of 2095 patients who underwent resection for rectal cancer, a total of 185 patients were selected, of whom 139 (75%) underwent LHR and 46 (25%) underwent an iAPR. Patients in the LHR group were non-significantly older than those in the iAPR group (mean 72 vs 68 years; $P = 0.055$). In both groups, 93.5% of the patients (130 and 43 patients respectively) received some form of preoperative treatment. An overview of baseline characteristics is shown in Table 1.

Intra-operative outcome

In the LHR group, 59 patients (42.4%) had their procedure performed laparoscopically compared to 25 patients (54.3%) in the iAPR group ($P = 0.156$). Fewer patients in the LHR group underwent a multivisceral resection [14 (10.1%) vs 10 (21.7%); $P = 0.041$]. Simultaneous resection of metastases was performed in four and two patients, respectively. An intra-operative complication occurred in four patients (2.8%) in the LHR group and in five patients (10.9%) in the iAPR group ($P = 0.049$). Intra-operative characteristics are described in Table 2. There were no significant differences in stage distribution and completeness of resection (Table 3).

Pelvic abscess

Overall, a pelvic abscess occurred in 23 patients (16.5%) following LHR and in five patients (10.9%) after iAPR ($P = 0.352$). In the LHR group, 11 of the 23 abscesses were diagnosed within 30 days, whereas all abscesses in the iAPR group were diagnosed beyond 30 days ($P = 0.041$). When censored for mortality or loss to follow-up, there was still no difference in the overall incidence of pelvic abscess between LHR and iAPR (Figure 1).

After LHR, the median time from surgery to diagnosis of the pelvic abscess was 21 days (IQR 10–151 days), compared to a median of 90 days (IQR 44–269 days) in the iAPR group ($P = 0.102$). The length of the rectal stump could not be determined;

Table 1. Baseline characteristics

	LHR (n=139)	**iAPR** (n=46)	**P value**
Sex (n, %)			0.634
Male	76 (54.7%)	27 (58.7%)	
Female	63 (45.3%)	19 (41.3%)	
Age at surgery (years), *mean (± SD)*	72 (±10.2)	68 (±11.5)	0.055
BMI[1], *median (IQR)*	25 (22-29)	24 (23-29)	0.435
ASA classification[2] (n, %)			0.683
1	26 (18.7%)	7 (15.2%)	
2	85 (61.2%)	30 (65.2%)	
3	24 (17.3%)	7 (15.2%)	
4	1 (0.7%)	1 (2.2%)	
Unknown	3 (2.2%)	1 (2.2%)	
Height of tumour on MRI			0.619
0 cm	6 (4.3%)	2 (4.3%)	
1 cm	9 (6.5%)	7 (15.2%)	
2 cm	13 (9.4%)	5 (10.9%)	
3 cm	19 (13.7%)	4 (8.7%)	
4 cm	29 (20.9%)	5 (10.9%)	
5 cm	34 (24.5%)	7 (15.2%)	
6 cm	29 (20.9%)	1 (2.2%)	
≥ 7 cm	-	10 (21.7%)	
Unknown	-	5 (10.9%)	
cTNM tumour stage			0.736
Stage 1	17 (12.2%)	3 (6.5%)	
Stage 2	29 (20.9%)	11 (23.9%)	
Stage 3	56 (40.3%)	20 (43.5%)	
Stage 4	12 (8.6%)	4 (8.7%)	
Unknown	25 (18.0%)	8 (17.4%)	
Preoperative treatment (n, %)	130 (93.5%)	43 (93.5%)	1.000
Type of preoperative treatment (n, %)			0.427
Short course radiotherapy	68 (48.9%)	15 (32.6%)	
Long course radiotherapy	4 (2.9%)	2 (4.3%)	
Chemoradiotherapy	50 (36.0%)	24 (52.2%)	
Chemotherapy	1 (0.7%)	-	
Radiotherapy unspecified	7 (5.0%)	2 (4.3%)	

iAPR, intersphincteric abdominoperineal resection; LHR, low Hartmann's resection; ASA, American Society of Anaesthesiology; BMI, body mass index.

however, subgroup analysis was performed in the LHR group depending on tumour location. Sixteen patients (11.5%) with a tumour located 3 cm or less from the anorectal junction on MRI developed a pelvic abscess, compared to seven patients (5.0%) with a tumour above 3 cm (P = 0.812).

All patients with pelvic abscess underwent one or more re-interventions. An overview of the type of treatment for all pelvic abscesses is displayed in Table 4. In two patients, who initially underwent LHR (1.4%), an intersphincteric resection of the rectal stump

Table 2. Intra-operative characteristics

	LHR (n=139)	**iAPR** (n=46)	**P value**
Technique (n, %)			0.156
Open	77 (55.4%)	20 (43.5%)	
Laparoscopic	59 (42.4%)	25 (54.3%)	
Unknown	3 (2.2%)	1 (2.2%)	
Conversion (n, %)	13 (9.4%)	3 (6.5%)	0.764
Accessibility	10	2	
Intra-operative complication	2	1	
Extensive tumour	1	-	
Multivisceral resection (n, %)	14 (10.1%)	10 (21.7%)	0.041
Omentoplasty (n, %)*	-	19 (41.3%)	-
Intra-operative complications (n, %)	4 (2.8%)	5 (10.9%)	0.049
Intra-operative bleeding	1	-	
Bowel injury	2	1	
Ureter injury	1	1	
Spleen injury	-	1	
Other	-	2	

iAPR, intersphincteric abdominoperineal resection; LHR, low Hartmann's resection.
* Omentoplasty in LHR was not registered.

Table 3. Oncological outcome

	LHR (n=139)	**iAPR** (n=46)	**P value**
ypTNM stage (n, %)			0.724
Stage 0	12 (8.6%)	3 (6.5%)	
Stage 1	26 (18.7%)	13 (28.3%)	
Stage 2	41 (29.5%)	11 (23.9%)	
Stage 3	42 (30.2%)	14 (30.4%)	
Stage 4	13 (9.4%)	4 (8.7%)	
Unknown	5 (3.6%)	1 (2.2%)	
Radical surgical resection (n, %)			0.128
R0	121 (87.1%)	44 (95.7%)	0.189
R1	10 (7.2%)	1 (2.2%)	0.295
R2	2 (1.4%)	-	1.000
Unknown	6 (4.3%)	1 (2.2%)	-
Circumferential Resection Margin <1mm (n, %)	7 (5.0%)	2 (4.3%)	1.000

iAPR, intersphincteric abdominoperineal resection; LHR, low Hartmann's resection.

was performed because of persistent pelvic abscess at 9 and 11 months postoperatively. In the LHR group, nine patients (6.5%) were readmitted because of pelvic abscess, of whom three (2.2%) were admitted within 30 days. Four patients in the iAPR group (8.7%) were readmitted because of a pelvic abscess, all beyond the 30-day postoperative period.

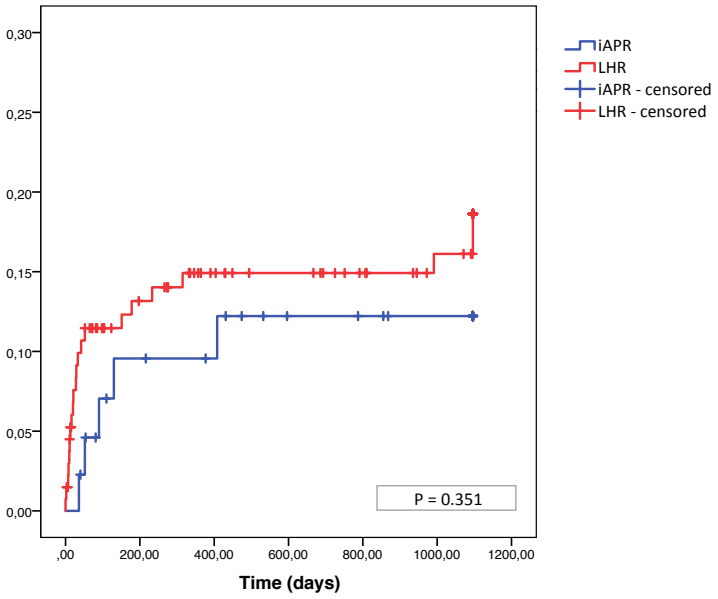

Figure 1. Time to pelvic abscess occurrence: 3-year cumulative incidence of pelvic abscess censored for mortality or loss to follow-up (competing risks).

Overall short-term surgical outcome

Postoperative complications, requiring surgical re-intervention within 30 days, occurred in eight out of 139 patients (5.8%) in the LHR group. Besides surgical drainage of a pelvic abscess in one patient, six other patients (4.3%) underwent a stoma related re-intervention, and the remaining patient underwent adhesiolysis because of an ileus. In the iAPR group, two out of 46 patients (4.3%) had a surgical re-intervention within 30 days, one stoma related re-intervention and one adhesiolysis.

Following LHR, eight patients (5.8%) were readmitted within 30 days. As mentioned above, three patients were readmitted because of a pelvic abscess, three because of a postoperative ileus, one patient had an infection of the abdominal wound and the last patient was readmitted because of dehydration. Readmission within 30 days was required in two patients (4.3%) following iAPR, both because of an ileus. In the LHR group, four patients (2.9%) died within 30 days, three being related to surgical complications: one patient had an ileus followed by progressive renal failure, one patient had peritonitis after iatrogenic bowel injury and the third patient died of sepsis because of an intra-abdominal abscess.

Overall long-term surgical outcome

Median duration of follow-up was 39 months in both groups, with an IQR of 13–45 months after LHR and an IQR of 19–44 months following iAPR (P = 0.841). In the iAPR group, the perineal wound was healed within 30 days in 65.2% of the patients (n = 30). An additional 19.6% (n = 9) of patients had a healed perineal wound within 3 months. No persisting perineal wound problems were reported. A total of five patients (10.9%) in the iAPR group developed a perineal hernia, of whom one patient (2.2%) underwent surgical repair.

Beyond 30 days, 22 patients underwent a total of 30 surgical re-interventions after LHR and 11 patients in the iAPR group underwent 21 surgical re-interventions. An overview of all surgical re-interventions is shown in Table 4. At any time during follow-up, a total of 26 patients (18.7%) were readmitted in the LHR group vs nine patients (19.6%) in the iAPR group (P = 0.900).

Discussion

This cross-sectional multicentre snapshot study revealed no significant differences in the overall incidence of pelvic abscess, the abscess related re-intervention or readmission rates between LHR and iAPR for distal rectal cancer. Pelvic abscesses after iAPR were all diagnosed beyond 30 days, while half of the abscesses were diagnosed in the early postoperative period after LHR (P = 0.041). Overall, a substantial percentage of patients underwent surgical re-intervention for any reason (20% after LHR and 28% after iAPR), and only a minority of these re-interventions were performed within 30 days postoperatively. Similarly, high readmission rates were found for both groups (19% after LHR and 20% after iAPR), also mostly occurring beyond 30 days.

Presumably, the formation of a pelvic abscess after LHR is mostly due to leakage or blowout of the staple line of the rectal stump. It has been suggested that the anal sphincter forms a barrier of high resistance for drainage of remaining fluid and mucous in the rectal stump causing the staple line to blow out. Considering this aetiology, pelvic abscesses subsequent to LHR might develop relatively soon following surgery, at a time when the blind ending rectal stump has not yet healed. After iAPR, however, pelvic abscesses probably develop from fluid collections in the presacral cavity following the total mesorectal excision dissection which then becomes secondarily contaminated. The layered closure of the pelvic floor with preserved external sphincter might contribute to formation of such fluid collections. This process might evolve more slowly, probably explaining the more delayed diagnosis of the abscess following iAPR compared with LHR.

Table 4. Surgical outcome

	LHR (n=139)	**iAPR** (n=46)	**P value**
Duration of admittance			0.554
Days, median (IQR)	9 (7-13)	8 (7-12)	
Pelvic abscess (n, %)*	23 (16.5%)	5 (10.9%)	0.352
Within 30 days	11 (7.9%)	0 (0%)	0.041
Time between surgery and diagnosis pelvic abscess			
Days, median (IQR)	21 (10-151)	90 (44-269)	0.102
All type of treatment for pelvic abscess			-
Percutaneous (transgluteal) drainage	2	2	
Transanal drainage	15	-	
Surgical drainage	8	2	
Surgical transperineal drainage	-	3	
Endo-SPONGE® treatment	1	2	
Patients with surgical reinterventions (n, %)	28 (20.1%)	13 (28.3%)	0.251
Within 30 days	8 (5.8%)	2 (4.3%)	1.000
Total number of surgical reinterventions	38	23	
Surgical treatment of pelvic abscess	9	7	
Stoma related surgical reintervention	22	10	
Correction perineal hernia	-	1	
Correction incisional hernia	1	-	
Adhesiolysis	4	1	
Intersphincteric resection of rectal stump	2	-	
Other	-	4	
Patients with one or more readmission (n, %)	26 (18.7%)	9 (19.6%)	0.900
Within 30 days	8 (5.8%)	2 (4.3%)	1.000
Mortality	44 (31.7%)	8 (17.4%)	0.068
Within 30 days	4 (2.9%)	0 (0%)	1.000

iAPR, intersphincteric abdominoperineal resection; LHR, low Hartmann's resection. * Number of patients, at any time during follow-up.

Literature on pelvic abscess formation after LHR and iAPR for rectal cancer is scarce and there also is substantial variability in reported outcome. Pelvic abscess rates between 3% and 33% have been reported after LHR and between 6% and 17% after iAPR.[1,2,4-6,10] Transection within 2 cm from the pelvic floor, previously described as an independent risk factor for pelvic abscess formation by Tøttrup et al., could not be statistically confirmed as a risk factor in this study although a tendency towards more pelvic abscesses was observed in patients with more distal tumours (12% vs 5%).[1] Variability in the use of preoperative radiotherapy might also explain the wide range in reported abscess rates given the reported association with postoperative intra-abdominal abscess formation after Hartmann's resection.[11] Recently the use of preoperative radiotherapy for rectal cancer in the Netherlands has been reduced following revision of the national guidelines.[12]

The low pelvic abscess rate of 3% after LHR in the 30-day postoperative period as observed by Sverrisson et al. illustrates that surgical outcome after rectal cancer surgery requires a sufficiently long follow-up.[4] This study shows that the majority of pelvic abscesses, re-interventions and readmissions after LHR and iAPR occur beyond 30 days postoperatively. Therefore, a 30-day postoperative follow-up of complications is insufficient.

Previous studies have compared LHR with APR and concluded that the high rate of pelvic abscesses following LHR is a more substantial problem than the incidence of perineal wound complications in APR.[2,10] However, a review by Musters et al. shows that a pooled proportion of 38% was found for perineal wound problems in a subgroup of patients undergoing APR with preoperative radiotherapy.[3] This might indicate that the perineal wound problems, after conventional APR or extralevator APR, are more substantial than suggested in the relatively small comparative studies. The present study shows that 85% of the iAPR patients had a healed perineal wound within 3 months, and no persistent wound problems were reported, suggesting a benefit of preserving the pelvic floor if oncologically possible regarding the risk of postoperative infectious complications.

In the iAPR group, significantly more patients underwent a multivisceral resection. This type of extensive surgery might be the reason for the higher rate of intra-operative complications. This baseline difference might be related to the fact that surgeons are more inclined to perform an APR procedure for a locally advanced rectal cancer. In cases of posterior exenteration in females, a colorectal anastomosis or stapled rectal stump runs the risk of formation of a fistula to the transected vagina.

With a growing population of frail, elderly rectal cancer patients, the need for tailored surgery increases.[13] Refraining from creating an anastomosis is a valuable option for these high risk patients, and LHR and iAPR are two such surgical options which can be performed without the need for restoration of bowel continuity. This is one of the first studies evaluating iAPR as a primary treatment for rectal cancer and one of the first to compare iAPR to LHR. Some limitations, however, should be discussed. Since the dataset was not designed to answer the specific question of this study, some potentially relevant variables are missing. For example, missing data do not allow analysis of the reason for not making an anastomosis, the reason for choosing either a LHR or an iAPR, evaluation of specific expertise or training of the operating surgeon, nor the handling of the rectal stump regarding type of closure and postoperative drainage. Furthermore, numbers and events are still small, despite being the largest series in current literature to our knowledge. The small sample size may cause a sparse data bias and statistical type II errors, hence possibly limiting the power to find significant statistical differences between groups, even though numerical differences are

observed.[14] These limitations should be borne in mind when interpreting the results of this study. Another limiting factor of this study is its retrospective design, which may have led to incomplete data. Additionally data on quality of life, after both techniques, were not available within the design of the study. This clearly will be of importance in the decision making process for the individual patient. Nevertheless, this snapshot study design provides a cross-sectional analysis of rectal cancer care in the Netherlands with high external validity and allowed us to include a relatively large number of still rarely performed procedures.

Conclusion

This cross-sectional snapshot study suggests that, although iAPR has fewer pelvic abscesses within 30 days, there is no difference in the overall incidence of pelvic abscess and related need for re-intervention or readmission between LHR and iAPR as primary treatment for rectal cancer. Both procedures are associated with substantial surgical events beyond the 30-day postoperative period, underlining the need for extensive follow-up.

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PART THREE

Salvage surgery following rectal cancer resection

CHAPTER 6

Outcome after redo surgery for complicated colorectal and coloanal anastomosis: a systematic review

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Abstract

Background
When a colorectal or coloanal anastomosis fails because of persistent leakage or stenosis, or the anastomosis has to be resected for recurrent cancer, constructing a new anastomosis might be an option in selected patients. This is a rare and complex type of redo surgery.

Objective
The aim of this review was to evaluate the current literature on redo anastomosis for complicated colorectal or coloanal anastomosis.

Data Sources
A systematic literature search of MEDLINE, EMBASE, the Cochrane Library, the PROSPERO register, clinicaltrials.gov, and the World Health Organization International Clinical Trials Registry Platform database was performed.

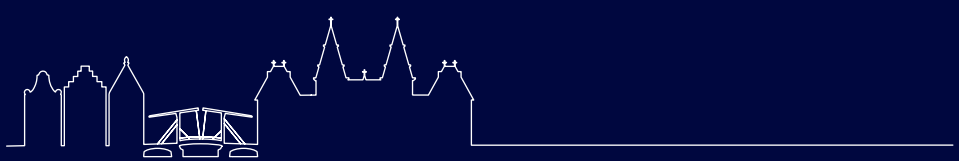
Study Selection
Two reviewers independently screened the available literature. All studies reporting on redo surgery and aiming at reconstruction of a prior low colorectal or coloanal anastomosis for any indication were included.

Main Outcome Measures
Primary outcome was successful restoration of continuity. Secondary outcomes were postoperative morbidity, pelvic sepsis, incontinence, and mortality.

Results
Nine studies were included, comprising 291 patients, of whom 76% had index surgery for colorectal cancer. Pooled proportions showed an overall success rate of 79% (95% CI, 69–86), with a pooled incidence of major postoperative morbidity of 16% (95% CI, 10–24). The pooled pelvic sepsis rate was 16% (95% CI, 9–27), and the pooled surgical reintervention and readmission rates were 11% (95% CI, 8–17) and 7% (95% CI, 3–15). Five studies reported on incontinence, with a pooled proportion of 17% (95% CI, 10–26).

Limitations
The limitations of this review are the lack of randomized controlled trials and high-quality studies, and the small sample sizes and heterogeneous patient populations in the included studies.

Conclusions
Redo surgery is a valuable treatment option for the complicated colorectal or coloanal anastomosis with 79% successful restoration of bowel continuity in the published literature from experienced tertiary centers.



Introduction

In sphincter-saving colorectal surgery with a primary colorectal or coloanal anastomosis, the anastomosis might eventually fail. The main reasons for failure are persisting anastomotic leakage and its secondary complications (ie, fistulas), as well as stenosis. If restoration of bowel continuity is pursued, complex surgical reintervention is required. Additionally, constructing a new anastomosis might be considered in a selected group of patients with locally recurrent rectal cancer.

Anastomotic leakage after low anterior resection is still frequently encountered, with reported incidences up to 26%.[1–3] Even more important, a substantial proportion of these leakages never heal.[4,5] A nonhealed anastomosis can result in a complex infectious problem in and outside the pelvis, and this is often the reason for not closing a diverting stoma.[6,7] Reconstruction of the anastomosis is the only chance to restore bowel continuity in highly selected cases of persistent anastomotic leakage, stenosis, or local recurrence. Pelvic redo surgery is complex, not widely performed, and mostly restricted to tertiary referral centers. Only a few patients are offered this last chance of restoration of bowel continuity, because the expertise on anastomotic reconstruction is scarce, the risk of failure of a redo anastomosis in an already complicated pelvis assumed to be high, and functional outcome to be worsened.[8,9]

The aim of this systematic review is to evaluate the current literature regarding the success rate, postoperative morbidity, and functional outcome after redo coloanal and colorectal anastomoses.

Materials and methods

The review protocol was registered in PROSPERO, the international prospective register of systematic reviews (registration number CRD42016043730) and was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.[10,11]

Search Strategy

A systematic literature search of MEDLINE (PubMed), EMBASE (Ovid), and the Cochrane Library for published studies and of the PROSPERO register, clinicaltrials.gov, and the World Health Organization International Clinical Trials Registry Platform database for ongoing studies was performed on August 31, 2017, using medical subject headings (MeSH) terms for MEDLINE, Emtree terms in Embase, and free text words in titles and abstracts. Search terms included: colon anastomosis, colorectal anastomosis, coloanal

anastomosis, reoperation, redo, redo surgery, outcome, morbidity, complications, success rate, and functional outcome. The detailed search strategy is presented in Appendix 1. No restrictions regarding publication date, study design, and language were applied for the search to ensure a high sensitivity of the review. Reference lists of eligible articles were manually screened to identify additional relevant articles.

Eligibility Criteria and Study Selection

Duplicates were removed before the process of study selection. Articles were considered eligible when reporting on redo surgery aiming at reconstruction of a prior low colorectal or coloanal anastomosis after (low) anterior resection for any indication. The redo anastomosis could be either straight or delayed (Turnbull-Cutait procedure), and could be constructed in any configuration (end-to-end, side-to-end, or coloanal pouch). Only transabdominal approaches were included. Transanal redo procedures were excluded because of assumed differences in indications, and to reduce heterogeneity in surgical technique. Both benign and malignant indications for redo surgery were included. The minimum size of the studied cohort was set at 5 patients, excluding case reports. Studies describing children, animal studies, and conference abstracts were excluded.

If a study contained data on redo anastomoses as well as primary anastomoses or other types of surgery, separate data on redo colorectal and redo coloanal anastomoses were extracted from the article, if possible, or the authors of these studies were contacted to request separate data. When separate data could be obtained, only these data were used in the analyses. When separate data could not be obtained, the article was excluded.

Two reviewers (E.W. and C.E.L.) independently screened titles and abstracts for the eligibility criteria. In the case of disagreement, consensus was reached by personal discussion, and, when necessary, the opinion of a third researcher (P.J.T.) was obtained. Subsequently, all selected articles were analyzed full-text by both reviewers (E.W. and C.E.L.) and a final selection of studies was agreed on.

Data Extraction

Both reviewers (E.W. and C.E.L.) independently performed data extraction for each selected study by using piloted forms. These forms were compared and, in the case of discrepancies, consensus was reached among the reviewers by personal discussion. Because of anticipated heterogeneity of study designs and participants, the full data of all selected studies were requested from the corresponding authors to enable subgroup analyses.

Outcomes

Primary outcome was success rate after redo surgery defined as the restoration of bowel continuity after at least 6 months of follow-up. Secondary outcomes were postoperative (30-day) morbidity, pelvic sepsis (defined as any pelvic infectious complication subsequent to the redo surgery, including anastomotic leakage, pelvic abscess, and fistula), incontinence, and mortality. Additional data extracted from selected studies included year and country of publication, number of patients, inclusion and exclusion criteria, patient characteristics, index surgery characteristics, redo surgery characteristics, and intraoperative characteristics. Outcomes were either displayed as reported originally or calculated from the obtained or reported raw data if possible.

Assessment of Methodological Quality of Studies

Eligible studies were assessed for methodological quality by using the Cochrane Risk of Bias Tool for Randomized Controlled Trials (RCTs) and the Methodological Index for Nonrandomized Studies (MINORS) quality assessment tool for nonrandomized studies when applicable.[12,13] In the MINORS quality assessment, points were rewarded (0 for not reported, 1 for reported but inadequate, 2 for reported and adequate) for 8 items in the case of noncomparative studies and 12 items in the case of comparative studies. Both reviewers (E.W. and C.E.L.) performed the quality assessment and, in the case of persistent discrepancies after personal discussion, the average score was granted. For this review, as proposed by Schreve et al,[14] a score of ≤8 was considered to be poor quality, 9 to 14 was considered to be moderate quality, and 15 to 16 was considered to be good quality for noncomparative studies and ≤14, 15 to 22, and 23 to 24 for comparative studies.

Statistical Analysis

All analyses were performed using R Statistical Software Version 3.3.1 (R Foundation for Statistical Computing, Vienna, Austria). For the outcome measures, pooled weighted proportions with corresponding 95% CIs were calculated using inversed variance weighting. A random-effects model was applied because of anticipated heterogeneity of study designs and participants. The heterogeneity of the included studies was evaluated by calculating the I^2 statistic. Homogeneity was assumed with a calculated I^2 <60%. Subgroup analysis was performed only for the primary outcome. Sensitivity analysis was performed to determine the robustness of findings by including and excluding studies with poor-quality assessment.

Results

Included Studies

Systematic search identified 1590 unique articles eligible for abstract review. This resulted in 30 articles suitable for full-text review, which yielded 9 studies meeting the eligibility criteria.[15–23] Figure 1 shows the PRISMA flow diagram of the study selection including the reasons for exclusion of full texts. From 1 study, subgroup data on patients fulfilling the eligibility criteria were obtained from the authors separately.[20] From 2 additional studies, full data were provided by the corresponding authors for subgroup analyses.[21,23]

Study Characteristics and Quality Assessment

The 9 selected studies included patients who were treated between 1992 and 2014 (Table 1). The majority of the studies (6/9) originated from France, but there was no overlap in patient populations. This was either stated in the articles or concluded by the reviewers based on different years included in the studies. All studies were retrospective cohort studies and there were no RCTs.

All studies were noncomparative, enabling a maximum score of 16 in the MINORS quality assessment. The mean MINORS score was 10 (SD ±1.4; range, 7–11). There were no studies assessed as a good-quality study, 8 studies were assessed as of moderate quality, and 1 as poor quality. Figure 2 shows the distribution of study quality across the studies. Because only published data were included in this systematic review, there is a likelihood of publication bias.

Patient and Treatment Characteristics

All studies comprised a total of 291 patients who were offered redo surgery, of whom 160 (55%) were men (Table 2). The pooled mean age was 58 years (±11; range, 24–84). The majority of patients (221/291, 76%) had their index surgery for colorectal cancer, and 147 of 258 (57%) patients were treated with preoperative radiotherapy before the index surgery. All indications for index surgery can be found in Supplement Table 1. Of the 291 patients undergoing redo surgery, 286 underwent construction of a new colorectal (57/286, 20%) or coloanal (229/286, 80%) anastomosis. In 5 patients, immediate failure during redo surgery was reported (Table 3).[17,21] Six studies described the location of the redo coloanal anastomosis, either at the level of the dentate line,[17,18,20,21] or at the level of the anal verge.[16,23] Only Lefevre et al[17] described the height of the redo colorectal anastomosis with a mean of 5.7 cm ±11 (range, 4–8) from the dentate line.

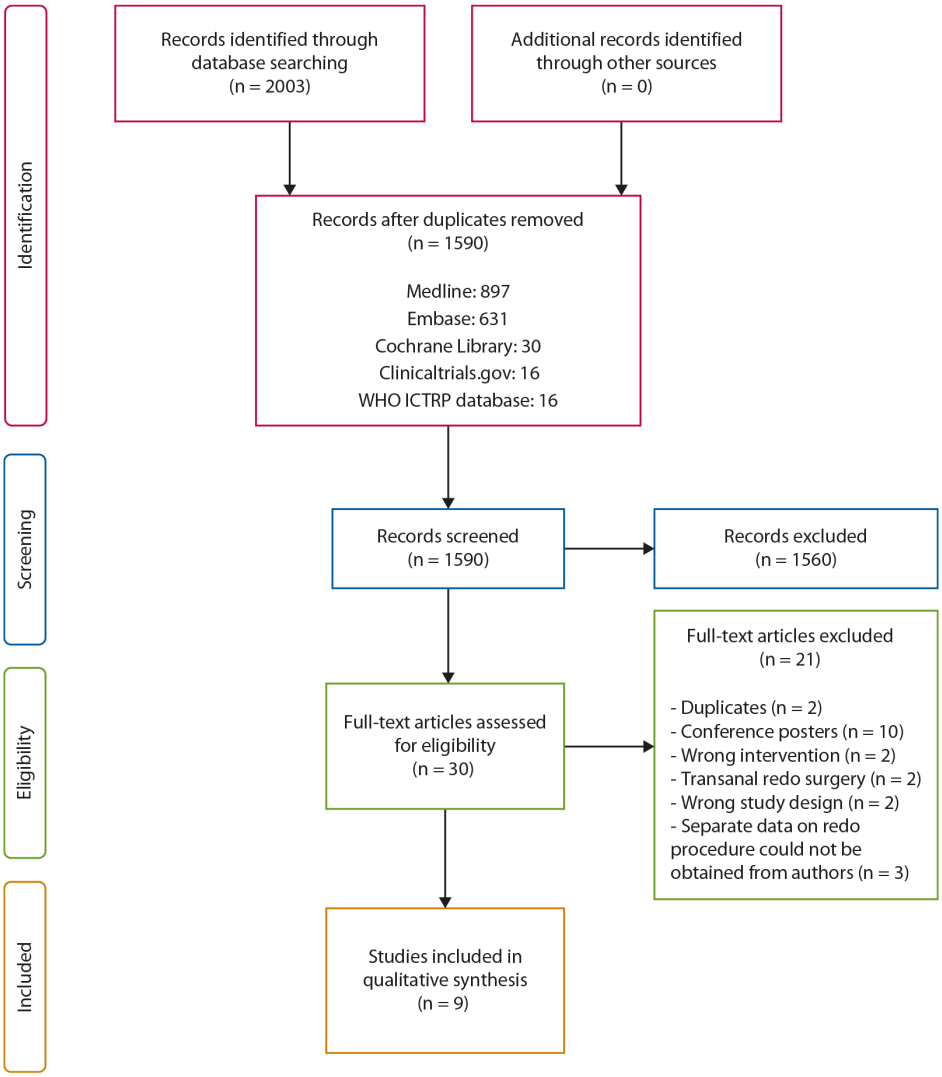


Figure 1. PRISMA flow diagram of study selection. PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; WHO ICTRP = World Health Organization International Clinical Trials Registry Platform.

In 4 studies, all procedures were performed using an open approach.[15,18,20,21] In the study by Lefevre et al,[17] 18% of procedures were performed laparoscopically, half of which was converted, and Westerduin et al[23] reported 97% open procedures. The other studies did not report on the operative technique.

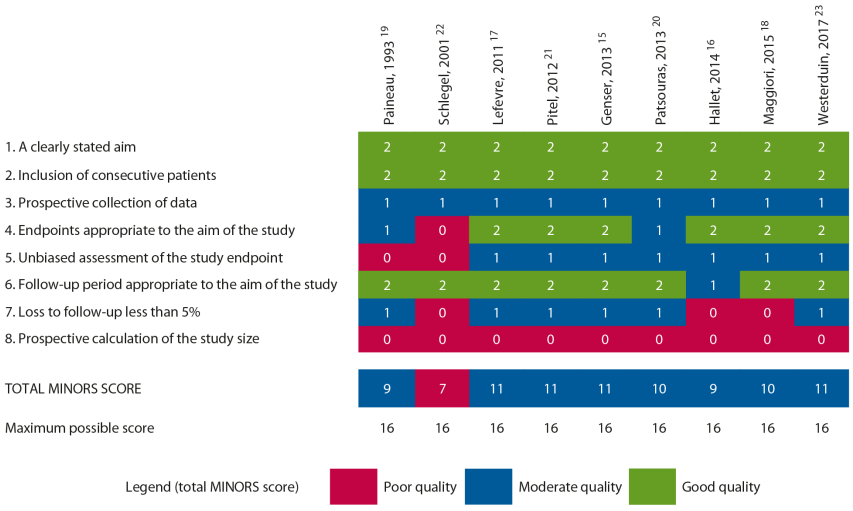


Figure 2. MINORS quality assessment. MINORS = Methodological Index for Nonrandomized Studies.

Postoperative Outcome

Pooled rates of morbidity after redo surgery are presented in Figure 3. Specifications regarding intraoperative and major postoperative complications can be found in Supplement Table 1. Eight studies reported on surgical reinterventions with a pooled proportion of 11% among 264 patients (95% CI, 8–17; I^2 9%).[15–21,23] The pooled readmission rate from 4 studies including 208 patients was 7% (95% CI, 3–15; I^2 49%).[15,17,21,23] An overview of intra- and postoperative outcome per study is shown in Table 4. No short-term mortality was reported in any of the studies. In 2 studies, overall pelvic sepsis rate (occurring at any time during follow-up) was reported.[18,23] This yielded a pooled overall pelvic sepsis rate of 29% (95% CI, 11–57; I^2 76%) among 83 patients.

Success Rate and Functional Outcome

All studies, except for 1 (Paineau et al[19]), reported on the success rate after redo surgery, defined as restoration of bowel continuity after at least 6 months of follow-up (Table 5). Pooled proportions showed an overall success rate of 79% (95% CI, 69–86; I^2 59%). Sensitivity analysis, excluding 1 study[22] assessed as poor quality, showed a pooled success rate of 77% (95% CI, 68–85; I^2 54%). Pooled success rates for subgroups of patients with index surgery for rectal cancer, index surgery for rectal cancer with preoperative radiotherapy, index surgery for rectal cancer and pelvic sepsis as reason for redo surgery, redo coloanal anastomosis and delayed redo anastomosis ranged between 70% and 74% (Figure 4).

Table 1. Study characteristics

Included studies			**Study characteristics**				**Follow-up**
Study	Year of publication	Duration of follow up	Study design	Number of patients	Included patients	Exclusion criteria	Duration of follow up
Paineau et al.[19]	1993	Mean 11 months ± 5 (range 3-14). Median 13 months (IQR 4-14).	Retrospective, observational, NC.	7	Consecutive patients with a redo anastomosis for cancer recurrence from June 1986- December 1992.	NR.	Mean 11 months ± 5 (range 3-14). Median 13 months (IQR 4-14).
Schlegel et al.[22]	2001	Mean 29 months ± 14 (range 5-60).	Retrospective, observational, NC.	27	Consecutive patients with redo anastomosis for stenosis of CRA from August 1992-October 1996.	Neoplasia.	Mean 29 months ± 14 (range 5-60).
Lefevre et al.[17]	2011	Mean 29 months ± 27 (range 3-91).	Retrospective, observational, NC.	33	Consecutive patients with redo anastomosis for failed CRA or CAA from January 1999- June 2008.	IPAA, local transanal approach.	Mean 29 months ± 27 (range 3-91).
Pitel et al.[21]	2012	Mean 48 months ± 38 (range 0-122). Median 36 months.	Retrospective, observational, NC.	66	Consecutive patients with redo CAA for failed CRA or CAA from January 2000-December 2010.	Local recurrence.	Mean 48 months ± 38 (range 0-122). Median 36 months.
Genser et al.[15]	2013	Mean 37 months (range 1-137). Median 21 months.	Retrospective, observational, NC.	50	Consecutive patients with redo anastomosis for previous failed CRA or CAA from October 1998-November 2011.	Exclusive perineal approach, local transanal repair.	Mean 37 months (range 1-137). Median 21 months.
Patsouras et al.[20]*	2013	NR.	Retrospective, observational, NC.	18	Consecutive patients with redo coloanal sleeve anastomosis for RVF and pelvic sepsis due to anastomotic leakage from January 1998-December 2012.	NR.	NR.
Hallet et al.[16]	2014	Median 274 days (IQR 259-394).	Retrospective, observational, NC.	7	Consecutive patients with redo with delayed CAA for failed CRA from October 2010-September 2011.	NR.	Median 274 days (IQR 259-394).

Table 1. *Continued*

Included studies			**Study characteristics**				**Follow-up**
Study	Year of publication	Duration of follow up	Study design	Number of patients	Included patients	Exclusion criteria	Duration of follow up
Maggiori et al.[18]	2015	Mean 29 months ± 19 (range 4-82).	Retrospective, observational, NC.	24	Consecutive patients with redo surgery with delayed CAA for failed low CRA or CAA with associated chronic pelvic sepsis and/or RVF from June 2007-December 2013.	Pelvic abscess, fistula tract or RVF present < 6 months.	Mean 29 months ± 19 (range 4-82).
Westerduin et al.[23]*	2017	Median 27 months (IQR 17-36).	Retrospective, observational, NC.	59	Consecutive patients with redo hand-sewn CAA for persistent anastomotic leakage following LAR for rectal cancer from January 2010 – September 2014.	Follow-up < 1 year.	Median 27 months (IQR 17-36).

NC = noncomparative, NR = not reported, CRA = colorectal anastomosis, CAA = coloanal anastomosis, LAR = low anterior resection, IPAA = Ileal Pouch Anal Anastomosis, RVF = rectovaginal fistula, IQR = interquartile range.
* Separate data on redo CRA/CAA obtained from article or authors, data presented in table may not be directly relatable to published data.

Table 2. Patient characteristics

Included studies	**Patient characteristics**					
Study	Sex	Age	ASA-score	Primary anastomosis	Indication primary surgery	Previous pelvic radiotherapy
Paineau et al.[19]	7 male (100%)	Mean 66 years ± 12 (range 45-79).	NR.	NR.	7 (100%) colorectal cancer	2 (29%)
Schlegel et al.[22]	7 male (26%)	Mean 51 years (range 24-66).	NR.	27 CRA (100%)	13 (48%) rectal cancer	9 (33%)
Lefevre et al.[17]	22 male (67%)	Mean 57 years ± 10 (range 39-79).	NR.	24 CRA (73%) 9 CAA (27%)	19 (58%) colorectal cancer	NR.
Pitel et al.[21]	35 male (53%)	Mean 58 years ± 12 (range 28-79).	ASA 1: 36 (55%) ASA 2: 28 (42%) ASA 3: 2 (3%)	44 CRA (67%) 22 CAA (33%)	52 (79%) colorectal cancer	42 (60%)
Genser et al.[15]	23 male (46%)	Median 62 years (range 40-84).	ASA 3-4: 20 (40%)	46 CRA (92%) 4 CAA (8%)	29 (58%) colorectal cancer	11 (22%)
Patsouras et al.[20]*	5 male (28%)	Mean 59 years ± 12 (range 24-75).	NR.	17 CRA (94%) 1 CAA (6%)	15 (83%) rectal cancer	8 (44%)
Hallet et al.[16]	3 male (42%)	Mean 60 years (range 49-74).	ASA 1: 2 (29%) ASA 2: 5 (71%)	7 CRA (100%)	7 (100%) rectal cancer	5 (71%)
Maggiori et al.[18]	13 male (54%)	Mean 58 years ± 15 (range 25-77).	ASA 1-2: 17 (71%) ASA 3-4: 7 (29%)	13 CRA (54%) 11 CAA (46%)	20 (83%) rectal cancer	17 (71%)
Westerduin et al.[23]*	45 male (76%)	Mean 59 years ± 9 (range 34-78).	ASA 1: 11 (19%) ASA 2: 35 (59%) ASA 3: 13 (22%)	39 CRA (66%) 20 CAA (34%)	59 (100%) rectal cancer	53 (90%)

NR = not reported, ASA = American Society of Anaesthesiologists score, CRA = colorectal anastomosis, CAA = coloanal anastomosis
* Separate data on redo CRA/CAA obtained from authors, data presented in table possibly not directly relatable to published data.

Table 3. Treatment characteristics

Included studies	**Treatment characteristics**					
Study	Time between primary surgery and redo surgery	Indication redo surgery	Redo anastomosis	Delayed CAA	Technique redo	Deviating ostomy
Paineau et al.[19]	Mean 27 months ± 17 (range 13-57). Median 24 months (IQR 13-43).	7 (100%) cancer recurrence	5 (71%) CRA 2 (29%) CAA	0	NR.	NR.
Schlegel et al.[22]	NR.	27 (100%) stricture	7 (26%) CRA 20 (74%) CAA	0	NR.	24/27 (89%)
Lefevre et al.[17]	Mean 41 months ± 82 (range 3-465).	17 (52%) stricture 5 (15%) chronic fistula 6 (18%) HR for anastomotic complications 5 (15%) cancer recurrence	19 (58%) CRA 12 (36%) CAA 2 (6%) immediate failure	2/12 (17%)	27 (82%) open 6 (18%) laparoscopic (of which 3 converted because of adhesions)	29/31 (94%)
Pitel et al.[21]	NR.	22 (33%) fistula 21 (32%) chronic pelvic abscess 13 (20%) HR for anastomotic complications 10 (15%) stricture	63 (95%) CAA 3 (5%) immediate failure	2/66 (3%)	66 (100%) open	63/63 (100%)
Genser et al.[15]	Median 14 months (range 5-172).	20 (40%) stricture 14 (28%) chronic pelvic sepsis 8 (16%) HR for anastomotic complications 5 (10%) cancer recurrence 3 (6%) RVF	26 (52%) CRA 24 (48%) CAA	2/24 (8%)	50 (100%) open	37/50 (74%)
Patsouras et al.[20]*	NR.	12 (67%) RVF 4 (22%) AL 2 (11%) RUF	18 (100%) CAA	0	18 (100%) open	18/18 (100%)

Table 3. *Continued*

Included studies	**Treatment characteristics**					
Study	Time between primary surgery and redo surgery	Indication redo surgery	Redo anastomosis	Delayed CAA	Technique redo	Deviating ostomy
Hallet et al.[16]	NR.	2 (29%) RVF 2 (29%) AL 1 (14%) CVF 1 (14%) colon ischemia 1 (14%) immediate failure anastomosis in primary surgery	7 (100%) CAA	7/7 (100%)	NR.	7/7 (100%)
Maggiori et al.[18]	Mean 22 months ± 15 (range 7-59).	15 (63%) chronic pelvic sepsis 9 (37%) RVF	24 (100%) CAA	24/24 (100%)	24 (100%) open	16/24 (67%)
Westerduin et al.[23]*	Mean 21 months ± 23 (range 1-147). Median 14 months (IQR 8-27).	59 (100%) persistent AL	59 (100%) CAA	5/59 (9%)	57 (97%) open 2 (3%) laparoscopic	59/59 (100%)

NR = not reported, CRA = colorectal anastomosis, CAA = coloanal anastomosis , HR = Hartmann's resection, RVF = rectovaginal fistula, AL = anastomotic leakage, CVF = colovesical fistula, RUF = rectourethral fistula.
* Separate data on redo CRA/CAA obtained from authors, data presented in table possibly not directly relatable to published data.

Supplement Table 1.

Included studies	Patient characteristics	Intra- and postoperative outcome				
Study	Extended indications primary surgery	Specifications of intra-operative complications	Overall morbidity	Detailed major complications	Specifications surgical reinterventions	Specifications readmissions
Paineau et al.[19]	4 sigmoidal cancer 2 rectosigmoidal cancer 1 rectal cancer	NR.	5/7 (71%)	Grade 3: necrosis of the left ureter.	Left nephrectomy after ureter necrosis.	NR.
Schlegel et al.[22]	13 rectal cancer 7 diverticulitis 2 Hirschsprung's disease 2 endometriosis 1 gynaecological cancer 1 RAAA with rectosigmoidal necrosis 1 RVF	NR.	5/27 (19%)	NR.	NR.	NR.
Lefevre et al.[17]	19 colorectal cancer 11 diverticulitis 2 Crohn's disease 1 Hirschsprung's disease	2 bladder injury leading to failure of redo anastomosis 10 organ injuries requiring additional surgical procedures	18/33 (55%)	Grade 3: see specifications reintervention Grade 4: 1 postoperative peritonitis after ureteral wound 1 necrosis of abdominal suture with wound dehiscence, complicated by pneumonia and septic shock	7 relaparotomies: 3 for AL 1 wound dehiscence 1 wound hernia 1 urinary diversion for uretero-colic fistula 1 intra-abdominal seeding	NR.
Pitel et al.[21]	52 colorectal cancer 4 benign colorectal lesions 3 diverticulitis 3 endometriosis 2 gynaecological cancer 1 Hirschsprung's disease 1 iatrogenic bowel perforation	4 bladder injury 3 small bowel lesions 1 other adjacent organ lesion	20/63 (32%)	Grade 3a: 1 AL Grade 3b: 4 AL 1 colonic necrosis 1 lower limb compartment syndrome 1 recurrence of RVF	6 relaparotomies: 4 surgical drainage AL 1 colonic necrosis 1 RVF 1 fasciotomy for lower limb compartment syndrome	NR.

Supplement Table 1. *Continued*

Included studies	Patient characteristics	Intra- and postoperative outcome				
Study	Extended indications primary surgery	Specifications of intra-operative complications	Overall morbidity	Detailed major complications	Specifications surgical reinterventions	Specifications readmissions
Genser et al.[15]	29 colorectal cancer 19 diverticulitis 1 resection villous adenoma 1 reversal HR after ischemic colitis	5 bladder injury 1 splenectomy	13/50 (26%)	Grade 4: 1 intra-abdominal haemorrhage related to presacral vein rupture	1 relaparotomy for haemorrhage related to presacral vein rupture	1 high output stoma
Patsouras et al.[20]*	15 rectal cancer 1 diverticulitis 1 Hirschsprung's disease 1 resection of villous adenoma	1 partial ureteric injury	NR.	Grade 3: 2 AL	2 drainage of AL under general anaesthesia	NR.
Hallet et al.[16]	7 rectal cancer	NR.	5/7 (71%)	NR.	1 APR for extensive colonic ischemia	NR.
Maggiori et al.[18]	20 rectal cancer 2 endometriosis 1 Crohn's disease 1 trauma	2 bleeding requiring transfusion	13/24 (54%)	Grade 3-4: 3 pelvic abscesses 1 incarcerated parastomal hernia 1 NR	1 laparotomy for incarcerated parastomal hernia	NR.
Westerduin et al.[23]*	59 rectal cancer	2 bladder perforations 1 ureteric injury	13/59 (22%)	Grade 3: 9 AL, 1 stricture Grade 4: ICU admittance for respiratory insufficiency	3 laparotomies for AL 2 endo-SPONGE® treatment for AL 1 transanal suturing AL	1 AL 1 suspected RVF

NR = not reported, NA = not applicable, HR = Hartmann's resection, RAAA = ruptured aneurysm of the abdominal aorta, RVF = rectovaginal fistula, AL = anastomotic leakage, APR = abdominoperineal resection.
* Separate data on redo CRA/CAA obtained from authors, data presented in table possibly not directly relatable to published data.

	No. of studies	Sample Size	Events	Pooled Proportions (95% CI)	I^2
Intra-operative complications	6	250	32	0.12 (0.06 – 0.23)	71
Overall complications	8	270	92	0.38 (0.27 – 0.52)	72
Major complications	7	257	37	0.16 (0.10 – 0.24)	37
Pelvic sepsis – short term	8	264	34	0.16 (0.09 – 0.27)	60
Pelvic sepsis – overall	2	83	28	0.29 (0.11 – 0.57)	76

Figure 3. Morbidity following redo surgery.

	No. of studies	Sample Size	Events	Pooled Proportions (95% CI)	I^2
Overall succes rate	9	284	227	0.79 (0.69 – 0.86)	59
Rectal cancer	4	131	94	0.71 (0.63 – 0.79)	2
Rectal cancer with preoperative RTx	4	108	78	0.71 (0.59 – 0.82)	28
Rectal cancer and redo for pelvic sepsis	4	122	86	0.70 (0.59 – 0.80)	24
Redo coloanal anastomosis	6	186	139	0.74 (0.66 – 0.81)	22
Redo delayed anastomosis	3	36	26	0.71 (0.54 – 0.84)	0

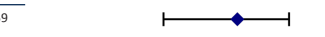


Figure 4. Subgroup analysis of success rate after redo surgery. RTx = radiotherapy.

Reasons for failure of the redo anastomosis are displayed in Table 5. Not all studies were clear about the final status of the patients with failure of the redo anastomosis. In 2 studies this was not reported[19] or not applicable.[22] We assume that patients who refused closure of the ileostomy or patients who were still scheduled for closure of the ileostomy at the time of publication still had their diverting ileostomy.[15,16,20,21] Some studies reported on patients with a definitive ostomy, but did not specify on the type of ostomy or possible additional salvage surgery.[15,17,18] An overview of the final status after failure of the redo anastomosis is shown in Table 5.

A total of 6 studies reported on functional outcome.[15,17,18,20–22] Incontinence was reported separately in 5 studies, resulting in a pooled proportion of 17% (95% CI, 10–26; I^2 25%).[15,17,20–22] In 4 of these studies, the incontinence was defined as incontinence for feces,[15,17,20,22] and in 1 study the definition for incontinence was not specified.[21] Furthermore, the type of incontinence for feces (eg, incontinence for solid stools, fluid stools, or soiling) and the frequency of the incontinence was not further specified in any study. One study determined functional outcome according to the Wexner score, with a median score of 8 (range, 0–17), and a score of 0 (optimal score) in 12 of 43

Table 4. Intra-operative and short-term outcome

Included studies	Morbidity							Mortality
Study	Intra-operative complications	Major complications (Clavien-Dindo ≥ 3)	Pelvic sepsis [a]	Anastomotic leakage	Isolated abscess	Surgical reinterventions	Readmissions	Death
Paineau et al.[19]	NR.	Grade 3: 1 (14%)	4 (57%)	0	0	1 (14%)	NR.	0
Schlegel et al.[22]	NR.	NR.	NR.	NR.	NR.	NR.	NR.	0
Lefevre et al.[17]	12 (36%)	Grade 3: 7 (21%) Grade 4: 2 (6%)	9 (27%)	4 (12%)	6 (18%)	7 (21%)	5 (15%)	0
Pitel et al.[21]	8 (12%)	Grade 3a: 1 (2%) Grade 3b: 7 (11%)	5 (8%)	NR.	NR.	7 (11%)	6 (9.3%)	0
Genser et al.[15]	6 (12%)	Grade 4: 1 (2%)	0	0	0	1 (2%)	1 (2%)	0
Patsouras et al.[20]*	1 (6%)	Grade 3: 2 (11%)	3 (17%)	2 (11%)	1 (6)	2 (11%)	NR.	0
Hallet et al.[16]	NR.	NR.	1 (13%)	0	1 (13%)	1 (13%)	NR.	0
Maggiori et al.[18]	2 (8%)	Grade 3-4: 5 (21%)	3 (13%)	0	3 (13%)	1 (4%)	NR.	0
Westerduin et al.[23]*	3 (5%)	Grade 3-4: 11 (19%)	9 (15%)	9 (15%)	0	6 (10%)	2 (3%)	0

NR = not reported. [a] Any pelvic infectious complication subsequent to the redo surgery, including anastomotic leakage, pelvic abscess and fistula.
* Separate data on redo CRA/CAA obtained from authors, data presented in table possibly not directly relatable to published data.

responding patients (28%).[21,24] Maggiori et al.[25] used the low anterior resection syndrome (LARS) score to assess functional outcome. No LARS was found in 7 of 17 (41%) of the responding patients, minor LARS in 7 of 17 (41%), and major LARS in 3 of 17 (18%) patients.[18]

Discussion

This systematic review on redo surgery with construction of a new coloanal or colorectal anastomosis shows a pooled success rate of 79% with a major postoperative complication rate of 16%. This was barely influenced by poor-quality studies included in the pooled proportions, because sensitivity analysis rendered almost the same result (77%). This suggests that redo surgery is a valuable treatment option in patients with a failed primary coloanal or colorectal anastomosis considering the current literature.

The high success rate is striking considering the complex type of surgery and might be partially explained by the high expertise in the centers performing the redo

procedures. Also, the relatively heterogeneous patient populations included in the studies might contribute to the high reported success rate. However, even in a subgroup analysis for patients with rectal cancer who had redo surgery for pelvic sepsis after the index surgery, a pooled weighted success rate of 70% was calculated. This is noteworthy, because it is a complex group of patients that will likely develop anastomotic leakage again. These patients often had preoperative radiotherapy that has been shown to be a significant risk factor for nonhealing of the anastomosis and chronic sinus formation.[7,26] The pelvis is expected to be fibrotic because of prolonged exposure to inflammation, in addition to harbor radiation fibrosis in the case of prior radiotherapy. One can hypothesize that a previously infected pelvis or still ongoing low-grade infection in a chronic sinus are prone to renewed inflammation and formation of pelvic abscesses. However, in the subgroup consisting of 144 patients who already had infectious problems preoperatively, the pooled proportion of pelvic sepsis was 14%. This surprising finding might be related to underreporting of overall pelvic sepsis (occur- ring at any time during follow-up), because in 7 of the 9 included studies, only short-term pelvic sepsis (occurring within 30 days postoperatively) was reported. A recent study showed that, in redo surgery, most cases of anastomotic leakage (63%) are diagnosed beyond this 30-day period.[23] This is also reflected by the pooled *overall* pelvic sepsis rate of 29% versus 16% *short-term* pelvic sepsis rate reported in the current review.

Also, technical causes for leakage or stenosis of the primary anastomosis, followed by a successful redo anastomosis must be considered. For example, too much tension on the initial anastomosis might be corrected by gaining additional bowel length during redo surgery. Based on our own experience, additional bowel length can often be obtained, because the splenic flexure was often not fully mobilized primarily and the inferior mesenteric vein was not divided at the pancreatic border. Differences in expertise between a referring center and the tertiary center that subsequently performs redo surgery may play a role. Another explanation might be the vascularization. The low or high tie as performed during the initial (low) anterior resection can compromise blood supply to the most distal end of the colon. This might be at such a degree that there is no obvious ischemia, but it is also not sufficient for anastomotic healing. Compensatory optimization of blood flow in the afferent colon may occur in the subsequent period until redo surgery. Such improved surgical conditions for anastomotic healing can also possibly explain the noteworthy high success rate in redo coloanal anastomoses.

The delayed anastomosis showed a relatively lower pooled success rate of 71%. However, it should be noted that only 3 studies reported on the success rate of the delayed anastomoses separately for a total of 36 patients.[16,18,23] An explanation for the

Table 5. Long-term outcome

Included studies	Morbidity	Success rate					Functional outcome	
Study	Pelvic sepsis at any time during follow-up	Restoration of bowel continuity	Timing assessment restoration of bowel continuity	Time between redo and stoma closure	Reasons for failure redo anastomosis	Final status after failure redo anastomosis	Functional outcome scale	Incontinence
Paineau et al.[19]	NR.	NR.	NR.	NR.	NR.	NR.	NR.	NR.
Schlegel et al.[22]	NR.	27/27 (100%)	At mean FU; 29 months ± 14 (range 5-60).	Median 3 months (range 3 weeks - 7 months).	NA.	NA.	NR.	0/27
Lefevre et al.[17]	NR.	23/33 (70%)	At FU more than 3 months after stoma closure.	Mean 4 months ± 4 (range 0.3-16).	2 peroperative failures. 1 chronic AL. 1 stricture. 1 cancer recurrence. 1 anal fistula. 1 poor functional result. 3 NR.	2 definitive colostomy for peroperative failure. 1 HR for AL. 7 NR.	NR.	4/23 (17%)
Pitel et al.[21]	NR.	54/66 (82%)	At median FU; 36 months, mean 48 months ± 38 (range 0-122).	Median 2 months (range 1-122).	3 peroperative failure. 3 pelvic sepsis recurrence. 4 refusal of ostomy closure. 1 poor functional result. 1 cecal perforation requiring cecostomy.	3 HR for peroperative failure. 4 refusal of ostomy closure. 1 cecostomy for cecal perforation. 4 NR.	Wexner score: Median Wexner score: 8 (range 0-17) Wexner score = 0: 12/43 (28%)	6/43 (14%)

Table 5. *Continued*

Included studies	Morbidity	Success rate					Functional outcome	
Study	Pelvic sepsis at any time during follow-up	Restoration of bowel continuity	Timing assessment restoration of bowel continuity	Time between redo and stoma closure	Reasons for failure redo anastomosis	Final status after failure redo anastomosis	Functional outcome scale	Incontinence
Genser et al.[15]	NR.	46/50 (92%)	At median FU; 21 months. Mean 37 months (range 1-137).	Median 3 months (range 2-10).	2 strictures. 1 scheduled for restoration. 1 poor functional result.	1 definitive stoma for poor functional results 1 scheduled for restoration. 2 NR.	NR.	7/44 (16%)
Patsouras et al.[20]*	NR.	15/18 (83%)	At time of stoma closure; at median 6 months after redo surgery (IQR 3-6).	Median 6 months (IQR 3-6).	2 refusal of ostomy closure. 1 scheduled for restoration.	2 refusal of ostomy closure. 1 scheduled for restoration.	NR.	4/12 (33%)
Hallet et al.[16]	NR.	4/7 (57%)	At median FU; 274 days (IQR 259-394).	Median 205 days (range 143-597).	1 scheduled for restoration. 1 refusal of ostomy closure. 1 colonic stump ischemia.	1 scheduled for restoration. 1 refusal of ostomy closure. 1 APR because of colonic stump ischemia.	NR.	NR.
Maggiori et al.[18]	4 (17%)	19/24 (79%)	At mean FU; 29 months ± 19 (range 4-82).	NR.	2 pelvic sepsis recurrence. 1 anastomotic stricture. 2 poor functional results.	5 definitive ostomy.	LARS score: 7/17 (41%) no LARS 7/17 (41%) minor LARS 3/17 (18%) major LARS	NR.

Table 5. *Continued*

Included studies	Morbidity	Success rate					Functional outcome	
Study	Pelvic sepsis at any time during follow-up	Restoration of bowel continuity	Timing assessment restoration of bowel continuity	Time between redo and stoma closure	Reasons for failure redo anastomosis	Final status after failure redo anastomosis	Functional outcome scale	Incontinence
Westerduin et al.[23]*	24 (41%)	39/59 (66%)	At median FU; 27 months (IQR 17-36).	Median 19 weeks (IQR 13-35).	18 AL. 1 scheduled for restoration. 1 restoration too high risk for patient.	14 intersphincteric resection + definitive colostomy. 6 diverting ileostomy still present.	NR.	NR.

Abbreviations: NR = not reported, NA = not applicable, FU = follow-up, HR = Hartmann's resection, AL = anastomotic leakage, APR = abdominoperineal resection, LARS = Low Anterior Resection Syndrome.

* Separate data on redo CRA/CAA obtained from authors, data presented in table possibly not directly relatable to published data.

lower success rate in the delayed anastomoses could be that these patients had a higher a priori risk of failure. Extensive fibrosis, persistent pelvic sepsis, or poor quality of a (short) rectal cuff might have been reasons for the operating surgeon not to create a definitive anastomosis during the first step of redo surgery.

Redo surgery is often performed as a last chance to restore bowel continuity and to avoid a definitive colostomy. However, successful restoration of bowel continuity is not the only factor contributing to ultimate success. Functional outcome might be even more important. Fibrosis following pelvic inflammation and previous radiotherapy might be reasons for impaired function.[27] A pooled incontinence rate of 17% was found, but this might range from daily incontinence for solid stools to soiling once a week. Furthermore, functionality is also determined by frequency, clustering of fragmented bowel movements, urgency, and increased intestinal gas. Maggiori et al[18] reported on 59% of patients with minor or major LARS, and the 72% of patients with a Wexner score higher than zero reported by Pitel et al[21] point in the same direction. Some patients persistently disapprove the option of a definitive colostomy, and might be satisfied with their quality of life despite a worse score on a functional test. Others eventually accept a colostomy in second or third instance, and conclude that they got their lives back because of not being bothered by their bowel movements the whole day long. This requires an intensive decision-making process and individualized approach.

The limitation of this review is the lack of RCTs and high-quality studies. The 9 included studies still comprise a relatively small and heterogeneous patient population, and only few raw data were available for subgroup analysis. This can be explained by the fact that redo surgery still is quite rare and only performed in highly motivated and selected patients by mostly expert centers. Especially the delayed anastomosis is expected to be performed for specific indications by surgeons with specific expertise. Therefore, the results will not be directly generalizable to all redo procedures. There is also a risk of publication bias, with the potential of incidentally performed redo procedures in nonexpert centers with disappointing results that are not reported. When interpreting the results of this review, one should keep in mind that these are results from expert centers and specialized surgeons. The outcome of this review can hopefully be used in the counselling of patients with a failed primary colorectal or coloanal anastomosis and shows the need for larger and homogeneous studies.

Conclusion

Redo surgery aiming at reconstruction of the anastomosis seems to be a valuable treatment option in selected patients with a complicated primary colorectal or coloanal anastomosis. Currently available literature is scarce, with only relatively small heterogeneous cohorts from tertiary centers. This illustrates the complexity of pelvic redo anastomosis that preferably is concentrated in a few dedicated centers, which also allows for optimization of the technique.

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Appendix 1. Search items

Date of search: August 31st 2017

MEDLINE (via Ovid)

Database(s): **Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)** 1946 to Present

Search Strategy

#	Searches
1	((Anastomosis, Surgical/ and (*intestinal diseases/su or exp *colonic diseases/su or exp *Rectal Diseases/su or *Colon/su or *Anal Canal/su or *Rectum/su)) or (colo* adj3 anastomos*).ti,ab,kw.) and (Reoperation/ or (redo* or repeat* or reoperat* or re-operat* or reanastomos* or re-anastomos* or pull-through).ti,ab,kw.)
2	exp treatment outcome/ or exp Postoperative Complications/ or exp Morbidity/ or exp Mortality/ or "Quality of Life"/ or (success rate* or functional outcome* or surgical outcome* or quality of life or morbidit* or complication*).ti,ab,kw. or ((short-term or long-term) adj3 (outcome* or result*)).ti,ab,kw.
3	1 and 2

EMBASE (via Ovid)

Database(s): **Embase Classic+Embase** 1947 to 2016 August 02

Search Strategy

#	Searches
1	(intestine anastomosis/ or colon anastomosis/ or colorectal anastomosis/ or rectum anastomosis/ or colon anastomosis/ or (colo* adj3 anastomos*).ti,ab,kw.) and (reoperation/ or pull through operation/ or (redo* or repeat* or reoperat* or re-operat* or re-operat* or reanastomos* or re-anastomos* or pull-through).ti,ab,kw.)
2	exp treatment outcome/ or exp postoperative complication/ or exp postoperative complication/ or exp mortality/ or exp morbidity/ or exp "quality of life"/ or (success rate* or functional outcome* or surgical outcome* or quality of life or morbidit* or complication* or ((short-term or long-term) adj3 (outcome* or result*))).ti,ab,kw.
3	1 and 2

Cochrane Library

ID Search Hits
#1 MeSH descriptor: [Anastomosis, Surgical] explode all trees
#2 MeSH descriptor: [Intestinal Diseases] explode all trees and with qualifier(s): [Surgery - SU]
#3 MeSH descriptor: [Colonic Diseases] explode all trees and with qualifier(s): [Surgery - SU]
#4 MeSH descriptor: [Rectal Diseases] explode all trees and with qualifier(s): [Surgery - SU]
#5 MeSH descriptor: [Colon] explode all trees and with qualifier(s): [Surgery - SU]
#6 MeSH descriptor: [Anal Canal] explode all trees and with qualifier(s): [Surgery - SU]
#7 MeSH descriptor: [Rectum] explode all trees and with qualifier(s): [Surgery - SU]
#8 #1 and (#2 or #3 or #4 or #5 or #6 or #7)
#9 colo* near/3 anastomos*:ti,ab,kw (Word variations have been searched)
#10 #8 or #9
#11 MeSH descriptor: [Reoperation] explode all trees
#12 redo* or repeat* or reoperat* or re-operat* or reanastomos* or re-anastomos* or pull-through:ti,ab,kw (Word variations have been searched)
#13 #11 or #12
#14 #10 and #13

Clinicaltrials.gov

https://clinicaltrials.gov/
searched for: pull-through anastomosis, redo anastomosis, reoperation coloanal anastomosis.

International clinical trials register platform (ICTRP):

WHO ICTRP Database http://apps.who.int/trialsearch/
Searched for: coloanal anastomosis, colorectal anastomosis.

CHAPTER 7

Redo coloanal anastomosis for anastomotic leakage after low anterior resection for rectal cancer: an analysis of 59 cases

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Abstract

Aim

The construction of a new coloanal anastomosis (CAA) following anastomotic leakage after low anterior resection (LAR) is challenging. The available literature on this topic is scarce. The aim of this two-centre study was to determine the clinical success and morbidity after redo CAA.

Method

This retrospective cohort study included all patients with anastomotic leakage after LAR for rectal cancer who underwent a redo CAA between 2010 and 2014 in two tertiary referral centres. Short- and long-term morbidity were analysed, including both anastomotic leakage and permanent stoma rates on completion of follow-up.

Results

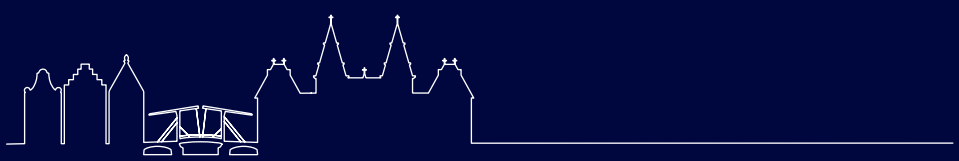
A total of 59 patients were included, of whom 45 (76%) were men, with a mean age of 59 years (SD ± 9.4). The median interval between index and redo surgery was 14 months [interquartile range (IQR) 8–27]. The median duration of follow-up was 27 months (IQR 17–36). The most frequent complication was anastomotic leakage of the redo CAA occurring in 24 patients (41%), resulting in a median of three reinterventions (IQR 2–4) per patient. At the end of follow-up, bowel continuity was restored in 39/59 (66%) patients. Fourteen (24%) patients received a definitive colostomy and six (10%) still had a diverting ileostomy. In a multivariable model, leakage of the redo CAA was the only risk factor for permanent stoma (OR 0.022; 95% CI 0.004–0.122).

Conclusion

Redo CAA is a viable option in selected patients with persisting leakage after LAR for rectal cancer who want their bowel continuity restored. However, patients should be fully informed about the relatively high morbidity and reintervention rates.

What does this paper add to the literature?

This is one of the largest homogeneous cohort studies on anastomotic leakage after low anterior resection for rectal cancer that is treated with the construction of a new coloanal anastomosis. This study shows that this complex and still quite rare procedure results in moderate success with significant associated morbidity.



Introduction

Low anterior resection (LAR) for rectal cancer with a low colorectal anastomosis (CRA) or coloanal anastomosis (CAA) is associated with substantial morbidity.[1,2] One of the most feared complications after colorectal surgery is anastomotic leakage, with a reported incidence of between 1% and 19%.[3-5] A diverting ileostomy has been shown to reduce symptomatic anastomotic leakage, but it still remains a serious complication with extensive consequences.[6,7]

Early management of anastomotic leakage following LAR usually consists of faecal diversion, if not already present, sometimes combined with transanal or percutaneous drainage of the presacral abscess. Leakage may even persist after more intensified treatment using an Endo-SPONGE® (B. Braun Medical B.V., Melsungen, Germany) and early transanal closure.[8] If early management of anastomotic leakage fails and continuity is desired, resection of the leaking anastomosis, followed by a new (redo) CAA, can be considered. Such an undertaking is likely to represent the patients' last opportunity for restoration of bowel continuity, but it may be associated with significant further impairment of functional outcome. Therefore, only highly selected patients who explicitly want to avoid a permanent stoma are eligible for redo surgery. Redo CAA is complex as a result of distorted pelvic anatomy and dense pelvic adhesions which occur following extensive prior dissection, prolonged pelvic sepsis and fibrosis following radiotherapy. Only a few studies with small and heterogeneous populations have described the outcome after this type of redo surgery. These are shown in Table 1.[9-13]

This two-centre study aimed to describe the intraoperative and postoperative outcomes, as well as the long-term results, including anastomotic healing and permanent stoma rates, after redo hand-sewn CAA for anastomotic leakage following LAR.

Method

Patients

Patients undergoing redo pelvic surgery were prospectively identified in two tertiary referral centres in Belgium (University Hospital Leuven) and the Netherlands (Academic Medical Centre, Amsterdam). Patients were eligible if there had been a persistent anastomotic leak following LAR with primary anastomosis performed for rectal cancer, in whom a new hand-sewn CAA was performed during redo surgery between January 2010 and December 2014. Both direct and delayed (Turnbull–Cutait) redo CAA were

Table 1. Overview of the literature on redo surgery

	Schlegel et al (2001)[13] n = 27	**Lefevre et al (2011)[10]** n = 33	**Pitel et al (2012)[12]** n = 66	**Genser et al (2013)[9]** n = 50	**Maggiori et al (2015)[11]** n = 24
Study period	1992-1996	1999-2008	2000-2010	1998-2011	2007-2013
Age at redo surgery (years)					
Mean	51	57	NR	NR	58
Median	NR	NR	60	62	NR
Range	24-66	39-79	28-79	40-84	25-77
Primary disease, n (%)					
Colorectal cancer	13 (48)	19 (58)	52 (79)	29 (58)	20 (83)
Diverticulitis	7 (26)	11 (33)	3 (5)	19 (38)	0
Hirschsprung's disease	2 (7)	1 (3)	1 (2)	0	0
Gynaecological	3 (11)	0	5 (8)	0	2 (8)
Other	2 (7)	2 (6)	5 (8)	2 (4)	2 (8)
Indications for redo surgery, n (%)					
Chronic pelvic sepsis	0	5 (15)	21 (32)	14 (28)	15 (63)
Prior Hartmann's procedure for AL	0	6 (18)	13 (20)	8 (16)	0
Stricture	27 (100)	17 (52)	10 (15)	20 (40)	0
Cancer recurrence	0	5 (15)	0	5 (10)	0
RVF	0	0	19 (29)	3 (6)	9 (37)
Other	0	0	3 (5)	0	0
Redo surgery					
Immediate failure of redo surgery, n (%)	0	2 (6)	3 (5)	0	0
Delayed anastomosis, n (%)	0	2 (6)	2 (3)	2 (4)	24 (100)
Location of redo anastomosis, n (%)					
Colorectal	7 (26)	19 (58)	0	26 (52)	0
Coloanal	20 (74)	12 (36)	63 (95)	24 (48)	24 (100)
Deviating stoma, n (%)	24/27 (89)	29/31 (94)	63/63 (100)	37/50 (74)	16/24 (67)
Intra-operative complications, n (%)	NR	12 (36)	8 (12)	6 (12)	2 (8)
Short-term outcomes					
Mortality, n (%)	0	0	0	0	0
Morbidity, n (%)					
Major Morbidity (Clavien-Dindo ≥3)	NR	9 (27)	8 (12)	1 (2)	5 (21)
Anastomotic leakage	NR	4 (12)	NR	0	NR
Pelvic abscess	NR	6 (18)	NR	0	3 (13)
Pelvic sepsis	NR	NR	5 (8)	NR	NR
Readmissions, n (%)	NR	5 (15)	6 (9)	1 (2)	NR
Surgical reinterventions, n (%)	NR	7 (21)	7 (11)	1 (2)	1 (4)
Long-term outcomes					
Duration of follow-up (months)					
Mean (SD)	29 (14)	29 (27)	48	37	29 (19)
Median	NR	NR	36	21	21
Range	5-60	3-91	0-122	1-137	4-82
Restoration of bowel continuity at last FU	27 (100)	23/31 (74)	54/63 (86)	46/50 (92)	19/24 (79)

NR = not reported, AL = anastomotic leakage, RVF = rectovaginal fistula, FU = follow-up.

included.[14-16] Patients with other indications for redo surgery, such as strictures, fistulas or local recurrence or a primary diagnosis other than rectal cancer were excluded. To increase homogeneity of the study cohort, stapled redo anastomosis, ileocolic interposition graft or ileo-anal pouch were also excluded. In order to adequately assess the long-term outcomes, only patients with a minimum follow-up of 1 year were included.

For this type of study with retrospective data collection, medical ethical approval and informed consent are not required by local law.

Surgical technique

Redo surgery was performed with both an abdominal and a perineal approach. For the abdominal phase, the patient was placed in the lithotomy position. The redo procedure was commenced laparoscopically where possible. Ureteric stents were inserted according to preferences of individual surgeons. Adhesiolysis was performed as necessary, followed by complete mobilization of the splenic flexure. A high-tie transection of the vessels (division of the inferior mesenteric artery 1 cm distally from the aorta and high ligation of the inferior mesenteric vein at the lower part of the pancreas) was performed in all cases to ensure adequate lengths of tension-free bowel. This provides a minimum of 10 cm additional colon length in comparison with low-tie transection.[17]

During the perineal phase, the (neo)rectum was excised distal to the leaking anastomosis. Sleeve mucosectomy was performed according to surgeon preference. The prone position was employed on occasions to increase accessibility to the leaking anastomosis. The colon was then pulled through the anal canal and either an immediate or delayed hand-sewn anastomosis between the colon and anus was performed. In delayed CAA, a colonic segment of 6–8 cm was exteriorized and wrapped in gauze and sutured with four absorbable stitches at the level of the future anastomosis. Viability of the colonic segment was checked daily and the anastomosis finished as a second stage, approximately 7–10 days later. At this time the colonic stump was transected at the level of the anal verge, and definitive sutures were placed. The delayed CAA enabled redo surgery in patients who had already undergone an ultra LAR.[14-16]

Data extraction

Patient and treatment characteristics were retrospectively collected from patient records. Patient charts, radiology reports and operative reports were searched for patient demographics, primary treatment characteristics, treatment characteristics of the redo surgery, hospital stay, complications, reinterventions, readmissions and mortality.

Definitions

The index operation was defined as the primary resection performed for rectal cancer. Anastomotic leakage was defined as a disruption of the anastomosis, identified at reoperation, endoscopy or extravasation of contrast during radiological imaging, irrespective of the presence of symptoms. As proposed by Caulfield et al.[18], an abdominal abscess or free pelvic fluid collection without extravasation of contrast was considered an occult anastomotic leak. Anastomotic leakage was assessed within 30 days and at the end of follow-up in order to include any delay in diagnosis of anastomotic leaks. A chronic presacral sinus was defined as anastomotic leakage present for at least 1 year after the index operation.

Short-term morbidity was graded according to the Clavien–Dindo classification of surgical complications within 30 days and was reported when graded III or higher.[19] This included all complications for which surgical, endoscopic or radiological intervention were required (grade III), all life-threatening complications for which intensive care management was required (grade IV), or when the death of a patient occurred (grade V). Long-term outcome was defined as occurring from 30 days postoperatively until the end of follow-up. Restoration of bowel continuity was defined as successful if there was no stoma present at the end of follow-up and there were no signs of recurrent pelvic sepsis.

Statistical analysis

According to distribution, numerical data were expressed as median with interquartile range (IQR) or mean with standard deviation (SD). Categorical variables were presented as number and proportion as a percentage. Variables with potential influence on successful restoration of bowel continuity at the end of follow-up were identified using univariable logistic regression analyses. Variables with a P-value < 0.10 were added to the multivariable model. An odds ratio (OR) < 1 indicated a decreased likelihood of successful bowel restoration. Analyses were performed using IBM SPSS Statistics for Windows (v.23.0, IBM Corp., Armonk, New York, USA).

Results

From an initial cohort of 114 redo procedures, a total of 59 patients were included, 40 patients from the University Hospital Leuven and 19 from the Academic Medical Centre, Amsterdam. All patients underwent redo surgery because of persistent anastomotic leakage after LAR. A total of 18 patients were not considered eligible for this study because of other indications for the index operation than rectal cancer, 12 patients

Table 2. Baseline characteristics

	n=59
Gender	
Male	45 (76%)
Female	14 (24%)
Age at redo surgery (years), *mean (± SD)*	59 (± 9.4)
BMI[1], m*edian (IQR)*	24.7 (22.6-26.2)
ASA[2] score as scored by anaesthesiologist	
1	11 (19%)
2	35 (59%)
3	13 (22%)
Type of anastomosis during index operation	
Colorectal	39 (66%)
Coloanal	20 (34%)
Neoadjuvant treatment	
None	6 (10%)
Short course radiotherapy	12 (20%)
Long course chemoradiation	41 (70%)
Patients with one or more reinterventions for anastomotic leakage after index operation	38[a] (64%)
Transanal drainage of abscess	19[b] (32%)
Percutaneous drainage of abscess	3[c] (5%)
One or more endo-sponge® treatment(s)	8 (14%)
Relaparotomy or relaparoscopy	4 (7%)
Acute Hartmann procedure	1 (2%)
Formation of diverting stoma	19 (32%)
Restoration of continuity after acute stoma	6 (10%)
Chronic presacral sinus prior to redo surgery	31 (53%)
Interval between index operation and redo surgery	
Months, median (IQR)	14 (8-27)

BMI, body mass index; ASA, American Society of Anaesthesiologists.
[a] Thirty-eight patients had 62 interventions,
[b] Nineteen patients had 20 transanal drainages,
[c] Three patients had 4 percutaneous drainages.

were not eligible because of indications for redo surgery other than anastomotic leakage and 25 patients were not considered eligible because their redo anastomosis was stapled. Forty-two (71%) patients were referred from other centres. The median time between the index operation and redo surgery was 13 months in the nonreferral group (IQR 4–32 months) and 14 months (IQR 11–28 months) in the referred group (P = 0.561). Baseline characteristics are shown in Table 2.

Intra-operative characteristics

All patients undergoing a redo CAA had a diverting stoma, of which 23 (39%) were created during the redo procedure (Supplement Table 1.). An open approach was used

in 57 (97%) patients and 5 (9%) patients underwent delayed suturing of the CAA (Turnbull–Cutait procedure). The Turnbull–Cutait procedure was indicated in patients with very low anastomoses in whom a conventional hand-sewn coloanal anastomosis would have resulted in an anastomosis at the site of the leak. Three intra-operative complications were reported (two bladder perforations and one ureteric injury).

Short-term outcomes

The median hospital stay was 11 days (IQR 8–14). A total of 11/59 (19%) patients developed one or more complications of Clavien–Dindo grade III or higher within 30 postoperative days. Anastomotic leakage occurred in nine patients, of whom three patients underwent a relaparotomy, with surgical drainage of a pelvic abscess in two patients and dismantling of the anastomosis in one patient. Two (3%) patients were readmitted within 30 postoperative days, one because of anastomotic leakage and one on suspicion of a rectovaginal fistula that could not be confirmed. There was no short-term mortality.

Long-term outcomes

The median follow-up time was 27 months (IQR 17–36 months). A complication requiring reintervention occurred in 25/59 patients (42%) more than 30 days after surgery. Of these patients, 14 (56%) were treated for anastomotic leakage of the redo CAA, 6 (24%) for an anastomotic stricture, 3 (12%) had an incisional hernia requiring reoperation and 2 (8%) patients were treated because of an enterocutaneous and colovesical fistula, respectively. Twenty patients (34%) were readmitted more than 30 days after surgery.

In addition to the nine patients with anastomotic leakage diagnosed within 30 postoperative days, delayed anastomotic leakage of the redo CAA (> 30 days) was observed in 15/59 (25%) patients. All needed reintervention, except for one patient who was successfully treated with intravenous antibiotics. The overall leakage rate was 24/59 (41%) with a median time from redo surgery until diagnosis of 8 weeks (IQR 2–19 weeks). The outcome data for these 24 patients are presented in Table 3.

A total of 9/59 patients (15%) died during follow-up. Six patients died because of progressive disease, two after an out-of-hospital cardiac arrest, and one patient died of metastatic melanoma. An overview of the long-term outcome is shown in Table 4.

Restoration of bowel continuity

The diverting ileostomy was closed, with or without constructing a definitive colostomy, in 53 patients (90%). The median time between the redo procedure and closure of the diverting ileostomy was 19 weeks (IQR 13–35 weeks). In four patients, leakage was

Supplement Table 1. Intra-operative characteristics

	n=59
Type of redo CAA *Direct (pull through)* *Delayed (Turnbull-Cutait)*	 54 (92%) 5 (9%)
Technique *Open* *Laparoscopic*	 57 (97%) 2 (3%)
Duration of surgery *Minutes, median (IQR)*	 197 (158-252)
Deviating stoma at time of redo *Initial stoma after index operation* *Deviating stoma after emergency surgery* *Deviating stoma created during redo surgery*	59 (100%) 20 (34%) 16 (27%) 23 (39%)
Intra-operative complications *Bladder perforation* *Ureter injury*	3 (5%) 2 1

CAA = coloanal anastomosis.

Table 3. Anastomotic leakage following redo coloanal anastomosis

	n=59
Total number of patients with AL of redo CAA *Treated by one or more reintervention(s)* *Treated conservatively*	24/59 (41%) 23 1
Number of reinterventions for anastomotic leakage, *median, (IQR)*	3 (2-4)
Reinterventions *Total number of drainages* *Transanal drainage* *Percutaneous drainage* *Surgical drainage*	 29[a] 14 10 5
Transanal closure of anastomotic defect One or more endo-sponge® treatment(s)	9[b] 6
Advancement flap	2
Placement of new diverting stoma	5[c]
Redo-redo CAA	1
Intersphincteric resection + definitive colostomy	13
Number of patients with AL who had neoadjuvant radiotherapy	22/24 (92%)
Patients with AL and restoration of bowel continuity at end FU	6/24 (25%)

AL, anastomotic leakage; CAA, coloanal anastomosis; IQR, interquartile range; FU, follow-up.
[a] In 22 patients.
[b] In eight patients.
[c] In three patients simultaneously with surgical drainage.

Table 4. Long-term outcomes

	n=59
Time of follow-up *Months, median (IQR)*	 27 (17-36)
Complications requiring reintervention	25 (42%)
Readmission *Anastomotic leakage* *Ileus* *High output stoma*	20 (34%) 15 4 1
Restoration of bowel continuity at 6 months	35 (59%)[a]
Restoration of bowel continuity at end of FU	39 (66%)[b]
Definitive colostomy at end of FU	14 (24%)
Ileostomy at end of FU	6 (10%)
Reason failure restoration bowel continuity at end FU *Anastomotic leakage* *Restoration of bowel continuity scheduled* *Patient considered too high risk for surgery*	 18[c] 1[d] 1
Mortality	9 (15%)

IQR, interquartile range; FU, follow-up. [a] Two of these patients did not have bowel continuity at end of follow-up, due to anastomotic leakage. [b] Six patients did not have bowel continuity at six months, but did have continuity at end of follow-up. [c] In five patients with ileostomy. [d] In one patient with ileostomy

diagnosed after closure of the diverting ileostomy at days 3, 26, 67 and 215, respectively. Two of these patients had a CT scan, one patient had a contrast enema and one patient underwent examination under general anaesthesia to assess the anastomosis before closure of the ileostomy.

At 6 months postoperatively, 35 of the 59 patients (59%) had restoration of bowel continuity. Two of these patients did not have bowel continuity at the end of follow-up due to anastomotic leakage that was diagnosed subsequent to the stoma reversal. At the end of follow-up, bowel continuity was successfully restored in 39 out of the 59 patients (66%). In 18 out of 20 patients, continuity was not restored due to leakage of the redo CAA (Table 4). In 14 of these 18 patients, the redo CAA was performed more than 1 year after the index operation (chronic sinus). Of the 20 patients without bowel continuity, 14 patients underwent an intersphincteric proctectomy with definitive colostomy, and in 6 patients, the diverting ileostomy was still present at the end of follow-up.

Univariable logistic regression analyses revealed that a chronic presacral sinus prior to the redo procedure ($P = 0.056$) and anastomotic leakage of the redo CAA ($P < 0.001$) were risk factors for unsuccessful restoration of bowel continuity (Table 5). Anastomotic leakage of the redo CAA remained the only independent predictor for permanent stoma ($P < 0.001$) in multivariable analysis.

Table 5. Uni- and multivariable analysis for successful restoration of bowel continuity at end of follow-up

	Univariable analysis		**Multivariable analysis**	
Variable	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Age	0.961 (0.904-1.022)	0.204	-	
ASA score 1 2 3	 1.000 (ref) 0.500 (0.113-2.210) 2.062 (0.277-15.357)	 0.200 0.361 0.480	 - - -	
Referral from other hospital	0.500 (0.139-1.802)	0.289	-	
Primary anastomosis *(CRA/CAA)*	1.875 (0.565-6.227)	0.305	-	
Chronic presacral sinus *(>1 year between index operation and redo surgery)*	0.331 (0.105-1.043)	0.059	0.469 (0.095-2.304)	0.351
Neoadjuvant radiotherapy	0.972 (0.162-5.823)	0.975	-	
Delayed redo anastomosis	0.750 (0.115-4.898)	0.764	-	
Laparoscopy	0.500 (0.030-8.439)	0.631	-	
Anastomotic leakage	0.020 (0.004-0.111)	<0.001	0.022 (0.004-0.122)	<0.001

ASA, American Society of Anaesthesiologists; CRA, colorectal anastomosis; CAA, coloanal anastomosis.

Discussion

The present study shows that redo CAA for non-healing leakage after LAR for rectal cancer prevents two-thirds of a highly selected group of patients from having a permanent stoma. Anastomotic leakage following redo hand-sewn CAA occurred in 41% of all patients and appeared to be the only risk factor for a permanent stoma in this group of patients.

Previous studies on redo anastomotic surgery have reported success rates of between 74% and 100%, which is higher than the 66% reported in our study.[9-13] Pitel et al.[12] reported successful restoration of bowel continuity in 54/63 patients (86%) with a complication rate of 17%, which included anastomotic leakage in 8%. Comparison with earlier studies is difficult because previously published series describe a mixture of redo CRA and redo CAA for multiple indications and a broad spectrum of primary diseases. The present study describes a homogeneous group of rectal cancer patients who underwent redo hand-sewn CAA for prior anastomotic leakage after LAR, with 90% having received preoperative radiotherapy.

Studies which included noninfectious indications for redo surgery, such as anastomotic strictures and cancer recurrences, might be expected to have lower

anastomotic leakage rates following redo surgery. In this study 25% of patients had a delayed diagnosis of anastomotic leakage, with a median time to diagnosis of the leakage of 8 weeks. This might be accounted for by persistent presacral sepsis eroding the new anastomosis. The observation that redo surgery is more frequently successful in studies including all or most patients undergoing redo surgery in the absence of pelvic sepsis supports this contention. Another factor that has probably contributed to the relatively high leakage rate is the level of the anastomosis. It is well recognized that the lower the anastomosis the higher the risk of leakage.[5,20-22] This study included only very low CAA, leaving this study population at higher risk of leakage compared to studies also including redo CRA.

Lefevre et al.[10] reported a significantly higher failure rate of the redo anastomosis after initial CAA than after initial CRA. This could not be reproduced in the current study (P = 0.305). This is explained by the fact that, in the study by Lefevre et al., in most patients with a prior CRA a new CRA could be created.

Another important factor in the aetiology of woundhealing problems and infectious complications is neoadjuvant radiotherapy. Radiotherapy has been associated with anastomotic leakage after rectal cancer surgery, with reported ORs varying from 1.34 up to 3.5.[20,21,23] Several other studies, including the Dutch TME trial[24], did not confirm the increased risk of anastomotic leakage after radiotherapy. However, that trial demonstrated that radiotherapy was an independent predictor of nonreversal of a secondary constructed stoma because of leakage.[25] This indicates that radiotherapy does have an impact on healing of the anastomosis after leakage has occurred. The present cohort of redo CAA revealed that 90% of the patients received neoadjuvant (chemo)radiotherapy prior to their index operation. This is in line with the hypothesis that radiotherapy is associated with nonhealing of a leaking anastomosis, and most likely played a role in subsequent secondary anastomotic leakage after redo surgery. Univariable analysis showed no direct association between neoadjuvant (chemo) radiotherapy and failure of the redo procedure, but this could be explained by the skewed distribution between groups, with a low number of patients (n = 6) in the group without any form of previous radiotherapy.

It is possible that we might achieve higher rates of restoration of intestinal continuity in the future. One patient is already scheduled for restoration after completion of adjuvant therapy and a further five are receiving active therapy for controlled leakage.

The median time between the index operation and redo surgery was 14 months, with half of the patients having a chronic pelvic sinus at the time of redo surgery. In current practice we attempt to plan redo surgery at an earlier stage, when the pelvis

is less fibrotic and the anatomy less distorted due to a shorter exposure to inflammation. Endoscopic vacuum-assisted systems, such as the Endo-SPONGE®, have the potential ability to sterilize the presacral abscess cavity prior to redo surgery and are being used more frequently in current practice.[26,27] In this study, eight patients were treated with an Endo-SPONGE® prior to redo surgery. Cleaning the presacral cavity with the Endo-SPONGE® might reduce the recurrence of presacral abscess and thereby decrease the risk of subsequent anastomotic leakage.

Even though redo surgery can be technically difficult because of fibrosis, inflammation and distorted anatomy, the intra-operative complication rate was low. This could be a result of the fact that this study was conducted in two tertiary referral centres for redo surgery. Despite the experience in redo surgery, the postoperative complication rate was still high, with more than 40% of the patients experiencing secondary anastomotic leakage. Patients should be informed of the high risk of postoperative morbidity beforehand, and should be closely involved in the decision-making process.

The minimally invasive approach through transanal minimally invasive surgery (TAMIS) is becoming more popular, not only for primary resection of rectal cancer but also for redo surgery.[28-30] In the current series, no patients underwent TAMIS, but it is now the preferred approach because of the greater accessibility and visibility, possibly leading to better results than conventional redo surgery with only the abdominal approach.[28]

The aim of redo surgery is to restore bowel continuity on the assumption that this is associated with improved quality of life. As such, the functional outcome after redo surgery is most important. Incontinence and irregular bowel action can be of such severity that patients may opt for a definitive stoma which can be more manageable. Patients should be made aware of the increased risk of an impaired functional outcome. Hallböök et al.[31] showed that there is a high probability of poor function of the neorectum due to decreased pliability caused by fibrosis following pelvic sepsis. Although we have conducted follow-up for at least 1 year after redo surgery, whereby restoration of continuity can be reliably assessed, this length of follow-up might not be sufficient for us to assess definitive functionality in all patients. There is still a chance that a small number of patients will eventually end up with functional failure and will require a definitive colostomy.

In our study we have focused solely on restoration of bowel continuity and surgery-related complications. Further research focusing on functional outcome after redo CAA is recommended to aid in the decision-making process for patients with a complicated postoperative course after LAR for rectal cancer.

Conclusion

Redo CAA is a useful surgical option in rectal cancer patients with anastomotic leakage after LAR, with a success rate of two out of three. However, the redo procedure is associated with a high rate of secondary anastomotic leakage. Therefore, it is crucial to inform patients of this risk beforehand whilst aspiring to bowel continuity.

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CHAPTER 8

Transanal minimally invasive surgical management of persisting pelvic sepsis or chronic sinus after low anterior resection

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Abstract

Background
Redo surgery of persisting pelvic sepsis or chronic presacral sinus after low anterior resection (LAR) for rectal cancer is challenging. Transanal minimally invasive surgery (TAMIS) improves visibility and accessibility of the deep pelvis.

Objective
The aim of this study was to compare the conventional approach with TAMIS for redo pelvic surgery with or without anastomotic reconstruction.

Design
This is a retrospective cohort study.

Settings
This study was conducted in a tertiary referral centre.

Patients
All consecutive patients undergoing redo pelvic surgery after low anterior resection for rectal cancer between January 2005 and March 2018 were included.

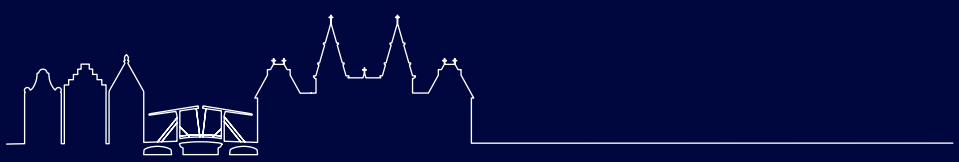
Interventions
Redo surgery was divided into redo anastomosis and intersphincteric completion proctectomy (ICP). TAMIS procedures since November 2014 were compared with the conventional approach.

Main outcome measures
Primary end-points were procedural characteristics and 90-day major complications.

Results
In total, 104 patients underwent redo surgery; 47 received a redo anastomosis (18 conventional and 29 TAMIS) and 57 underwent ICP (35 conventional and 22 TAMIS). The transabdominal part of the TAMIS procedures was performed laparoscopically in 72% and 59% of redo anastomosis and ICP, respectively, compared to 6% and 34%, respectively, in the conventional group ($P < 0.001$ and $P = 0.100$). Ninety-day major complication rate was 33% and 45% after redo anastomosis ($P=0.546$) and 29% and 41% after ICP ($P=0.349$) in conventional surgery and TAMIS, respectively.

Limitations
Limitation of this study is the relatively small sample size.

Conclusions
This study suggests that TAMIS is a valid alternative to conventional top-down redo pelvic surgery for persisting pelvic sepsis or chronic sinus, with more often a laparoscopic approach for the abdominal part.



Introduction

Anastomotic leakage remains a significant problem following surgery for rectal cancer and has been reported to occur in up to 20% of cases following low anterior resection.[1] Anastomotic leakage mandates early management including faecal diversion, transanal or percutaneous drainage, treatment with endo-SPONGE® (B. Braun Medical B.V., Melsungen, Germany), or endo-SPONGE® assisted transanal closure of the anastomotic defect.[2] However, pelvic sepsis might persist or ultimately a symptomatic chronic sinus might develop.[1, 3]

In the fit patient, who is highly motivated to preserve bowel continuity, the leaking anastomosis can be excised and a new anastomosis constructed after further mobilization of the descending colon. In less fit patients with additional comorbidities or patients with less motivation for preservation of bowel continuity, a chronic sinus may require intersphincteric completion proctectomy (ICP) with excision of the leaking anastomosis, debridement of the abscess cavity and fistula tracts, and filling of the presacral cavity with omentoplasty to control chronic sepsis and its secondary complications.

The most distal part of the pelvic dissection deep down in the pelvis is very demanding because exposure behind the prostate or vagina is limited. The pelvic dissection removing the leaking low anastomosis is quite demanding due to inflammatory, radiation-induced and surgical fibrotic scarring and adhesions. A recent systematic review on conventional redo surgery describes an overall success rate for redo anastomosis after pelvic sepsis of 70%, with a pooled rate of major postoperative morbidity of 16%.[4]

Since its first introduction as a technique for the resection of rectal cancer in 2010, transanal minimally invasive surgery (TAMIS) has gained popularity.[5] Total mesorectal excision (TME) through TAMIS (TaTME) has shown to be a feasible and safe approach compared to conventional laparoscopic TME when considering postoperative and short-term oncological outcome.[6-9] The strength of the TAMIS platform is the facilitated dissection deep down in the pelvis due to improved visibility and accessibility. The TAMIS platform might therefore be particularly helpful in redo surgery for the leaking anastomosis, overcoming the hazards in the deep pelvis caused by prior surgery, radiotherapy and chronic sepsis. The aim of this study is to describe the procedural characteristics and postoperative short-term outcomes of TAMIS redo surgery after low anterior resection for rectal cancer including both redo anastomosis and ICP, and to compare these to outcomes following conventional redo pelvic surgery.

Materials & Methods

Patients and data collection

All patients undergoing redo pelvic surgery after low anterior resection for rectal cancer, consisting of a redo anastomosis or ICP, were prospectively registered in our centre. Conventionally, redo pelvic surgery consisted of open or laparoscopic abdominal surgery, combined with an open transanal approach. Since November 2014, the transanal part of the procedure was performed using TAMIS. All consecutive patients undergoing TAMIS redo surgery between November 2014 and March 2018 were compared to a consecutive cohort of patients who underwent conventional redo surgery between January 2005 and August 2016. Conventional redo patients included between late 2014 and August 2016 were only ICP patients in whom adequate visualization using only a Lone Star Retractor® (Cooper Surgical, Trumbull, United States) could be achieved. All indications for redo surgery were included. All patients had a primary failed anastomosis within 5 centimeter from the anorectal junction, both in the conventional and redo group. Patients with a primary underlying disease other than rectal cancer and patients with a follow-up of less than 90 days were excluded, not excluding patients who died within the 90-day postoperative period. Patient and treatment characteristics were retrospectively collected from patient charts. The Institutional Review Board of the Academic Medical Centre in Amsterdam approved of this study and concluded that written informed consent was not obligatory due to the retrospective data collection and anonymous analysis of data.

Surgical technique

Redo pelvic surgery for leaking anastomosis consists of a rendezvous between a top-down abdominal phase, either open or laparoscopic, and a bottom-up transanal phase. The top-down dissection was conventionally continued towards the pelvic floor with a limited open transanal approach to complete intersphincteric dissection, followed by hand-sewn anastomosis in case of restoration of continuity. With the use of TAMIS, the top-down dissection can be restricted to the upper pelvis, and the bottom-up approach is extended towards the mid-pelvis. This combines the most effective parts of the two approaches, aiming to perform a more precise dissection and to theoretically avoid the risk of nerve injury and hemorrhage. Furthermore, this enables a two-team approach that facilitates a complex procedure with reduction of operative time.

The abdominal phase consists of adhesiolysis if necessary and further mobilization of the left colon to enable sufficient reach to bring the conduit down. Preferably, the left colonic artery is preserved. The inferior mesenteric vein, which limits the reach of the efferent colon to the deep pelvis, is always ligated if not done so during the primary

operation, and sometimes it is necessary to take down the inferior mesenteric artery as well if still present. The abdominal phase can be done open, hand-assisted or by straight laparoscopy depending on the extent of the adhesions and fibrosis, and the presence of incisional hernia.

The operative technique for TAMIS was first elaborately described by Attalah *et al* in 2009 and more recently by Trépanier *et al*.[5, 10] TAMIS for redo anastomosis starts with installation of a Lone Star Retractor® (Cooper Surgical, Trumbull, United States). A pudendal nerve block with levobupivacaine is given to optimise anal sphincter muscle relaxation, after which the single port (GelPOINT® Path Transanal Access Platform, Applied Medical, Rancho Santa Margarita, United States) is introduced. There is no lower limit to what can be managed by TAMIS. In the lowest cases, dissection starts with only Lone Star® retraction, followed by the GelPOINT® single port when the level of the puborectal sling is passed. In most cases a purse-string is not possible due to the limited distance between the anus and the anastomosis. The rectum is transected just below the old anastomosis and the dissection is continued bottom-up close to the neorectum in order to avoid damage to the pelvic sidewall structures. After resection of the leaking anastomosis, extensive debridement of the septic pockets is necessary before pulling through the newly created afferent colon loop. The new (redo) anastomosis can either be hand-sewn or stapled by use of an intraluminal circular stapling device (Chex™, Frankenman International Ltd., Sheung Wan, Hong Kong) depending on the length of the remaining rectal cuff. It is our practice to reinforce the stapled anastomosis with an intraluminally placed running suture Monoplus® 3.0 and a diverting ileostomy may be created if not already present.

ICP by TAMIS starts with incision of the anoderm in the intersphincteric groove after installation of the Lone Star Retractor® (Cooper Surgical). The dissection of the anus and rectal remnant is then continued cephalad following the intersphincteric plane until enough space is created to dock the single port (GelPOINT®, Applied Medical). The rest of the dissection is done via TAMIS after creating a pneumopelvis. Once again, care is taken to stay close to the afferent colonic conduit to avoid any inadvertent damage to the surrounding vital structures. After rendezvous with the top-down mobilization, the afferent colon loop is trimmed, resecting the leaking part. An omentoplasty vascularised by either the left or right gastroepiploic artery is created, large enough to fill the pelvic cavity after extensive debridement.

Evaluation of the redo anastomosis

Local protocol for evaluation of the redo anastomosis in an uncomplicated postoperative course, comprises an endoscopy two weeks postoperative. If endoscopy shows a healed anastomosis, confirmation by CT-scan with rectal contrast is pursued.

When early postoperative complications are suspected, a CT-scan is the modality of first choice. If a leak is detected in either CT or endoscopy, endo-SPONGE® treatment is started.

End-points and definitions

Primary end-points were procedural characteristics (i.e. proportion of laparoscopy and technique of the anastomosis) and major complications including pelvic sepsis, reinterventions, readmissions and mortality, all within 90 days postoperatively. Bowel continuity after redo anastomosis was also assessed. Complications were only scored if they were directly related to the redo surgery. Complications were graded according to the Clavien-Dindo classification and major complications were defined as graded class three or higher, including all complications requiring surgical, endoscopic or radiological intervention (grade three), life-threatening complications requiring intensive care management (grade four) or death (grade five).[11, 12] Anastomotic leakage was defined as a disruption of the anastomosis, diagnosed at endoscopy, radiological imaging or during reoperation. Pelvic sepsis was defined as either anastomotic leakage, pelvic abscess or fistula. Pelvic sepsis was considered *chronic* when present for at least one year after index surgery.

Statistical analysis

Numerical data were presented as mean with standard deviation (SD) and range or median with interquartile range (IQR) according to distribution. Categorical variables were presented as number and proportion in percentages. Comparison between groups for discrete variables was made by the Chi square test, Chi square test for trend or the Fischer exact test when appropriate. The independent t-test was used to compare normally distributed continuous variables and the Mann-Whitney U test was used to compare continuous variables not normally distributed. $P < 0.05$ was considered statistically significant. Analyses were performed using IBM SPSS Statistics for Windows (Version 24.0. Armonk, NY: IBM Corp).

Results

In total, 104 patients undergoing redo surgery after low anterior resection for rectal cancer were included, of whom 47 received a redo anastomosis (18 via conventional technique and 29 via TAMIS) and 57 underwent redo ICP (35 via conventional technique and 22 via TAMIS). All procedures were performed by the same surgeons (WAB and PJT). Of the TAMIS patients, ten (7 redo anastomosis and 3 ICP) were previously

published by Borstlap et al., who described outcomes for a group of patients undergoing redo surgery for a variety of indications via TAMIS.[13] Also, 25 patients in the conventional ICP group and all patients in the conventional redo anastomosis group were previously described by Musters et al. and Westerduin et al. respectively.[14, 15] For all these patients, additional data from extended follow-up was obtained.

A total of 96 patients (92%) were referred for redo surgery from other centers. Baseline characteristics for both redo anastomosis and ICP are shown in Table 1.

Procedural characteristics

In TAMIS redo surgery, a successful rendezvous between the top-down and bottom-up approach was achieved in all patients. An overview of procedural characteristics for redo anastomosis and ICP is presented in Table 2. The abdominal phase in the redo anastomosis group was performed with an open approach in 28% of the patients (8 out of 29) in the TAMIS group and 94% (17 out of 18) in the conventional group. The TAMIS bottom-up dissection enabled the top-down dissection to be done with a minimally invasive approach in a significantly higher percentage compared to the conventional redo procedures (72% versus 6%, (P<0.001)). In ICP, 41% of the patients (9 out of 22) in the TAMIS group underwent an open abdominal approach, compared to 66% (23 out of 35) in the conventional group. Subsequently, 13 out of 22 (59%) and 12 out of 35 (34%) patients undergoing TAMIS and conventional ICP had minimally invasive procedures (P = 0.100).

Intra-operative complications during redo anastomosis occurred in one patient (6%) in the conventional group and four patients (14%) in the TAMIS group (P = 0.636). In the patient in the conventional group, a full thickness injury of the bowel was made, for which sutures were placed. In TAMIS, all four patients had venous bleeding requiring blood transfusion. Intra-operative complications during ICP occurred in five patients (14%) using a conventional approach, and two patients (9%) using TAMIS (P = 0.695). In the conventional group, complications consisted of two bladder injuries including the ureter in one, two bleedings requiring transfusion and intensive care

Table 1. Baseline characteristics redo anastomosis and intersphincteric completion proctectomy

		Redo anastomosis			**Intersphincteric Completion Proctectomy**		
		Conventional (n=18)	TAMIS (n=29)	P-value	Conventional (n=35)	TAMIS (n=22)	P-value
Gender	Male, n (%)	13 (72)	21 (72)	1.000	23 (66)	17 (77)	0.391
Age	Years, mean ± SD (range)	55 ± 8.4 (43-68)	59 ± 10.4 (36-76)	0.221	64 ± 10.3 (33-78)	68 ± 6.7 (54-79)	0.216
Body-mass index	Kg/m^2, median (IQR)	25 (23-26)	25 (22-27)	0.974	26 (23-29)	26 (24-30)	0.737
ASA-classification	ASA 1, n (%)	11 (61)	5 (17)	0.517	9 (26)	2 (9)	0.567
	ASA 2, n (%)	7 (39)	22 (76)		13 (37)	14 (64)	
	ASA 3, n (%)	0	2 (7)	0.517	13 (37)	5 (23)	0.567
	ASA 4, n (%)	0	0		0	1 (4)	
Neoadjuvant radiotherapy	Any form, n (%)	17 (94)	26 (90)	1.000	33 (94)	22 (100)	0.518
	Short course radiotherapy, n (%)	9 (50)	13 (45)	0.834	23 (66)	14 (64)	0.433
	Long course chemoradiotherapy, n (%)	8 (44)	13 (45)		8 (23)	7 (32)	
Index surgery	Low anterior resection, n (%)	18 (100)	29 (100)	1.000	34 (97)	19 (86)	0.288
	Hartmann's procedure, n (%)	0	0		1 (3)	3 (14)	
Index anastomosis	CRA, n (%)	17 (94)	27 (93)	1.000	29 (83)	17 (77)	0.222
	CAA, n (%)	1 (6)	2 (7)		2 (6)	2 (9)	
	None, n (%)	0	0		1 (3)	3 (14)	
Time between index surgery and redo surgery	Months, median (IQR)	16 (11-27)	16 (10-32)	0.913	42 (20-73)	46 (21-107)	0.486
	At least 12 months, n (%)	10 (56)	18 (62)	0.763	34 (97)	20 (91)	0.553
Indication redo surgery	Pelvic sepsis, n (%)	18 (100)	25 (86)	0.257	35 (100)	21 (96)	0.386
	Stenosis of anastomosis, n (%)	0	3 (10)		0	0	
	Cancer recurrence	0	1 (3)		0	0	
	Functional failure	0	0		0	1 (4)	

Abbreviations: TAMIS = transanal minimally invasive surgery, n=number of patients, CAA=coloanal anastomosis, CRA=colorectal anastomosis, ASA=American Society of Anesthesiologist

Table 2. Procedural characteristics redo anastomosis and intersphincteric completion proctectomy

		Redo anastomosis			**Intersphincteric Completion Proctectomy**		
		Conventional (n=18)	TAMIS (n=29)	P-value	Conventional (n=35)	TAMIS (n=22)	P-value
Duration of surgery	Minutes, median (IQR)	286 (237-351)	322 (273-421)	0.084	263 (185-346)	308 (231-387)	0.116
Blood loss	Millilitres, median (IQR)	300 (225-400)	350 (200-819)	0.657	630 (475-1448)	600 (210-875)	0.144
Abdominal approach	Laparoscopy, n (%)	1 (6)	5 (17)	<0.001	0	7 (32)	<0.001
	Hand-assisted laparoscopy, n (%)	0	16 (55)		7 (20)	6 (27)	
	Laparotomy, n (%)	17 (94)	8 (28)		23 (66)	9 (41)	
Type of anastomosis	CAA, n (%)	14 (78)	27 (93)	0.100	N/A	N/A	N/A
	CPAA, n (%)	4 (22)	1 (3)		N/A	N/A	
	CRA, n (%)	0	1 (3)		N/A	N/A	
Technique redo anastomosis	Stapled, n (%)	0	18 (62)	<0.001	N/A	N/A	N/A
	Hand-sewn, n (%)	18 (100)	11 (38)		N/A	N/A	
Configuration of redo anastomosis	Side-End, n (%)	0	19 (66)	<0.001	N/A	N/A	N/A
	End-End, n (%)	18 (100)	10 (34)		N/A	N/A	
Reinforcement of stapled anastomosis	Total, n (%)	N/A	16/18 (89)	-	N/A	N/A	N/A
Omentoplasty	Total, n (%)	7 (39)	6 (21)	0.169	34 (97)	21 (96)	1.000
Ostomy after redo surgery	Total, n (%)	18 (100)	24 (83)	0.141	35 (100)	22 (100)	1.000

Abbreviations: TAMIS = transanal minimally invasive surgery, n=number of patients, CAA=coloanal anastomosis, CRA=colorectal anastomosis, CPAA=colonpouch anal anastomosis, N/A=non-applicable.

unit admission, and one bowel injury requiring segmental resection. After TAMIS ICP, complications were bowel perforation requiring partial resection and presacral bleeding with temporary desaturation.

In both TAMIS redo anastomosis and TAMIS ICP, all intra-operative complications could be managed by TAMIS. There were no ureter injuries diagnosed intra-operatively in TAMIS, but in one patient ureter injury was diagnosed postoperatively for which the patient was readmitted.

Postoperative outcome

An overview of modalities used for evaluation of the redo anastomosis is presented in Supplementary Table 1. Pelvic sepsis requiring one or more reinterventions after redo anastomosis, including endo-SPONGE® treatment, transanal closure of the anastomotic leak, drainage of pelvic abscess, creation of a new ileostomy and salvage surgery, was observed in six (33%) and twelve patients (41%) in the conventional group and TAMIS group, respectively (P = 0.759). An overview of postoperative outcome within 90 days after redo anastomosis and ICP is presented in Table 3. All reinterventions shown in Table 3 were performed because of pelvic sepsis, except for nephrostomy placement in two patients because of hydronephrosis. Three patients (17%) in the conventional group and ten patients (29%) in the TAMIS group were readmitted once or more within 90 days because of pelvic sepsis (P = 0.315). Other reasons for readmission within 90 days after redo anastomosis were ileus, high output ileostomy, pulmonary embolism and urosepsis.

After ICP, six patients in both the conventional group and the TAMIS group (29% and 41%, respectively) experienced pelvic sepsis requiring one or more reinterventions (P = 0.506), which led to readmission within 90 days for two patients in both groups (6% and 9% respectively, P = 0.635). Two patients (9%) in the TAMIS group developed necrosis of the omentoplasty which required necrosectomy. Other major complications after ICP included pneumosepsis, urosepsis and cardiac failure. Other postoperative reinterventions were negative pressure wound therapy (NPWT) in the TAMIS group and a diagnostic laparotomy for sepsis in the conventional group. In the latter, no focus for sepsis was found. Other reasons for readmission after ICP included wound infection and urosepsis.

There was no postoperative mortality after redo anastomosis. In the conventional ICP group, two patients died, one because of pneumosepsis, the second patient because of sepsis caused by a pelvic abscess. In the TAMIS ICP group, one patient died of cardiac failure.

Table 3. Ninety-day postoperative outcome after redo anastomosis and intersphincteric completion proctectomy.

		Redo anastomosis			**Intersphincteric Completion Proctectomy**		
		Conventional (n=18)	TAMIS (n=29)	P-value	Conventional (n=35)	TAMIS (n=22)	P-value
Length of hospital stay	Days, median (IQR)	8 (6-11)	7 (5-8)	0.129	9 (6-14)	9 (5-20)	0.786
Major complications	Patients, n (%)	6 (33)	13[a] (45)	0.546	10 (29)	9 (41)	0.394
	Pelvic sepsis	6	12		6	6	
	Necrosis of omentoplasty	0	0		0	2	
	Ileus	0	0		4	0	
	Wound infection	0	0		1	1	
	Other	0	2		2	1	
Reinterventions	Patients, n (%)	6 (33)	13 (45)	0.546	9 (26)	8 (36)	0.553
	Endo-SPONGE® treatment	13	55		3	0	
	Endoscopic clip of anastomotic leak	0	1		N/A	N/A	
	Transanal closure of anastomotic leak	2	6		N/A	N/A	
	Percutaneous drainage of pelvic abscess	4	4		7	8	
	Surgical drainage of pelvic abscess	0	1		0	1	
	Creation of new ileostomy	0	2		N/A	N/A	
	Redo-redo anastomosis	0	2		N/A	N/A	
	Completion proctectomy + colostomy	0	2		N/A	N/A	
	Necrosectomy of omentoplasty	0	0		0	2	
	Surgical exploration for ileus	0	0		4	0	
	Exploration of necrotising fasciitis	0	0		2	0	
	Other	0	2		1	1	
Readmissions	Patients, n (%)	3 (17)	12 (41)	0.111	5 (14)	4 (18)	0.722
	Pelvic sepsis	3	15		2	2	
	Ileus	0	0		4	0	
	Other	0	5		1	2	
Mortality	Total, n (%)	0	0	-	2 (6)	1 (5)	1.000

[a] One patient had two major complications. Definitions: Postoperative outcome is defined as events occurring within 90 days postoperative. Major complications are defined as scored grade 3 or higher according to the Clavien-Dindo classification. Abbreviations: TAMIS = transanal minimally invasive surgery, n=number of patients.

Supplementary Table 1. Evaluation of the redo anastomosis

		Conventional redo anastomosis n=18	**TAMIS redo anastomosis** n=29
Modality used for evaluation of anastomosis	Endoscopy only, n (%)	0	1 (3)
	CT-scan only, n (%)	7 (39)	2 (7)
	Endoscopy and CT-scan, n (%)	11 (61)	24 (83)
	No evaluation of anastomosis, n (%)	0	2 (7)
Reason for not evaluating the anastomosis	No diverting stoma, n (%)	N/A	2 (7)
Interval between redo surgery and endoscopy	Days, median (IQR)	59 (32-75)	28 (18-35)
Interval between redo surgery CT-scan	Days, median (IQR)	34 (20-60)	22 (10-33)
Outcome endoscopy	Healed anastomosis, n (%)	7/11 (64)	14/25 (56)
	Non-healed anastomosis, n (%)	4/11 (36)	11/25 (44)
Outcome CT-scan	Healed anastomosis, n (%)	9/18 (50)	17/25 (68)
	Non-healed anastomosis, n (%)	5/18 (28)	7/25 (28)
	Healed anastomosis, but pelvic abscess, n (%)	4/18 (22)	1/25 (4)

Long-term outcome

Median duration of follow-up in patients with a redo anastomosis was 36 months (IQR 8-42) in the conventional group and 13 months (IQR 8-20) in the TAMIS group (P = 0.060). In patients undergoing ICP, median duration of follow-up was 30 months (IQR 13-45) in the conventional group and eight months (IQR 3-15) in the TAMIS group (P < 0.001). An extensive overview of long-term outcome beyond 90 days after redo anastomosis and ICP can be found in Supplementary Table 2.

After redo anastomosis, 32 out of 47 patients (68%) had their bowel continuity restored at the end of follow-up; 11 patients (61%) in the conventional group and 21 patients (72%) after TAMIS (P = 0.524). Reason for a presence of stoma at end of follow-up was recurrent pelvic sepsis in five patients (28%) in the conventional group and seven patients (24%) in the TAMIS group (P = 1.000). The remaining patient in the TAMIS group was awaiting stoma reversal at time of analysis of the data and the two remaining

patients in the conventional group died before the diverting ileostomy could be reversed (Figure 1).

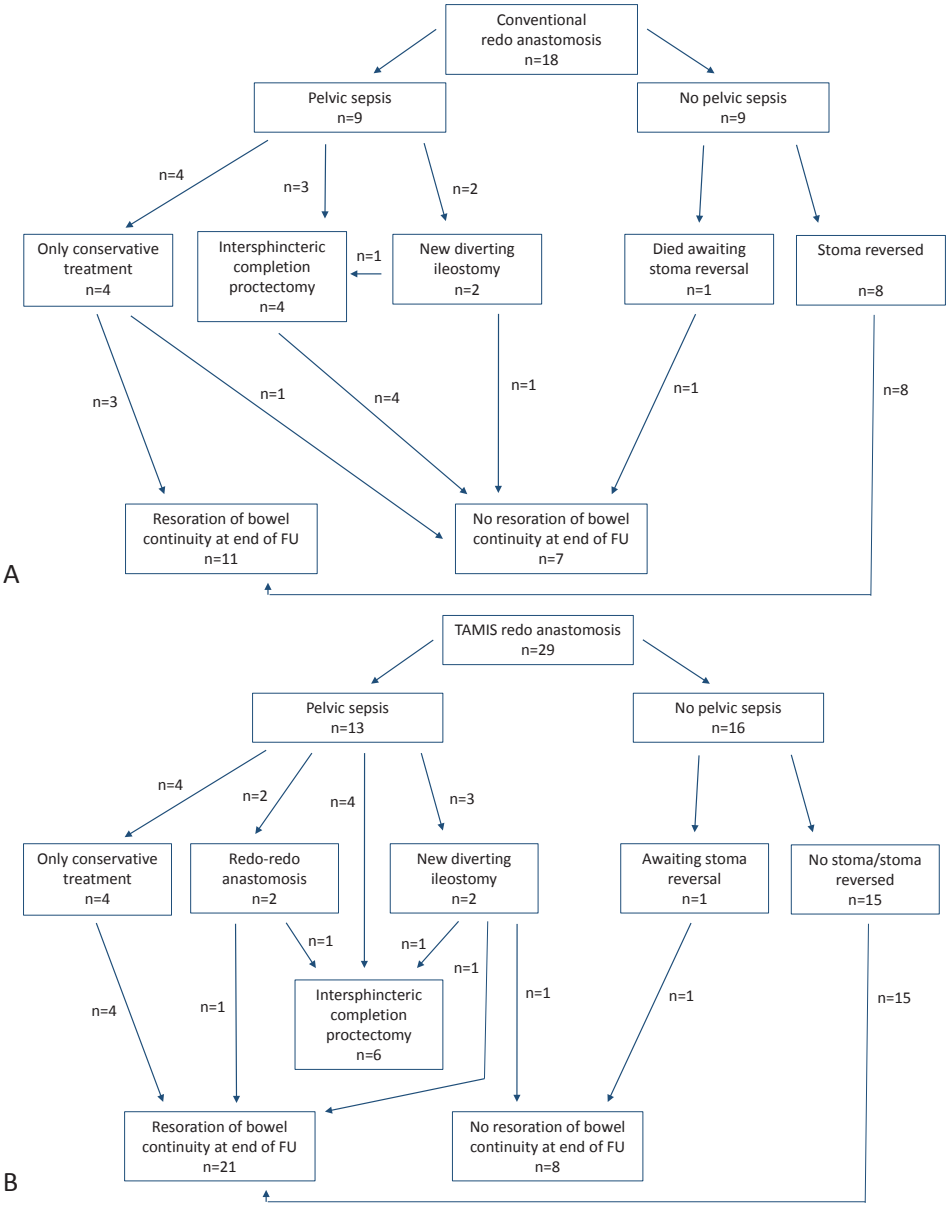


Figure 1. Fate of the redo anastomosis. A. TAMIS redo anastomosis. B. Conventional redo anastomosis. The figure includes pelvic sepsis and reinterventions at any time during follow-up.

Supplementary Table 2. Long-term outcome after redo anastomosis and intersphincteric completion proctectomy

		Redo anastomosis			**Intersphincteric Completion Proctectomy**		
		Conventional (n=18)	TAMIS (n=29)	P-value	Conventional (n=35)	TAMIS (n=22)	P-value
Complications requiring reintervention	Patients, n (%)	6 (33)	2 (7)	0.041	11 (31)	2 (9)	0.060
	Pelvic sepsis	3	1		13	1	
	Anastomotic stricture	1	0		N/A	N/A	
	Wound infection	0	1		0	0	
	Stoma prolapse/parastomal hernia	2	0		3	0	
	Incisional hernia	1	0		2	0	
	Perineal hernia	N/A	N/A		0	1	
Reinterventions	Patients, n (%)	7 (39)	5 (17)	0.168	10 (29)	3 (14)	0.331
	Endo-SPONGE® treatment	15	28		0	0	
	Transanal closure of anastomotic leak	2	1		N/A	N/A	
	Dilatation of anastomotic structure	1	0		N/A	N/A	
	Percutaneous drainage of pelvic abscess	0	0		5	1	
	Surgical drainage of pelvic abscess	0	0		8	0	
	Reposition of omentoplasty	0	0		1	0	
	Correction of fistula	0	1		0	1	
	Creation of emergency ileostomy	2	1		N/A	N/A	
	Closure of emergency ileostomy[a]	0	1		N/A	N/A	
	Correction stoma prolapse/parastomal hernia	2	0		2	1	
	Correction incisional hernia	1	0		1	0	
	ICP + colostomy	4	4		N/A	N/A	

Supplementary Table 2. *Continued*

		Redo anastomosis			Intersphincteric Completion Proctectomy		
		Conventional (n=18)	TAMIS (n=29)	P-value	Conventional (n=35)	TAMIS (n=22)	P-value
Readmissions	Patients, n (%)	6 (33)	4 (14)	0.150	10 (29)	2 (9)	0.103
	Pelvic sepsis	8	4		12	1	
	Serious functional failure	0	1[b]		N/A	N/A	
	Perineal wound problems	N/A	N/A		1[c]	1[d]	
	Ileus	1	-		1	-	
	Parastomal hernia	1	-		1	-	
	Incisional hernia	-	-		1	-	
Mortality	Total, n (%)	4 (22)	2 (7)	0.185	2 (6)	2 (9)	0.635

a Closure of planned ileostomies prior or during redo surgery excluded. b This patient experienced invalidating frequency and urgency of defaecation, despite electrostimulation techniques and bowel irrigation, after which the patient chose a definitive colostomy as a more manageable situation. c Perineal wound dehiscence. d Correction of a perineal hernia.

Definitions: long-term outcome is defined as events occurring from 90 days postoperative until end of follow-up, excluding outcomes within 90 days as presented in Table 3.

Abbreviations: TAMIS = transanal minimally invasive surgery, n=number of patients

Discussion and Conclusion

This study suggests that TAMIS is a valid surgical technique for redo pelvic surgery after low anterior resection for rectal cancer when compared to a conventional approach. By extending the transanal dissection further upwards by using a TAMIS approach in addition to only Lone Star® retraction, the abdominal part could be performed using laparoscopy in two-thirds of the patients.

Non-healing of a low anastomosis after rectal cancer treatment with persisting and even progressive pelvic infectious complications is a challenging condition. In current literature, redo surgery is associated with high morbidity and success rates ranging from 66-100%.[4, 14-20] Within the context of a national referral center for such patients, the potential advantages of the TAMIS approach for primary surgery of rectal cancer were immediately extrapolated to redo surgery, regarding improved access and visualization and application of the double purse-string single-stapled anastomosis.

Although laparoscopy is known to be beneficial with regard to postoperative complications, it has not been frequently described in redo surgery. Exposure of the failed anastomosis is often very challenging due to adhesions and fibrosis following (chronic) pelvic sepsis, causing the old anastomosis to be reachable only by laparotomy. In the two largest series reporting on conventional redo surgery, only two out of a total of 125 patients were operated laparoscopically.[15, 19] This study showed that TAMIS facilitates the bottom-up dissection and a laparoscopic top-down approach of the leaking anastomosis with complete debridement of the septic foci, making a rendezvous at the level of the vesicles or top of the vagina possible in all patients. A total of 67% of patients received a fully laparoscopic or hand-assisted approach in TAMIS redo surgery. This might also be partially explained by the increased experience of the surgeons with both redo surgery and laparoscopy. Laparoscopy improves patient outcome compared to laparotomy in general, by reducing wound infection and postoperative complications, minimizing scars with associated incisional hernias, and reducing postoperative hospital stay and time to first defecation.[21-24] The increased visibility and exposure of the leaking anastomosis provided by TAMIS might also cause more patients to be eligible for a redo anastomosis. These are reasons that TAMIS is the preferred technique for redo procedures in our institution since its introduction late 2014. However, the theoretical advantages regarding bleeding complications and reduced operative time by the two-team approach were not observed in this study. There was even slightly more blood loss and increased operative time, probably related to more complex cases in recent years.

Using TAMIS, it is also possible to leave a sufficient rectal cuff to enable a stapled anastomosis (62% vs 0%, respectively) instead of a hand-sewn anastomosis in more

patients. Using a conventional approach, the open transanal technique does not allow for transection of the rectum above the anorectal junction, leaving insufficient rectum to create a stapled coloanal anastomosis. Whether this has a potential positive impact on functional outcome is yet to be determined. A non-significant higher proportion of bowel continuity after TAMIS redo procedures was observed, but more experience is needed to confirm this finding.

Recurrent pelvic sepsis is an important problem in redo surgery for pelvic sepsis. This study shows a recurrent pelvic sepsis rate of 30% within 90 days. This provides an explanation for the frequent use of CT in the early postoperative period. This practice is in contrast to the current protocol in our center, in which endoscopy is described as a first modality for evaluation of the redo anastomosis. Endoscopy is now more frequently used as a confirmatory test of continuity after prior CT.

Recurrent pelvic abscess might constitute a big problem, as this tends to perforate via the newly made anastomosis, causing leaking of the anastomosis. Although the neorectum in redo anastomosis or the omentoplasty in ICP is meant to fill the pelvic cavity after resection of the anastomosis and debridement of the septic foci, there is a high chance of recurrent sepsis and abscesses causing late leaks. In an attempt to reduce this complication, we started to pre-treat the septic cavity with endo-SPONGE® therapy for several days to weeks, aiming to clean the septic cavity shortly before reconstructive surgery. Recently, we started to check the viability of the omentoplasty using indocyanin green fluorescence angiography, since a number of patients were reported to have necrosis of the omentoplasty.[25, 26] Complication rates and rates of reinterventions after TAMIS were similarly high compared to the conventional group. These results are also comparable to numbers in literature reporting on conventional redo surgery, reflecting the difficult underlying condition.[14, 15, 17, 19] Apparently, technical improvements and increased experience did not lower major complication rates yet. What we have learned over time, is that immediate salvage treatment (<90 days) in case of failure of the redo anastomosis is better, explaining the difference in early reinterventions. Despite the poor outcomes when considering redo anastomosis, it is often the last chance for patients to preserve bowel continuity and highly motivated patients should not be precluded from a chance to live without a stoma.

A limitation of this study is the relatively small sample size, which causes limited possibility for statistical analysis. However, to our knowledge, this is the largest cohort describing TAMIS as a technique for redo surgery so far. This can be explained by the overall rarity of redo surgery after failed colorectal or coloanal anastomosis and the slow implementation of TAMIS for benign conditions. This study is a valuable addition to the scarce literature available on redo surgery and it shows the value of the TAMIS surgical platform to approach complex problems deep down in the pelvis.

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CHAPTER 9

Functional outcomes and quality of life after redo anastomosis in rectal cancer patients: an international multicentre comparative cohort study

Submitted

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Abstract

Objective

The aim of this study was to compare functional outcomes and quality of life after redo anastomosis and primary healed anastomosis following total mesorectal excision (TME).

Summary Background Data

Redo anastomosis can be considered in selected patients with non-healing of an anastomotic leak. This is technically challenging and little is known about the functional outcomes after this seldomly performed surgery.

Methods

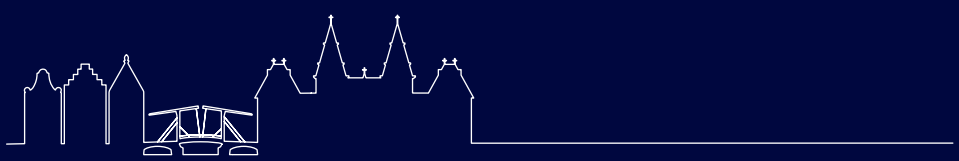
Patients from three tertiary referral centres in the Netherlands, Belgium and France undergoing redo anastomosis were compared to patients that had a primary healed anastomosis after TME for rectal cancer. Low Anterior Resection Syndrome (LARS) Score, EORTC QLQ-C30, and QLQ-CR29 questionnaires were used to assess outcomes.

Results

In total, 170 patients were included; 52 redo anastomosis and 118 controls. Significantly more patients in the redo group had radiotherapy (83% vs. 58%, P=0.001). Major LARS occurred in 73% after redo anastomosis compared to 68% following primary healed anastomosis (P=0.517). The redo group had worse EORTC QLQ-CR29 mean scores for faecal incontinence (P=0.032) and flatulence (P=0.008). There were no differences in urinary (P=0.482) or sexual dysfunction, neither in men (P=0.832) nor in women (P=0.756). Significantly worse scores in the redo group were found for global health (P=0.002), role-(P=0.049), and social function (P=0.006), body image (P=0.025) and anxiety (P=0.022).

Conclusions

Redo anastomosis is associated with significantly worse quality of life when compared to patients with primary healed anastomosis. However, major LARS was comparable between groups and should not be a reason to preclude restoration of bowel continuity in highly motivated patients.



Introduction

Total mesorectal excision (TME) for rectal cancer is still associated with a high risk of complications. The most feared among these complications is anastomotic leakage, with incidences reported in up to 20% of all patients undergoing low anterior resection (LAR).[1, 2] When anastomotic leakage persists despite surgical or non-surgical treatment and restoration of bowel continuity is still desired, resection of the leaking anastomosis with creation of a new (redo) anastomosis can be considered. A redo anastomosis might also be pursued in patients with severe anastomotic strictures or selected patients with locally recurrent rectal cancer. The creation of a redo anastomosis is challenging: chronic pelvic sepsis, radiation fibrosis and/or adhesions make a difficult operation deep down in the pelvis even more complicated. A recent review on redo anastomosis showed an overall technical success rate of 79%. When performed for chronic pelvic sepsis, this number even decreased to 70%.[3]

Redo surgery itself is associated with a high risk of postoperative complications, and if technically successful, the functional outcome might be disappointing. It can be expected that functional outcome will further deteriorate after redo surgery in patients with already reduced anorectal function following TME. Like most patients having had TME for distal rectal cancer, patients undergoing redo anastomosis are likely to suffer from a other functional sequelae besides low anterior resection syndrome (LARS), including urinary- and sexual dysfunction.[4] This can result in impaired quality of life.[5] Literature on this topic is scarce. Only six studies have described functional outcomes after redo anastomosis, with incontinence rates ranging from zero up to 33%.[6]

It is of great importance to have a proper estimate of the functional outcomes and quality of life of patients having had technically successful redo surgery. Only then, proper counselling and shared decision making is possible. Therefore, the aim of this study was to assess the functional outcomes and quality of life after redo anastomosis compared to outcomes following primary healed anastomosis after TME for rectal cancer in a multicentre setting.

Methods

Patients

Patients from three different European tertiary referral hospitals specialized in redo surgery and redo anastomosis were included; the Amsterdam University Medical Centres – location Academic Medical Centre (Amsterdam UMC – AMC) in the Netherlands, the University Hospital Leuven (UZ Leuven) in Belgium and the Beaujon

Hospital in Clichy, France. The study was designed as a comparative cohort study. For the redo anastomosis group, all patients who received a redo anastomosis between August 2007 and June 2017 after prior resection for rectal cancer were identified. All indications for redo surgery were included. Both conventional and transanal redo procedures, as well as both stapled and hand-sewn redo anastomosis in all types of configuration were included. The group of redo patients was compared to a control group of patients undergoing TME for rectal cancer in the same period of time. Only patients with a primary healed anastomosis without any signs of infectious pelvic complications after TME were included in the control group. Patients undergoing proximal mesorectal excision (PME) were excluded in the control group. Exclusion criteria for both groups were partial or complete resection of the internal sphincter during either primary or redo surgery, patients with a stoma at the time of receiving the questionnaires and patients who were unable to read and/or understand the information letter and questionnaires. Only patients with at least one year of follow-up after restoration of bowel continuity were included.

All participating centres obtained ethical approval from the local authorities and informed consent was obtained as required by local law.

Surgical technique

Primary resection for rectal cancer was performed according to the TME principle, thereby creating a coloanal or low colorectal anastomosis.[7, 8] If deemed necessary by the operating surgeon, the anastomosis could be temporarily diverted, followed by closure of the diverting ileostomy within weeks to months after surgery when the anastomosis was considered intact on either imaging or endoscopy.

The creation of a redo anastomosis consists of an abdominal phase and a transanal phase. The surgical technique for redo anastomosis is extensively described in Appendix 1. In most cases, a diverting ileostomy is created after the redo anastomosis, if not already present.

Data collection and questionnaires

Patient-reported functional outcomes and quality of life (QoL) measurements were collected by sending questionnaires at least one year after bowel continuity was achieved. Three questionnaires were used: the low anterior resection syndrome (LARS) score questionnaire, the European Organization for Research and Treatment of Cancer (EORTC) QLQ-CR29 and QLQ-C30 version 3.0.[9-11] Last follow-up for this study was determined by the date of completion of the questionnaires.

The LARS score questionnaire consists of five questions addressing incontinence for flatus, incontinence for liquid stool, frequency of bowel movements, clustering of stool

and urgency. The LARS score is divided into three categories: no LARS (0-20 points), minor LARS (21-29 points) and major LARS (30-42 points).[9, 12]
The QLQ-C30 questionnaire measures quality of life using three scales: a functional scale consisting of five items, a symptom scale with nine items and a global health status. The procedure of scoring as described in the EORTC scoring manual was used. A higher score on the symptom scale indicates a worse quality of life. In contrast, a higher score on the functional scales and global health status indicates better quality of life.[10, 13]

The QLQ-CR29 questionnaire is a supplementary module complementing the QLQ-C30, which consists of 29 items, which are divided into four scales and 19 single items, including flatulence, faecal incontinence and sexual interest. Scoring and interpretation of results are comparable to the QLQ-30.[11]

Outcomes and definitions

Primary outcome was ano-neorectal function measured by the LARS score. Secondary outcome was quality of life, as measured by the several scales and items of the EORTC QLQ-C30 and QLQ-CR29, with special attention to global health status, flatulence, faecal incontinence, and urinary- and sexual function. To determine the clinical relevance of the significant differences found in the EORTC questionnaires, the mean difference between groups was determined. A mean difference of 5 – 10 points was considered a small, 10 – 20 points a moderate, and at least 20 points a major clinically relevant difference.[10] A mean difference <5 points was considered not clinically relevant.

Complications were only scored if directly related to the redo anastomosis. Only complications graded class three or higher according to the Clavien-Dindo classification were reported.[14, 15] Anastomotic leakage was defined as a disruption of the anastomosis, diagnosed at endoscopy, radiological imaging or during reoperation. Pelvic sepsis was defined as either anastomotic leakage, pelvic abscess or fistula.

Statistical analysis

Continuous variables were presented as mean and standard deviation (SD) or median and interquartile range (IQR) according to their distribution, while categorical variables were presented as numbers and percentages. Student's *t*-test or Mann-Whitney U test was used to detect differences between groups for continuous data, and Chi-square test or Fisher's exact test was used for categorical data when appropriate. Logistic regression was used to detect the association between major LARS and different independent variables reporting odds ratios and 95% confidence intervals. P-values <0.05 were considered statistically significant. Statistical analyses were performed using STATA statistical software version 12 (StataCorp LP, College Station, Texas, USA).

Results

Patients and response rate

In total, 286 potentially eligible patients were selected from existing databases in the participating hospitals. Of these patients, 44 did not fulfil inclusion criteria, resulting in a total of 253 patients that were approached for participation in the study. Eighty-three patients did not respond, resulting in an overall response rate of 67%. This was similar among the two groups; 68% in the redo anastomosis group and 67% in the control group. A total of 170 patients were included for analysis; 52 patients with redo anastomosis and 118 patients with primary healed anastomosis following TME. A flow chart of inclusions per hospital is displayed in Figure 1.

Baseline and surgical characteristics

An overview of baseline characteristics after primary surgery per group is presented in Table 1. In total, 119 patients had a diverting ileostomy following initial TME surgery, 37 (71%) in the redo group and 82 (69%) in the control group (P=0.827). Median time between primary surgery and redo anastomosis was 16 months (IQR 9-30). After redo-anastomosis 45 of 52 patients (87%) had an ileostomy, including patients who had a diverting ileostomy prior to the redo surgery. Median follow-up after redo anastomosis was 33 months (IQR 23-51). The majority of patients (n=48, 92%) underwent redo surgery because of pelvic sepsis, including ten patients (19%) with a secondary fistula originating from the anastomosis or chronic sinus (e.g. perianal, trochanteric, vaginal). Intra-operative and postoperative outcomes following redo anastomosis can be found in Table 2. In two patients (4%) redo surgery was associated with multiple postoperative complications comprising recurrent pelvic abscess with stenosis and fistula formation in one. Median time between index surgery and closure of the ileostomy was 3.55 months (IQR 2.58-6.36) in the control group, compared to median 4.7 months (IQR 3.16-7.53) after redo surgery (P=0.0521).

Functional outcome and quality of life

Patients completed the questionnaires with a median time interval of 56 months (IQR 24-75) after restoration of bowel continuity following TME with primary healed anastomosis, and a median of 24 months (IQR 12-43) after restoration of bowel continuity following redo anastomosis (P<0.0001).

Only a minority of patients in both groups did not report LARS; 2 patients (4%) following redo surgery versus 16 patients (14%) following primary healed anastomosis (P=0.047). Minor LARS was reported in 12 (23%) versus 22 (19%) patients (P=0.483) and major LARS was reported in 37 (73%) versus 79 (67%) patients (P=0.517) following redo

Table 1. Baseline characteristics at primary TME

		Redo anastomosis n = 52	**TME with primary healed anastomosis** n = 118	**P-value**
Gender	Male, n (%)	34 (65)	79 (67)	0.842
Age	Years, mean ± SD	63 ± 8.88	68 ± 9.94	0.0009
Preoperative radiotherapy	Total, n (%)	43 (83)	68 (58)	0.001
	Short course (5x5 Gy), n (%)	16 (39)	13 (19)	0.023
	Long course (25x2 Gy), n (%)	25 (61)	55 (81)	
Preoperative chemotherapy	Total, n (%)	29 (56)	55 (47)	0.271
(y)pT stage	Tx	6 (12)	3 (3)	0.177
	T0	1 (2)	5 (4)	
	T1	6 (12)	13 (11)	
	T2	16 (31)	40 (34)	
	T3	23 (44)	52 (44)	
	T4	0	5 (4)	
(y)pN stage	Nx	7 (13)	4 (3)	0.072
	N0	24 (46)	71 (60)	
	N1	14 (27)	31 (26)	
	N2	7 (13)	12 (10)	
Technique anastomosis	Hand-sewn, n (%)	8 (19)	14 (12)	0.268
	Stapled, n (%)	34 (81)	102 (88)	
Configuration anastomosis	Side-to-end, n (%)	24 (55)	81 (71)	0.131
	End-to-end, n (%)	11 (25)	20 (18)	
	Pouch, n (%)	9 (21)	13 (11)	
Postoperative chemotherapy	Total, n (%)	9 (17)	21 (18)	0.939
Time since primary surgery	Months, median (IQR)	54 (40-93)	48 (26-75)	0.0615

anastomosis and primary healed anastomosis, respectively. Furthermore, the median LARS score did not differ significantly between groups; 37 (IQR 29-39) in the redo group versus 34 (IQR 27-37) in the primary healed anastomosis group (P=0.063). Comparison between groups for individual items of the LARS score are displayed in Supplementary Table 1. In univariate logistic regression, no variables were identified as individual predictors for major LARS following redo anastomosis, therefore no multivariate logistic regression was performed (Table 3).

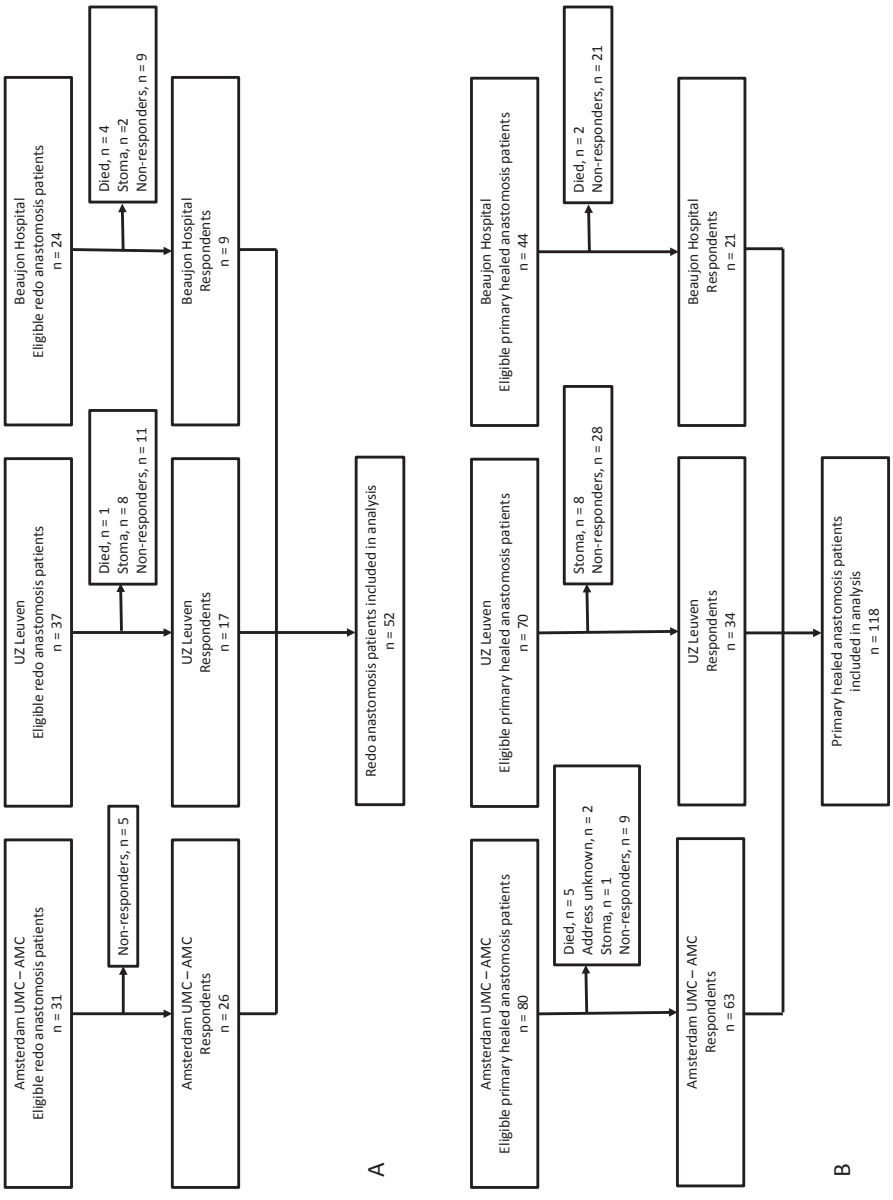


Figure 1. Patients included in the study: A. redo anastomosis. B. TME with primary healed anastomosis.

Table 2. Intra-operative and postoperative outcomes of redo anastomosis

		Redo anastomosis n = 52
Indication redo surgery	Pelvic sepsis, n (%)	48 (92)
	Anastomotic stenosis, n (%)	2 (4)
	Local recurrence, n (%)	2 (4)
Perineal approach	Conventional, n (%)	36 (69)
	TAMIS, n (%)	16 (31)
Abdominal approach	Open, n (%)	35 (67)
	Laparoscopic, n (%)	17 (33)
Technique anastomosis	Hand-sewn, n (%)	40 (77)
	Stapled, n (%)	10 (19)
	Turnbull-Cutait, n (%)	2 (4)
Configuration anastomosis	Side-to-end, n (%)	5 (10)
	End-to-end, n (%)	40 (77)
	Pouch, n (%)	6 (12)
	Unknown, n (%)	1 (2)
Temporary stoma	Total, n (%)	45 (87)
Complications following redo anastomosis	Total, n (%)	17 (33)
	Pelvic sepsis, n (%)	13 (25)
	Stenosis, n (%)	5 (10)
	Prolapse of neorectum, n (%)	1 (2)
Reinterventions following redo anastomosis	Total, n (%)	19 (37)
	Percutaneous drainage, n (%)	4 (8)
	Endo-SPONGE® + transanal closure of defect[a]	4 (8)
	Dilatation of stenosis[b]	4 (8)
	Redo-redo anastomosis	3 (6)
	New temporary stoma	1 (2)
	Endoscopy under general anaesthesia[c]	4 (8)
	VAAFT	1 (2)

Abbreviations: VAAFT = Video Assisted Anal Fistula Treatment. [a] One or multiple Endo-SPONGE® (B. Braun Medical B.V., Melsungen, Germany) treatments, exact number of treatments not reported. [b] One or multiple dilatations, exact number of treatments not reported. [c] No additional interventions during endoscopy.

Considering quality of life as measured by the EORTC QLQ-C30, only items regarding role function, social function, overall global health, fatigue and pain were found to be significantly different, favouring the primary healed anastomosis group (P=0.049, P=0.006, P=0.002, P=0.040 and P=0.002, respectively). The clinical relevance of differences among these domains were small, moderate, small, moderate and small, respectively. Figure 2a and 2b show the comparison between groups of EORTC QLQ-C30 scores.

Supplementary Table 1. Low Anterior Resection Syndrome Score.

		Redo anastomosis n = 52	**TME with primary healed anastomosis** n = 118	**P-value**
Flatus incontinence	No, never, n (%)	7 (13)	22 (19)	0.016
	Yes, < once per week, n (%)	6 (12)	34 (29)	
	Yes, >once per week, n (%)	39 (75)	62 (53)	
Liquid stool incontinence	No, never, n (%)	9 (17)	35 (30)	0.233
	Yes, < once per week, n (%)	23 (44)	46 (39)	
	Yes, >once per week, n (%)	20 (39)	37 (31)	
Frequency of bowel movement	>7 times per day, n (%)	8 (15)	9 (8)	0.152
	4-7 times per day, n (%)	21 (40)	44 (37)	
	1-3 times per day, n (%)	19 (37)	49 (42)	
	< once per day, n (%)	3 (6)	16 (14)	
	Missing, n (%)	1 (2)	0	
Fragmentation of stools	No, never, n (%)	1 (2)	5 (4)	0.392
	Yes, < once per week, n (%)	10 (19)	26 (22)	
	Yes, >once per week, n (%)	40 (77)	87 (74)	
	Missing, n (%)	1 (2)	0	
Urgency	No, never, n (%)	4 (8)	15 (13)	0.703
	Yes, < once per week, n (%)	16 (31)	35 (30)	
	Yes, >once per week, n (%)	32 (62)	67 (57)	
	Missing, n (%)	0	1 (1)	

Regarding the EORTC QLQ-CR29 questionnaires, two items on the function scale were significantly different in favour of the primary healed anastomosis group: body image (P=0.025) and anxiety (P=0.022). Based on the mean differences, these items were categorized as small and moderate clinical relevance, respectively. On the symptom scale, abdominal pain (P=0.030), buttock pain (P=0.005), flatulence (P=0.008), faecal incontinence (P=0.032) and sore skin (P=0.0007) were found to be significantly different in favour of the primary healed anastomosis group. The mean difference in abdominal pain was categorized as no clinical relevance, while the other items all had a moderate clinically relevant difference. No significant differences were found between groups for urinary and sexual function. In Figure 2c and 2d, the comparison between groups of EORTC QLQ-CR29 scores are displayed.

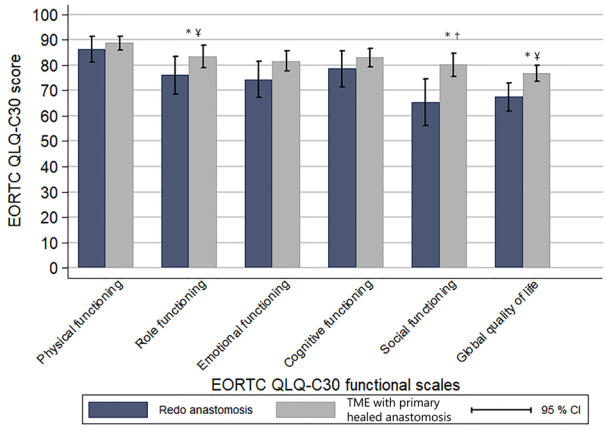
Table 3. Logistic regression analysis for predictors of major LARS following redo anastomosis

		Univariate OR (95% CI)	P-value
Age	Years	0.92 (0.85-1.01)	0.070
Preoperative radiotherapy before primary surgery	No	1.00 (ref)	
	Yes	2.56 (0.57-11.40)	0.218
Type of radiotherapy before primary surgery	Short course (5x5Gy)	1.00 (ref)	
	Long course (25x2Gy)	1.90 (0.39-9.14)	0.418
Postoperative chemotherapy following primary surgery	No	1.00 (ref)	
	Yes	1.4 (0.25-7.72)	0.699
Time between primary surgery and redo anastomosis	Months	1.00 (0.98-1.03)	0.562
Time between redo anastomosis and closure of ileostomy	Weeks	0.99 (0.97-1.02)	0.953
Time between closure of ileostomy and questionnaires	Months	1.01 (0.97-1.06)	0.463
Perineal approach	Conventional	1.00 (ref)	
	TAMIS	1.2 (0.31-4.62)	0.791
Configuration anastomosis	End-to-end	1.00 (ref)	
	Side-to-end	0.45 (0.06-3.12)	0.419
	Pouch	0.3 (0.05-1.75)	0.181
Pelvic sepsis following redo anastomosis	No	1.00 (ref)	
	Yes	0.77 (0.19-3.16)	0.727

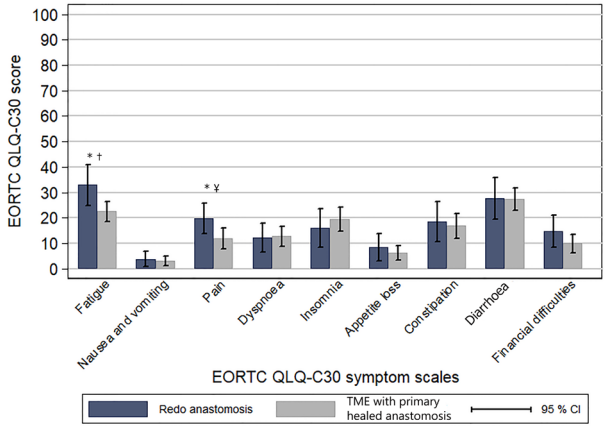
Discussion

This study revealed no difference in the occurrence of major LARS in patients that had TME with primary healed anastomosis (68%) or a redo anastomosis after complicated TME (73%). Flatulence and faecal incontinence were scored significantly worse in the redo anastomosis group, with a moderate clinical relevance. Overall global health was significantly better after primary healed anastomosis, but with only small clinical relevance. There were no differences in urinary and sexual function.

Allthough there is no difference in the occurrence of major LARS between groups, this study shows high rates of major LARS, even in the primary healed anastomosis group (68%). Recent meta-analysis on LARS shows an estimated prevalence of major LARS of 41%. The same meta-analysis identified radiotherapy and tumour height as major risk



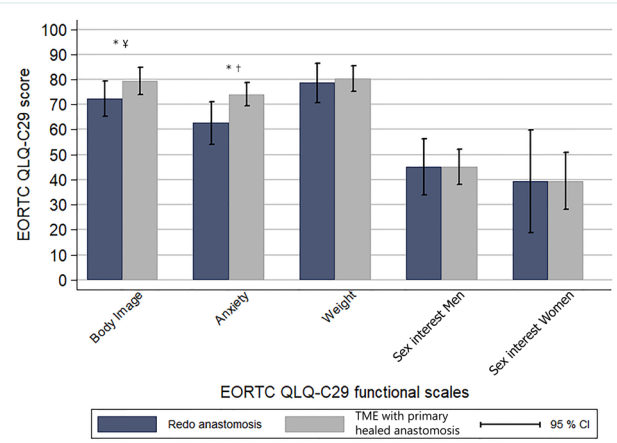
A. Functional scales EORTC QLQ-C30.



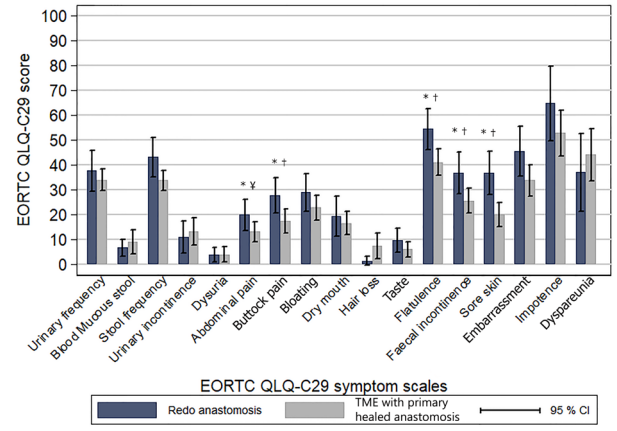
B. Symptom scales EORTC QLQ-C30.

Figure 2. Comparison of EORTC QLQ-C30 and QLQ-CR29 scores after redo anastomosis and TME with primary healed anastomosis.
Values are means with 95% confidence intervals. * Statistical significant difference with P<0.05. Degree of clinical relevance: ¥ small, † moderate, ‡ major.

factors for the occurrence of major LARS. The relatively high proportion of radiotherapy might be one of the explanations for the high major LARS rate found in this study. In one of the largest recent studies describing 282 patients undergoing low anterior resection (LAR), only 19% of patients underwent neoadjuvant radiotherapy and still 49% major LARS was reported.[16] In the current study, neoadjuvant radiotherapy rates were 58% and 83% in the primary healed anastomosis and redo groups, respectively. The high proportion of radiotherapy in the redo group reflects the indication for redo anastomosis, because radiotherapy impairs healing of a leaking anastomosis.



C. Functional scales EORTC QLQ-CR29.



D. Symptom scales EORTC QLQ-CR29.

Figure 2. *Continued*

Another explanation for the relatively high major LARS rate in the control group of the present study is related to exclusively including TME. Most studies included in the meta-analysis also included patients who underwent partial mesorectal excision (PME) for proximal rectal cancer with preservation of the distal rectum. Bondeven et al. reported that bowel function deteriorates as the level of the anastomosis approaches the anal verge.[17] This also explains the high rate of major LARS in the redo anastomosis group. Redo anastomosis is by definition an ultra-low anastomosis, after creating a new anastomosis even distal to the level of primary anastomosis after TME.

Even though a redo anastomosis is mostly performed only in highly motivated and fit patients and the prevalence of major LARS is not significantly different from patients with primary healed anastomosis, redo patients rated a worse global health score. The high motivation for restoring bowel continuity can probably suppress preoperative information on expected functional outcomes in patients undergoing redo anastomosis. Furthermore, experience of an extensive complicated course following primary TME surgery itself might already have a negative impact on the appreciation of quality of life. The significantly higher rate of anxiety in the redo anastomosis group compared to the uncomplicated TME group in this study might support this hypothesis. Similar observations regarding quality of life have been reported following successful repair of bile duct injuries.[18]

A number of patients provided feedback regarding an important limitation of the questionnaires used; they do not take into consideration the current treatment of symptoms. Many patients have indicated to use laxatives, fibres, antidiarrheal medication or transanal irrigation to control the symptoms of LARS. Especially transanal irrigation was reported as effective treatment by several patients, which is also supported by literature.[19] Another limitation of this study is the risk of response bias in both groups, possibly resulting in overestimation of the proportion of patients with major LARS.

Patient reported outcomes (PROMs) provide us with important knowledge about the experience of patients. However, we still have to learn how to interprete these PROMS properly and how to use them in daily practice. The findings of this study once again underpins the caution with which these PROMs should be interpreted: it is important to realize that there are discrepancies in outcomes between individual items of the LARS questionnaire and items of the EORTC QLQ-CR29 questionnaire adressing the same topic (e.g. incontinence for liquid stools).

The present study showed that the impact of redo surgery on quality of life is significantly different compared to primary healed anastomosis. Considering similar LARS scores in both groups, redo anastomosis can still be considered a valid treatment option in patients highly motivated for restoration of bowel continuity. This is an important message for those surgeons who are reluctant to offer redo anastomosis to their patients having a failed anastomosis after TME surgery.

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Appendix 1. Surgical technique of the redo anastomosis.

The creation of a redo anastomosis consists of an abdominal phase and a transanal phase. The open or laparoscopic abdominal phase starts with adhesiolysis if necessary, followed by complete mobilization of the splenic flexure. A high-tie ligation of the inferior mesenteric vein, if not yet done during primary surgery, is performed in order to gain sufficient length for a tension-free redo anastomosis. The inferior mesenteric artery and left colonic artery are preserved whenever possible. The colonic conduit is top-down dissected until rendez-vous with the bottom-up transanal dissection.
During the transanal phase, the rectum is transected distal to the old anastomosis and dissected until rendez-vous with the top-down dissection is established. The dissection is then continued along the previous TME plane, after which the colon is transected above the old anastomosis. Debridement of the presacral cavity with excision of fibrosis is performed in case of chronic presacral sinus. The afferent colon loop is pulled down and a redo anastomosis can be created in the appropriate configuration. The type of anastomosis depends on the length of the efferent colon, the length of remaining rectal cuff and the amount of remaining presacral space that might be restricted because of scarring. The configuration is made either stapled or manual and either end-to-end, side-to-end or as a coloanal pouch. Occasionally, the Turnbull-Cutait delayed anastomosis can be used.[1-3]
Recently, redo surgery using the TAMIS platform has been described. In TAMIS, a single port transanal platform is introduced in the anal canal after a perianal nerve block, improving exposure to the leaking anastomosis and facilitating dissection and debridement of septic pockets. It furthermore enables a secondary stapled anastomosis and the possibility of endoluminal suture reinforcement of the redo anastomosis.[4]

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APPENDICES

Summary

The surgical treatment of rectal cancer is an ongoing developing field. The number of possible surgical techniques for rectal cancer resection are expanding, dependent on tumour stage, location of the tumour, patient characteristics and patient preferences. The same applies to surgical treatment after failure of a primary anastomosis. All new, mostly minimally invasive techniques, can offer substantial advantages for the individual patient, but they are also associated with their own specific complications, of which anastomotic leakage and pelvic sepsis are the most feared sequelae. All treatment options, including possible complications, should be considered carefully and discussed with the patient to achieve a personalized treatment plan.

In this thesis, **Part I** and **Part II** address complications, reinterventions and reoperations following non-rectum preserving rectal cancer resection. **Part I** focusses on restorative rectal cancer resection (*with* creation of an anastomosis). **Part II** focusses on non-restorative rectal cancer resection (*without* restoration of bowel continuity). **Part III** of this thesis focusses on redo surgery following anastomotic leakage. We have looked at the success of redo anastomosis for anastomotic leakage when considering bowel continuity, the complication rate and the functional outcomes following redo surgery.

Part I - Restorative rectal cancer resection

In **Chapter 1**, a cross-sectional overview of anastomotic leakage and chronic presacral sinus formation following low anterior resection (LAR) in the Netherlands is presented. These are results of a snapshot study on rectal cancer resection performed in 71 hospitals in the Netherlands, comprising 2095 patients. The study showed that in 13.4% of 998 included patients undergoing LAR for rectal cancer, anastomotic leakage was diagnosed within 30 days. This number increased to 20.0% beyond 30 days. Of all patients with anastomotic leakage, nonhealing of the anastomosis was observed in 48%, resulting in an overall proportion of chronic presacral sinus of 9.5%. Independent predictors for anastomotic leakage at any time during follow-up were neoadjuvant therapy (OR 2.85; 95% CI 1.00-8.11) and a distal tumour location, defined as a tumour ≤3cm from the anorectal junction on MRI (OR 1.88; 95% CI 1.02-3.46). The study also shows that the long-term anastomotic leakage rate is similar, with or without the creation of a diverting stoma.

This last finding forms an important base for the next chapter, since from a historical perspective, a diverting ileostomy is thought to reduce severity of the symptoms in anastomotic leakage and reduce the number of urgent reoperations. **Chapter 2** compares patients who underwent laparoscopic total mesorectal excision (TME) and were routinely diverted to a group of patients who underwent only highly selective diversion in combined laparoscopic and transanal TME with reinforcement of the anastomosis with a continuous suture. Anastomotic leakage occurred in 20% following routine diversion, compared to 8% following highly selective diversion after a median follow-up of 36 and 19 months respectively. This difference was not significantly different. There was however, a significant difference in one-year stoma-related readmission and reoperation rate (stoma reversal included); 84% and 86%, respectively, following routine diversion compared to 17% and 17%, respectively, following highly selective diversion.

Part II - Non-restorative rectal cancer resection

Chapter 3 aimed to evaluate current practice regarding rectal cancer resection without restoration of bowel continuity. Surgeons from 37 Dutch hospitals responded to an online survey with questions addressing low Hartmann's resection (LHR) and intersphincteric abdominoperineal (iAPR) as non-restorative treatment options. Of 42 responding surgeons, 36% indicated not to distinguish between a high or low Hartmann's resection based upon the estimated length of the rectal remnant. Overall, in 86% iAPR was the preferred technique and 62% indicated that they would consider a different technique in tumours at 1cm from the pelvic floor compared to tumours at 5cm. The incidence of pelvic abscesses after LHR was thought to be higher, equal or lower than after iAPR in 36%, 36% and 21% respectively.

In **Chapter 4**, the incidence of pelvic abscess formation following LHR and iAPR was assessed in a small retrospective comparative cohort study including 40 patients undergoing LHR and 12 patients after iAPR. There were no significant differences in major complications within 30 days postoperative (18% vs 33%, respectively) or overall pelvic abscess formation (10% vs 17%, respectively). Limiting factor of this study was the small number of patients. Therefore, a study with a similar design, but within a larger cohort from a collaborative snapshot study is discussed in **Chapter 5**. We included 139 patients after LHR and 46 patients after iAPR. Overall, a pelvic abscess occurred in 17% of patients following LHR and 11% after iAPR. This showed not to be a significant difference, also when censored for mortality or loss to follow-up.

Nevertheless significantly more abscesses were diagnosed beyond 30 days postoperative after iAPR. The study also revealed a high number of surgical reinterventions and readmissions for any reason, with only a minority occurring within 30 days postoperative.

Part III – Salvage surgery following rectal cancer resection

In **Chapter 6** the results of a systematic review on outcomes following redo surgery with the creation of a new (redo) anastomosis after anastomotic leakage is presented. We included nine studies, comprising 291 patients. It showed a pooled success rate of 79% (95% CI 69-86), with a pooled incidence of major postoperative morbidity of 16% (95% CI 10-24) and a pooled pelvic sepsis rate of 16% (95% CI 9-27).

Clinical success and morbidity after the construction of a redo coloanal anastomosis (CAA) because of anastomotic leakage after LAR in a cohort of 59 cases is presented in **Chapter 7**. It revealed that anastomotic leakage was the most frequent complication following redo CAA (41%). In 66% of patients, bowel continuity was restored at the end of follow-up and in 24% of patients, a definitive end colostomy was constructed. In a multivariate model, leakage of the redo CAA was the only risk factor for a permanent stoma (OR 0.022; 95% CI 0.004-0.122). This cohort study also showed that 97% of all procedures is performed through an open approach. This is thought to be caused by poor visibility and accessibility of the deep pelvis due to location, prior surgery and inflammation. In **Chapter 8**, the use of transanal minimally invasive surgery (TAMIS) for redo surgery is described, because of its possible ability to overcome these obstacles encountered in conventional redo surgery. Both salvage surgery with creation of a redo anastomosis as well as intersphincteric completion proctectomy (ICP) with end colostomy through TAMIS were described and compared to series of patients undergoing conventional redo anastomosis or ICP. By extending the transanal dissection further upwards by using a TAMIS approach, the abdominal part could be performed using laparoscopy in two-thirds of the patients. There were no significant differences between TAMIS and conventional approach in intra-operative complications and 90-day postoperative outcomes and a stapled redo anastomosis could be done in 62% of the TAMIS procedures, while all conventional redo anastomosis were hand-sewn.

Finally, **Chapter 9** focusses not on the surgical outcomes, but on the patient reported functional outcomes and quality of life following redo anastomosis. Outcomes were compared to patients with a primary healed anastomosis after TME for rectal cancer.

In total, 52 redo anastomosis patients from three European tertiary referral centres were included, of whom 83% had radiotherapy. Outcomes were assessed using the low anterior resection syndrome (LARS) score and the EORTC QLQ-C30 and QLQ-CR29 questionnaires and revealed comparable major LARS scores between groups; 73% after redo anastomosis compared to 68% following primary healed anastomosis. The redo group had significantly worse EORTC QLQ-CR29 mean scores for faecal incontinence and flatulence, but there were no differences in urinary or sexual dysfunction neither in men nor in women. Global health, role-, and social function, body image and anxiety were scored significantly worse in the redo group.

Future perspectives

The anastomotic leak rate during complete duration of follow-up as described in **Chapter 1,** and representing nationwide performance in the Netherlands in 2011, is high in comparison to the literature, which can be partially explained by the inclusion of *late* diagnosed leaks. Most studies presented in current literature present only 30-day outcomes and often only the in-hospital outcomes. Furthermore, scrutinizing the patient files retrospectively by residents a few years later, as performed in the collaborative research project of Chapter 1, revealed several problems that would never have been reported as anastomotic leakage in any registry. This underlines the need for an internationally accepted broad definition of anastomotic leakage including any infectious pelvic problem within one year after construction of the anastomosis, thereby also including for example rectovaginal fistulas. Only then, published literature can be meaningfully compared regarding leak rates. From all the correspondence with journals and reviewers about this study, as well as discussions during (inter)national meetings, it has become clear that we are often not talking about the same thing. Discussions are also blurred by social influences in which there might be restricted willingness to honestly talk about surgical complications, the frequency in which these are seen, and the problems in managing these complications.

The cross-sectional snapshot design with long-term follow-up raises the question whether the early diagnosis of anastomotic leakage is adequate. This is of great importance, since early diagnosis enables less invasive treatment options and will lead to better outcomes. Better outcomes of early proactive management are related to several aspects, namely early control of pelvic sepsis thereby minimizing deterioration of the patient's condition, prevention of retraction of the efferent limb with the possibility of reconstruction, prevention of extensive fibrosis resulting in anastomotic stricture, and preserving compliance of the neorectum by reducing formation of fibrosis as a consequence of long lasting secondary healing with related functional problems because of a stiff neorectum. Many Dutch hospitals have now implemented measurement of the inflammatory marker C-reactive protein (CRP) as a test to early detect anastomotic leaks in their postoperative protocols. Together with the implementation of a revised Dutch colorectal cancer guideline in 2014, in which the use of neoadjuvant radiotherapy was restricted, a decrease in both late diagnosis and non-healing of the leak are hopefully seen in the coming years. A new snapshot study with cross-sectional data collection of for example the year 2017 would therefore be of great interest. The Dutch Snapshot Research Group (www.snapshotresearch.nl) has increasingly become an effective collaboration for this type of research, and is planning to repeat a snapshot study on rectal cancer surgery.

Currently, the group at the Amsterdam UMC has initiated a national multicentre study (IMARI) in which five measures for prevention and early treatment of anastomotic leakage after TME surgery are being prospectively evaluated. These include preoperative oral antibiotics with bowel preparation for positively influencing the intestinal microbiome, quality controlled tailored splenic flexure mobilisation for reducing tension on the anastomosis, intraoperative ICG fluorescence angiography for assessment of anastomotic perfusion, day 3 CRP measurement with subsequent protocoled re-measurement and CT scanning with rectal contrast, and endosponge assisted early anastomotic reconstruction. Hopefully, this will further improve outcome of restorative rectal cancer resection in the Netherlands.

A diverting ileostomy has become standard of care because it can prevent the clinical consequences of anastomotic leakage. But inherently, it thereby also hides the occurrence of disruption of anastomotic integrity. These leaks are often referred to as occult leakages and considered to be of less clinical relevance because of supposed spontaneous healing in the majority of patients. However, apparently several of those leaks do not spontaneously heal, especially after radiotherapy. Furthermore, occult leaks might be very tiny and difficult to diagnose with endoscopy or imaging at the time a decision is made about stoma reversal. As a consequence, diverting stoma's might be closed in the presence of a persisting 'micro' leakage.

In the weeks to months, and even years, following stoma closure in the presence of an occult leakage, the underlying sinus is reactivated and growing in the presence of an adequately functioning anal sphincter. The sphincter keeps pressure on the micro leakage and stows air, mucous and faecal material into the sinus. Because of the thick fibrotic capsule that has been formed around the occult leakage, this process might still be asymptomatic in the beginning. But the sinus subsequently becomes bigger and might give rise to formation of fistula tracks along routes of less resistance than the anal sphincter ('sinus hypertension'). These routes are for example extrasphincteric fistula tracts to the perineal skin, or along the piriformis muscle to the trochanteric areas. These phenomenons have been observed and pathophysiological mechanisms have been formulated when the Amsterdam UMC became a centre for 'anastomotic failure' during the last decade.

It is remarkable that there is only limited literature on long term consequences of anastomotic failure and options for treatment. This is not explained by the low incidences of these problems, but more likely related to the fact that worldwide these problems are dealt with by the primary treating surgeons. Rectal cancer surgery is still

not a very centralized type of care, despite some countries are implementing minimal volume standards. For this reason, only a few patients with anastomotic failure and long-term non-healing of a low anastomosis are seen by each surgeon. Managing anastomotic leakage is high complex, low volume surgical care, that needs centralization. Only when this type of care is centralized, this will lead to bigger cohorts, from which we can learn about pathophysiology and determine optimized treatment strategies. But this requires surgeons who are prepared to send their problems to colleagues working in a tertiary referral 'anastomotic failure unit'. Hopefully, this will happen in the near future, thereby increasing the body of literature on this topic.

Given the potential problems related to silent leaks, it was thought that we actually have to clinically see that a low anastomosis is leaking, but at the earliest possible moment, with subsequent immediate and appropriate surgical management. Because routine diversion delays the diagnosis of anastomotic leakage besides several other disadvantages, only highly selective diversion should probably become the new standard of care after restorative rectal cancer resection, but only when proactive standardized evaluation of anastomotic integrity and early proactive management is guaranteed by an institutional protocol. **Chapter 2** has shown that routine diversion can be safely omitted in a unit that fulfils these prerequisites. Of course, these findings must be confirmed in larger studies in the future by other centres and in other clinical settings. The conclusions of **Chapter 2**, for now, are only applicable to low rectal cancer resection with a low anastomosis, performed through transanal minimally invasive surgery (TAMIS), at an institution with a dedicated colorectal team that is willing and able to perform therapeutic faecal diversion at any time during the week when anastomotic leakage occurs.
This sensational revolutionary change in diversion of low anastomoses has been enormously criticized in the international colorectal community. However, there is a national trend in the Netherlands, showing less routine diversion.[1] But this is probably the only country worldwide that currently adapts the strategy regarding diversion of anastomoses after TME surgery.

With these high rates of anastomotic leakage, restoration of bowel continuity might not always be the best option in specific patient populations. For example, a low anastomosis is better omitted in frail elderly patients with multiple comorbidities in whom major complications might have devastating consequences. This growing population has a need for tailored counselling and surgery. In **Chapter 3**, surgeons have indicated to perform both low Hartmann's resection (LHR) and intersphincteric abdominoperineal resection (iAPR) with end colostomy when bowel continuity with

creation of an anastomosis is not desired, with an iAPR as the preferred technique. **Chapter 4 and 5** show that both techniques show similar rates of pelvic abscess formation, postoperative complications and reinterventions, and can therefore both be safely offered to patients. However, leaving a rectal remnant might cause different discomforts, such as persisting mucus production and pain, which are not assessed in these studies. Future studies should focus on these parameters, also including quality of life, as well as the length of the rectal remnant. These are important questions to address in order to develop a valid advise with regard to the preferred surgical technique for rectal cancer resection without restoration of bowel continuity.

When anastomotic leakage occurs and minimally invasive treatment options fail, often a definitive end colostomy is the only treatment option left. But in highly motivated, relatively healthy patients, a redo anastomosis can also be offered, although there is no consensus on the use of redo anastomosis, both nationally and internationally. This can mainly be attributed to questions regarding the success and functional outcome following redo anastomosis, since it is a rare procedure with only small studies and case series describing outcomes. As the systematic review in **Chapter 6** shows, there is a relatively high success rate following redo surgery, which is supported by the outcomes of **Chapter 7 and 8**. An approximately 70% chance of successful restoration of bowel continuity versus no bowel continuity at all will persuade many patients to choose a redo anastomosis. However, the high rate of complications and recurrent pelvic sepsis with extensive reinterventions and readmissions should be discussed with patients on beforehand. A 30-40% chance on pelvic sepsis with subsequent reinterventions might discourage these patients who are already traumatized by an extensively complicated postoperative course.
Maybe even more important than the success rate in the counselling of patients for redo surgery, is the functional outcome. With successful restoration of bowel continuity, but very frequent faecal incontinence, a stoma would provide a more manageable situation for some patients. As described in **Chapter 9**, even though redo anastomosis seems to have a negative impact on quality of life when compared to primary healed anastomosis, the comparable anorectal function shows us that redo anastomosis might still be a valid treatment option in patients highly motivated for restoration of bowel continuity.

As well as for primary rectal cancer resection, we believe TAMIS is also a promising technique for redo surgery, since it enables more procedures to be performed laparoscopically, as shown in **Chapter 8**, and possibly even qualifies more patients for a redo anastomosis, since the leaking anastomosis can be accessed more frequently by use of the transanal technique.

The high numbers of late diagnosed complications, such as anastomotic leakage and pelvic abscess, and reinterventions beyond 30 days postoperative in both primary surgery and redo surgery, described in multiple chapters in this thesis, highlight the importance of long-term follow-up when assessing complications following rectal cancer resection. Possibly, anastomotic leakage rate is underestimated in studies only including 30-day postoperative follow-up. Future studies should take this information into account and extend the duration of follow-up. Adequate information on complications and outcomes is crucial in the counselling of patients and can aid in the draft of tailored treatment plans for the individual patient, as well as guide design of future research that aims to improve outcomes after restorative rectal cancer surgery.

References

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Samenvatting

De chirurgische behandeling van het rectumcarcinoom is voortdurend in ontwikkeling. Het aantal mogelijke chirurgische technieken voor de resectie van het rectumcarcinoom, afhankelijk van tumor stadium, locatie van de tumor, patiënt karakteristieken en voorkeur van de patiënt, breidt nog steeds uit. Hetzelfde geldt voor de operatieve behandeling na het falen van de primaire anastomose. Alle nieuwe, voornamelijk minimaal invasieve technieken bieden mogelijk substantiële voordelen voor de individuele patiënt, maar brengen ook hun eigen specifieke complicaties met zich mee. Hiervan zijn naadlekkage en infectie in het kleine bekken het meest gevreesd. Alle behandelopties, inclusief mogelijke complicaties, moeten zorgvuldig gewogen en besproken worden met de patiënt om zo tot een gepersonaliseerd behandelplan te komen.

Dit proefschrift richt zich in **Deel I** en **Deel II** op complicaties, re-interventies en her-operaties na niet-rectum sparende resectie van het rectumcarcinoom. **Deel I** richt zich op darmcontinuïteit herstellende resectie van het rectumcarcinoom (waarbij *wel* een anastomose wordt gemaakt). **Deel II** richt zich op resectie van het rectumcarcinoom *zonder* herstel van darmcontinuïteit. In **Deel III** van dit proefschrift richten we ons op zogenaamde redo chirurgie na naadlekkage. Er is daarbij gekeken naar het succes van redo anastomosen bij naadlekkage, met inachtneming van herstel van darmcontinuïteit, aantal complicaties en functionele uitkomsten na redo chirurgie.

Deel I – Resectie van het rectumcarcinoom met herstel van darmcontinuïteit

In **Hoofdstuk 1**, wordt een overzicht van het voorkomen van naadlekkage en chronische presacrale sinus na een lage anterieure resectie (LAR) in Nederland gepresenteerd. Dit zijn resultaten van een snapshot-studie over rectumcarcinoom, dat werd uitgevoerd in 71 Nederlandse ziekenhuizen, waarbij 2095 patiënten werden geïncludeerd. De studie laat zien dat in 13.4% van de 998 geïncludeerde patiënten die een LAR ondergingen in verband met rectumcarcinoom, er binnen 30 dagen postoperatief naadlekkage werd gediagnosticeerd. Dit aantal liep op naar 20.0% na 30 dagen. Van alle patiënten met naadlekkage werd er in 48% gezien dat de anastomose niet heelde. Dit resulteert in een totaalpercentage chronische pre-sacrale sinus van 9.5%. Onafhankelijke voorspellers van naadlekkage waren neo-adjuvante therapie (OR 2.85; 95% CI 1.00-8.11) en een distale (≤3cm van de anorectale overgang op MRI) tumor (OR

1.88; 95% CI 1.02-3.46). De studie laat ook zien dat het voorkomen van naadlekkage op de lange termijn vergelijkbaar is met of zonder het aanleggen van een deviërend stoma.

Dit laatste gegeven vormt een belangrijke basis voor het volgende hoofdstuk, gezien er vanuit historisch perspectief wordt gedacht dat een deviërend stoma de ernst van de symptomen van naadlekkage en het aantal spoedeisende her-operaties vermindert. In **Hoofdstuk 2** werden patiënten die een laparoscopische totale mesorectale excisie (TME) ondergingen met routinematig aanleggen van een deviërend stoma vergeleken met patiënten die slechts zeer selectief een deviërend stoma kregen in combinatie met transanale TME met versterking van de anastomose met een continue hechting. Naadlekkage werd gediagnosticeerd in 20% van de patiënten die routinematig een stoma kregen, vergeleken met 8% van de patiënten die slechts selectief een stoma kregen. Dit verschil was niet significant verschillend. Er was echter wel een significant verschil in het aantal stoma-gerelateerde heropnamen en her-operaties (inclusief opheffen van het stoma) binnen één jaar; respectievelijk 84% en 86% na routinematig aanleggen van een deviërend stoma en respectievelijk 17% en 17% na het slechts selectief aanleggen van een stoma.

Deel II - Resectie van het rectumcarcinoom zonder herstel van darmcontinuïteit

In **Hoofdstuk 3** werd de huidige praktijk met betrekking tot de resectie van het rectumcarcinoom zonder herstel van darmcontinuïteit geëvalueerd. Chirurgen uit 37 Nederlandse ziekenhuizen reageerden op een online vragenlijst met vragen betreffende lage Hartmann resectie (LHR) en intersfincterische abdominoperineale resectie (iAPR) als chirurgische technieken zonder herstel van darmcontinuïteit. Van de 42 chirurgen die reageerden, gaf 36% aan geen onderscheid te maken tussen een hoge of een lage Hartmann resectie, gebaseerd op de geschatte lengte van de rectumstomp. Over het geheel genomen was in 86% iAPR de techniek van voorkeur en 62% gaf aan een andere techniek te overwegen bij tumoren binnen 1cm of 5cm van de bekkenbodem. De respondenten schatten de incidentie van bekkenabcessen na LHR hoger, gelijk of lager dan na iAPR in respectievelijk 36%, 36% en 21%.

In **Hoofdstuk 4** werd het voorkomen van bekkenabcessen na LHR en iAPR onderzocht in een kleine, retrospectieve studie, waarbij 40 patiënten die een LHR ondergingen werden geïncludeerd en 12 patiënten na iAPR. Er waren geen significante verschillen

in majeure complicaties binnen de 30-dagen postoperatieve periode (respectievelijk 18% en 33%) of bekkenabcessen gedurende de gehele studieperiode (respectievelijk 10% en 17%). Een beperkende factor van deze studie was het kleine aantal patiënten. Daarom werd er een studie met eenzelfde opzet, maar met een groter cohort patiënten vanuit een snapshot-studie gepresenteerd in **Hoofdstuk 5**. Hierbij werden 139 LHR- en 46 iAPR-patiënten geïncludeerd. Een bekkenabces kwam voor bij 17% van de patiënten na LHR en bij 11% na iAPR. Dit bleek geen significant verschil, zelfs niet na correctie voor mortaliteit of verlies uit de follow-up. Daarentegen werden er wel significant meer abcessen gediagnosticeerd na de 30-dagen postoperatieve periode na iAPR. De studie liet ook hoge aantallen chirurgische re-interventies en heropnamen zien, waarvan slechts een klein deel binnen 30 dagen postoperatief plaatsvond.

Deel III – Hersteloperaties na resectie van het rectumcarcinoom

Hoofdstuk 6 laat de resultaten van een systematisch literatuuronderzoek naar uitkomsten na redo chirurgie met het aanleggen van een nieuwe (redo) anastomose zien. We includeerden negen studies, met in totaal 291 patiënten. Het onderzoek liet een samengesteld succespercentage van 79% (95% CI 69-86) zien, met een samengestelde incidentie van majeure postoperatieve morbiditeit van 16% (95% CI 10-24) en een samengestelde incidentie van infectie in het kleine bekken van 16% (95% CI 9-27).

Hoofdstuk 7 beschrijft het klinische succes en de morbiditeit na het aanleggen van een redo coloanale anastomose (CAA) voor naadlekkage na LAR in een cohort van 59 casus. Het laat zien dat naadlekkage de meest voorkomende complicatie is na redo CAA (41%). In 66% van de patiënten was de darmcontinuïteit hersteld aan het einde van de follow-up en in 24% van de patiënten werd een definitief colostoma aangelegd. In een multivariaat model bleek lekkage van de redo CAA de enige risicofactor voor een definitief stoma (OR 0.022; 95% CI 0.004-0.122). Deze cohortstudie liet ook zien dat 97% van alle procedures middels open benadering werd verricht. Er wordt gedacht dat dit te wijten is aan het matige zicht en de slechte bereikbaarheid van het kleine bekken door de locatie, eerdere operatie(s) en infectie in het kleine bekken. In **Hoofdstuk 8** wordt het gebruik van transanale minimaal invasieve chirurgie (TAMIS) voor redo chirurgie beschreven. TAMIS heeft mogelijk het vermogen om de obstakels die men bij conventionele redo chirurgie ondervindt te overwinnen. Zowel redo chirurgie met het aanleggen van een nieuwe anastomose, als ook de intersfincterische completerende proctectomie (ICP) met eindstandig colostoma werden beschreven en

vergeleken met patiënten die een conventionele redo anastomose of ICP ondergingen. Door de transanale dissectie verder naar boven uit te breiden door het gebruik van TAMIS, kon het abdominale deel van de operatie in twee derde van de patiënten laparoscopisch worden gedaan. Er was geen significant verschil in intra-operatieve complicaties of 90-dagen postoperatieve uitkomsten tussen TAMIS en conventionele redo chirurgie. Wel kon in 62% van de patiënten die een TAMIS-procedure ondergingen een anastomose met nietjes gemaakt worden, waar alle conventionele redo anasomosen handgelegd waren.

Tot slot richt **Hoofdstuk 9** zich niet op de chirurgische uitkomsten, maar op functionele uitkomsten en kwaliteit van leven na redo anastomosen, zoals patiënten dit ervaren. Uitkomsten na redo anastomose werden vergeleken met patiënten met een primair genezen anastomose na TME voor rectumcarcinoom. In totaal werden er 52 patiënten met een redo anastomose geïncludeerd, vanuit drie Europese verwijscentra, waarvan 83% radiotherapie had ondergaan. Uitkomsten werden onderzocht middels de lage anterieure resectie syndroom (LARS) score en de EORTC QLQ-C30 en QLQ-CR29 vragenlijsten. Deze lieten vergelijkbare majeure LARS scores zien tussen de groepen; 73% na redo anastomose en 68% na primair genezen anastomose. De redo groep scoorde significant slechter op fecale incontinentie en flatulentie van de EORTC QLQ-CR29 vragenlijst, maar er waren geen verschillen in urine- of seksuele disfunctie bij zowel mannen als vrouwen. Algehele gezondheid, rol- en sociale functie, lichaamsbeeld en angst scoorden significant slechter in de redo groep.

Toekomstperspectieven

Het percentage naadlekkage zoals dat is beschreven in **Hoofdstuk 1** geeft de nationale uitkomsten binnen Nederland in 2011 weer, maar is hoog in vergelijking met de literatuur. Dit kan deels verklaard worden door de inclusie van *laat* gediagnosticeerde naadlekkage. De meeste studies die in de huidige literatuur worden gepresenteerd, geven alleen de 30-dagen uitkomsten en vaak zelfs alleen de uitkomsten gedurende de ziekenhuisopname weer. Bovendien onthulde het retrospectieve statusonderzoek door arts-assistenten binnen de snapshot-studie, waarbij de patiëntgegevens enkele jaren later zorgvuldig onder de loep werden genomen, verschillende problemen en complicaties die niet binnen enige reguliere registratie gerapporteerd werden. Dit benadrukt de behoefte aan een internationaal geaccepteerde, brede definitie voor naadlekkage, waarbij elk infectieus probleem in het bekken binnen één jaar na aanleggen van de anastomose wordt meegenomen. Hierbij moeten bijvoorbeeld ook rectovaginale fistels worden geïncludeerd. Alleen dan kan het voorkomen van naadlekkage binnen de literatuur betekenisvol worden vergeleken. Uit alle correspondentie met tijdschriften en recensenten over deze studie en door discussies op (inter)nationale bijeenkomsten blijkt dat we vaak niet over hetzelfde praten. Discussies worden vaak ook vertroebeld door sociale invloeden, waarbij er mogelijk beperkte bereidheid is om het op eerlijke wijze te hebben over chirurgische complicaties, de frequentie hiervan en de problemen die men tegenkomt bij het oplossen van deze complicaties.

De dwarsdoorsnede die de snapshot-studie met lange termijn follow-up biedt, roept de vraag op of de vroege diagnose van naadlekkage wel adequaat geschiedt. Dit is van groots belang, aangezien vroege diagnose minder invasieve behandelopties mogelijk maakt en tot betere uitkomsten leidt. Betere uitkomsten door vroeg, proactief ingrijpen zijn gerelateerd aan meerdere aspecten, namelijk: vroegtijdige controle van lokale sepsis, waarbij verslechtering van de conditie van de patiënt wordt geminimaliseerd, het voorkomen van het retraheren van de efferente darmlis met de mogelijkheid tot reconstructie, het voorkomen van uitgebreide fibrose resulterend in stricturen van de anastomose en het behouden van de soepelheid van het neorectum door reductie van fibrose veroorzaakt door langer bestaande secundaire genezing met bijbehorende problemen door een stijf neorectum. Veel Nederlandse ziekenhuizen hebben nu het meten van de ontstekingsparameter C-reactive protein (CRP) toegevoegd aan hun postoperatieve protocollen om zo naadlekkage in een vroeg stadium te kunnen diagnosticeren. Samen met de implementatie van een gereviseerde versie van de Nederlandse richtlijn “colorectaalcarcinoom”, waarin het gebruik van neo-adjuvante

radiotherapie sterk wordt beperkt, kan er hierdoor in de komende jaren hopelijk een afname van laat gediagnosticeerde en niet-genezende naadlekkages worden gezien. Een nieuwe snapshot-studie met data van bijvoorbeeld 2017 zou daarom zeer interessant zijn. De 'Dutch Snapshot Research Group" (www.snapshotresearch.nl) ontwikkelt zich steeds meer tot een effectief samenwerkingsverband voor dit type onderzoek en er zijn plannen voor herhaling van een snapshot-studie aangaande het rectumcarcinoom.

Op dit moment wordt in het Amsterdam UMC een nationale multicenterstudie opgezet (IMARI), waarin vijf maatstaven voor preventie en vroege behandeling van naadlekkage na TME chirurgie prospectief worden geëvalueerd. Hieronder vallen preoperatieve orale antibiotische darmvoorbereiding om het intestinale microbioom positief te beïnvloeden, gerichte mobilisatie van de flexura lienalis waarbij de kwaliteit hiervan wordt gecontroleerd om zo een spanningsloze anastomose te creëren, intra-operatieve beoordeling van de doorbloeding van de anastomose met ICG fluorescentie, CRP-meting op de derde postoperatieve dag met bijbehorende, geprotocolleerde aanvullende metingen en CT-scans met rectaal contrast en vroege sluiting van het naaddefect na behandeling met endo-SPONGE®. Dit zal hopelijk de uitkomsten na resectie van het rectumcarcinoom met herstel van darmcontinuïteit in Nederland verder verbeteren.

Een deviërend stoma wordt standaard aangelegd omdat het de klinische consequenties van naadlekkage kan voorkomen. Maar inherent hieraan vermindert het ook het vóórkomen van dehiscentie van de anastomose. Dit type naadlekkage wordt vaak een occult lek genoemd en wordt klinisch minder relevant geacht, omdat in de meeste patiënten spontane genezing optreedt. Echter genezen enkele van deze lekkages niet spontaan, met name na radiotherapie. Daarnaast kunnen deze occulte lekken erg klein zijn en daardoor moeilijk te diagnosticeren tijdens endoscopie of beeldvorming ten tijde van controle van de anastomose en het plannen van het opheffen van het stoma. De consequentie hiervan is dat het deviërend stoma mogelijk wordt gesloten, terwijl er een persisterende 'micro'-lekkage aanwezig is.

In weken tot maanden, soms zelfs jaren, na opheffen van het stoma in aanwezigheid van een occult lek, wordt de onderliggende sinus gereactiveerd en groeit deze, door een adequaat functionerende anale sfincter. De sfincter behoudt druk op de microlekkage en verplaatst zo lucht, slijm en fecaal materiaal naar de sinus. Door het dikke fibrotische kapsel dat rondom het occulte lek gevormd is, is het mogelijk dat dit proces in het begin asymptomatisch is. Maar, de sinus wordt vervolgens groter en

veroorzaakt mogelijk fistelgangen door routes met minder weerstand dan de anale sfincter ('sinus hypertensie'). Deze routes zijn bijvoorbeeld extrasfincterische fisteltrajecten naar de perineale huid, of langs de musculus piriformis naar het trochanter gebied. Deze fenomenen werden gezien en bijbehorende pathofysiologische mechanismen werden geformuleerd toen het Amsterdam UMC gedurende het laatste decennium een centrum werd voor 'de gefaalde anastomose'.

Het is opmerkelijk dat er slechts weinig literatuur is waarin de lange termijn consequenties van het falen van de anastomose en bijbehorende behandelopties worden beschreven. Dit wordt niet verklaard door het weinig voorkomen van deze problemen, maar is waarschijnlijk gerelateerd aan het feit dat deze problemen wereldwijd door de primair behandeld chirurg worden behandeld. Chirurgie voor rectumcarcinoom wordt nog steeds niet veel gecentraliseerd, ondanks het feit dat sommige landen standaarden voor minimale volumina hebben geïmplementeerd. Hierdoor ziet elke chirurg slechts weinig patiënten met naadlekkage zonder genezingstendens op de lange termijn. De behandeling van naadlekkage is hoog-complexe en laag-volume chirurgische zorg, waarvoor centralisatie nodig is. Alleen als dit type zorg gecentraliseerd wordt, zal dat leiden tot grotere cohorten waaruit we kunnen leren over de pathofysiologie en we optimale behandelstrategieën kunnen bepalen. Dit vereist echter chirurgen die bereid zijn hun problemen naar collega's in een verwijscentrum voor naadlekkage door te sturen. Dit kan hopelijk in de nabije toekomst gerealiseerd worden, waardoor de hoeveelheid literatuur aangaande dit onderwerp zal toenemen.

Gezien de mogelijke problemen die veroorzaakt worden door stille naadlekkages, wordt er gedacht dat we daadwerkelijk moeten zien dat er lekkage is van een lage anastomose, op een zo vroeg mogelijk moment met opeenvolgend directe en passende chirurgische behandeling. Omdat het routinematig plaatsen van een deviërend ileostoma, naast andere nadelen, de diagnose van naadlekkage vertraagt, wordt er gesuggereerd dat bij resectie van rectumcarcinoom met herstel van darmcontinuïteit slechts zeer selectief een deviërend stoma aangelegd moet worden. Maar alleen wanneer er proactieve en gestandaardiseerde evaluatie van de anastomose en vroege proactieve behandeling protocollair gegarandeerd kan worden binnen een instituut. **Hoofdstuk 2** heeft laten zien dat een deviërend stoma veilig achterwege kan worden gelaten in een centrum dat aan deze eisen voldoet. Uiteraard moeten deze bevindingen nog bevestigd worden door grotere studies in andere centra. De conclusies van **Hoofdstuk 2** zijn vooralsnog alleen toepasbaar op resectie van rectumcarcinoom met een lage anastomose, uitgevoerd middels transanale minimaal invasieve chirurgie (TAMIS), binnen een

centrum met een toegewijd colorectaal team dat te allen tijde bereid en in staat is om in verband met naadlekkage een therapeutisch deviërend stoma aan te leggen. Deze sensationele verandering in het deviëren van lage anastomosen heeft veel kritiek gekregen binnen de internationale colorectale gemeenschap. Er is echter een nationale trend in Nederland, die een afname van het routinematig deviëren van de anastomose laat zien.[1] Maar dit is waarschijnlijk het enige land ter wereld dat op dit moment deze strategie ten aanzien van het deviërend ileostoma bij anastomosen na TME chirurgie aanneemt.

Gezien deze hoge kans op naadlekkage, is voor specifieke patiëntengroepen het herstel van darmcontinuïteit mogelijk niet altijd de beste optie. Een lage anastomose kan bijvoorbeeld beter vermeden worden bij kwetsbare, oudere patiënten met veel co-morbiditeit, bij wie grote complicaties mogelijk ernstige gevolgen kunnen hebben. Deze groeiende populatie behoeft geïndividualiseerde begeleiding en chirurgie. In **Hoofdstuk 3** hebben chirurgen aangegeven zowel een lage Hartmann resectie (LHR) als een intersfincterische abdominoperineale resectie (iAPR) met eindstandig colostoma te verrichten als darmcontinuïteit middels het aanleggen van een anastomose niet gewenst is, waarbij iAPR de techniek van voorkeur is. **Hoofdstuk 4 en 5** laten zien dat er vergelijkbare aantallen bekkenabcessen, postoperatieve complicaties en re-interventies voorkomen bij beide technieken. Daarom kunnen beide technieken veilig aan patiënten worden aangeboden. Het achterlaten van een rectumstomp brengt mogelijk wel andere ongemakken met zich mee, zoals persisterende slijmproductie en pijn. Dit is niet onderzocht in deze studies. Toekomstige onderzoeken moeten zich zowel op deze parameters richten, alsook op kwaliteit van leven en de lengte van de rectumstomp. Om een gedegen advies te kunnen geven over een techniek van voorkeur voor de resectie van rectumcarcinoom zonder herstel van darmcontinuïteit moet er meer duidelijkheid komen betreffende deze parameters.

Wanneer naadlekkage optreedt en alle minimaal invasieve behandelingen falen, is een definitief eindstandig colostoma vaak de enige overgebleven behandeloptie. Echter aan zeer gemotiveerde en relatief gezonde patiënten kan een redo anastomose worden aangeboden, al is hier zowel nationaal als internationaal geen consensus over. Dit is voornamelijk te wijten aan de vragen die er bestaan omtrent de succeskans en de functionele uitkomsten na redo anastomose, aangezien het een zeer zeldzame procedure is waarover slechts kleine studies zijn beschreven. Het systematische literatuuronderzoek in **Hoofdstuk 6** laat zien dat er een relatief hoog succespercentage is. Dit wordt bevestigd door de uitkomsten van **Hoofdstuk 7 en 8**. Een kans van bijna 70% op succesvol herstel van de darmcontinuïteit zal menig patiënt overhalen tot het

kiezen van een redo anastomose. Het hoge percentage complicaties en infectieuze problemen in het bekken met uitgebreide re-interventies en heropnamen echter, zal ook vele patiënten die vaak reeds getraumatiseerd zijn door het eerdere uitgebreid gecompliceerde beloop ontmoedigen.

Misschien nog belangrijker dan het succespercentage bij het informeren van patiënten over redo anastomose zijn de functionele uitkomsten. In het geval van een succesvol herstel van darmcontinuïteit, maar zeer frequente fecale incontinentie, zal een stoma voor sommige patiënten een meer acceptabele en handelbare situatie opleveren. Zoals beschreven in **Hoofdstuk 9** laat de vergelijkbare anorectale functie, ondanks het negatieve effect op de kwaliteit van leven wanneer de uitkomsten worden vergeleken met primair genezen anastomosen, zien dat een redo anastomose mogelijk een waardevolle behandeloptie is voor patiënten die zeer gemotiveerd zijn voor het behoud van darmcontinuïteit.

TAMIS is volgens onze studiegroep, net als binnen de primaire behandeling van rectumcarcinoom, een veelbelovende techniek voor redo chirurgie. Het zorgt ervoor dat meer operaties laparoscopisch uitgevoerd kunnen worden, zoals **Hoofdstuk 8** laat zien, en mogelijk komen zelfs meer patiënten in aanmerking voor redo chirurgie, omdat de lekkende anastomose met deze transanale techniek beter bereikt kan worden.

Meerdere hoofdstukken in dit proefschrift laten hoge aantallen laat gediagnosticeerde complicaties, zoals naadlekkage, bekkenabcessen en re-interventies ná 30 dagen postoperatief zien in zowel primaire als redo chirurgie. Dit benadrukt het belang van lange termijn follow-up bij het onderzoeken van complicaties na rectumchirurgie. Mogelijk wordt het percentage naadlekkage onderschat in studies die slechts 30 dagen follow-up beschrijven. Toekomstige studies zullen hier rekening mee moeten houden en de duur van de follow-up moeten verlengen. Adequate informatie over complicaties en uitkomsten is cruciaal in de begeleiding van patiënten en kan helpen in het opstellen van een gepersonaliseerd behandelplan voor de individuele patiënt. Tevens kan het helpen in het opzetten van toekomstig onderzoek om zo de uitkomsten na rectumchirurgie te verbeteren.

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PHD portfolio

Name PhD student: Emma Westerduin
PhD period: July 2015 – May 2019
Name PhD supervisor: Prof. dr. W.A. Bemelman

1. PhD training

	Year	Workload (ECTS)
General courses		
• Expert Management of Medical Literature	2015	0.3
• Scientific Writing in English for Publication	2015	1.5
• Clinical Epidemiology: Systematic Reviews	2016	0.7
• Clinical Epidemiology: Observational Clinical Epidemiology	2016	0.6
• Practical biostatistics	2016	1.1
• Basic course legislation and organisation for clinical researchers (BROK)	2016	1.0
• Advanced topics in biostatistics	2017	2.1
Seminars, workshops and master classes		
• Weekly department seminars, AMC	2015-2017	1.5
• Journal club	2016-2017	1.5
• Symposium Lage Naadlekkage. Wat doet u?	2016	0.25
• Symposium on minimal invasive treatment of anastomotic leakage, AMC	2017	0.25
• Value Based Healthcare (VBHC) masterclass, Amsterdam	2017	0.2
• Medical Business Masterclass, Amsterdam	2017	0.6
• WCP symposium midden Nederland, Bosch en Dal	2018	0.25
Oral presentations		
• Wat doen we met de rectumstomp? Lage Hartmann resectie vs intersfincterische resectie voor het lage rectumcarcinoom. WCP symposium midden Nederland, Bosch en Dal	2018	0.5

Poster presentations

• Redo coloanal anastomosis; an analysis of 59 cases. Tergooi wetenschapssymposium, Hilversum	2016	0.5
• Low Hartmann Procedure or Intersphincteric Abdominoperineal Resection for lower rectal carcinoma; infectious complications and the influence of the rectal remnant. Tergooi wetenschapssymposium, Hilversum	2016	0.5

Invited peer-review

• Colorectal Disease	2017	0.5

(Inter)national conferences

• Chirurgendagen, Veldhoven	2016	0.5
• ESCP Annual Meeting, Milan	2016	0.5
• Chirurgendagen, Veldhoven	2017	0.5
• ESCP Annual Meeting, Berlin	2017	0.5
• Chirurgendagen, Veldhoven	2018	0.5

2. Teaching

	Year	Workload (ECTS)
Tutoring, Mentoring		
• Master thesis: R. Stam - Functional outcome of TaTME in rectal carcinomas compared to functional outcome after Low Anterior Resection and reconstruction of anastomosis.	2016	1.0

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Curriculum Vitae

Emma Westerduin was born in The Hague on June 4th 1987. She attended high school at the Christelijk Gymnasium Sorghvliet in the Hague, after which she got accepted to medical school at the University of Amsterdam. She graduated as a medical doctor in 2013. During her studies she was active in the organization of several social events and boards and was introduced to scientific research during her research internship at the department of oncological surgery at the Antoni van Leeuwenhoek hospital.

After obtaining her medical degree, she started working as a surgical resident not in training at the Tergooi hospital in Hilversum. Here, she started multiple research projects, under supervision of dr. A.A.W. van Geloven. These projects have been the start of a collaboration with prof. dr. W.A. Bemelman and dr. P.J. Tanis at the department of colorectal surgery in the Amsterdam UMC – location AMC and have eventually resulted in this thesis.

For the most part, Emma has worked on her PhD trajectory simultaneously with her clinical work in both the Tergooi Hospital in Hilversum under supervision of dr. A.A.W. van Geloven and the OLVG in Amsterdam under supervision of dr. M.F. Gerhards. In January 2019, she started her training in General Surgery from the Academic Medical Centre and is currently back in the Tergooi Hospital as surgical resident in training.