process. Additionally, Balcom *et al.* concluded that the use of PEG significantly reduced pancreatic secretion in the drain fluid postoperatively and was well tolerated *in vivo*, in a canine model [26].

LOE	Author/ year	Model	N	Tissue adhesive	Methods	Outcome
-	Bonanomi / 2004 13	Pig	20	FG (Tisseel)	Gastrojejunal anastomosis	+
-	Nguyen / 2004 a* 14	Pig	16	FG (Tisseel)	Gastrojejunal anastomosis	+
-	Weiss / 2011 15	Rat	64	CA (Histoacryl Blue)	Gastrojejunal anastomosis	+/-
-	Nandakumar / 2010 16	Pig	30	BioGlue	Gastrojejunal anastomosis	+
1b	Silecchia / 2006+2008 17, 70	Clinical (RCT)	340	FG (Tisseel)	LRYGB**	+/-
3b	Liu / 2003 18	Clinical	480	FG (Tisseel)	RYGB	+
2b	Sapala / 2004 20	Clinical	738	FG (Hemaseel APR, Tisseel)	Gastrojejunal anastomosis	+
2b	Cottam / 2006 21	Clinical	126	FG (Tisseel)	Laparoscopic sleeve gastrectomy	+
2b	Raquel / 2009 22	Clinical	100	FG (Tissucol)	LRYGB)/ Laparoscopic sleeve gastrectomy	+
2b	Fullum / 2009 23	Clinical	760	FG (not specified)	LRYGB	+
2b	Nguyen / 2004 b* 14	Clinical	66	FG (Tisseel)	Gastrojejunal anastomosis	+
2b	Efthimiou / 2010 19	Clinical	474	FG (Tisseel)	LRYGP	-
4	Brady / 2006 24	Clinical	10	APG (autologous platelet gel)	Gastrojejunal anastomosis	+

Table 3. Sealants in gastric / bariatric surgery.

Clinical

Fibrin Glue

Clinically, level 1b evidence was derived from Lillemoe *et al.* who presented a RCT with 124 patients undergoing pancreaticoduodenal resection in which PJ was sealed with FG [27]. In this study the use of FG did not reduce the incidence of pancreatic fistula, length of hospital stay, total complications or death. Oida *et al.* reported a prospective series of 26 patients undergoing pancreaticoduodenectomy and subsequent sealing of the pancreaticogastrostomy with FG and round ligament [28]. In this study no leakage was seen in any patients.

Cyanoacrylate
No clinical studies were performed on CA sealing.

Other categories
One retrospective case-control study on 64 patients in which the PJ was sealed with glutaraldehyde-albumin glue (BioGlue) showed no statistically significant differences in the incidence or severity grades of postoperative pancreatic fistulas between the BioGlue and control groups [29].

LOE*	Author/ year	Model	N	Tissue adhesive	Methods	Outcome
-	Argyra / 2009 25	Pig	10	PEG (Focalseal L)	Pancreaticojejunal anastomosis	+
1b	Lillemoe / 2004 26	Clinical (RCT)	125	FG (Not specified)	Pancreatico-duodenectomy	+/-
4	Oida / 2009 27	Clinical	26	FG (not specified)	Pancreatico-duodenectomy	+
3b	Fisher / 2008 28	Clinical	64	BioGlue	Pancreatectomy	-

Table 4. Sealants in pancreatic surgery

Sealants in ileal anastomosis

Experimental

Fibrin Glue
Experimentally, Li *et al.* performed two rat studies in which they combined FG with human derived growth hormone (GH). They found that FG benefited anastomotic healing up to 5 days, and FG/GH worked synergistically to improve anastomotic healing up to 14 days [30]. Wang *et al.* also reported that FG/GH sealing decreases AL and improves anastomotic healing in a pig model of traumatic shock [31]. Another study on canine jejunal anastomoses compared hemostatic and adhesive effects of two FG (Greenplast and Tisseel). It was reported that both glues have similar haemostatic and adhesive properties and may be useful as anastomotic sealants [32].

Cyanoacrylate
Elemen *et al.* used industrial grade ethyl-2-cyanoacrylate (Pattex) for the creation of ileal anastomosis in a rat model [33]. In this study the glued anastomoses caused less tissue damage and healed better than the controls. Another cyanoacrylate (n-butyl-2-cyanoacrylate (nB2cA); Glubran 2) was evaluated by Ensäri *et al.* In this study jejunal anastomoses were sealed with Glubran 2 in 40 rats and ischemia reperfusion

was induced prior to anastomosis creation [34]. The authors reported that Glubran 2 significantly increases ABP with or without existence of ischemia/reperfusion and also increases adhesion formation around the anastomosis.

Other categories
In a study by Sweeney *et al.* PEG sealant (Focalseal-L) was tested in a rabbit model for incomplete ileal anastomosis [35]. According to this study an incomplete ileal anastomosis sealed with Focalseal-L is not inferior to a sutured anastomosis in terms of adhesion formation, stenosis and ABP.

Clinical

Fibrin Glue
One clinical study was performed, a level 2b cohort study by Wang *et al.* in which patients with intra-abdominal sepsis underwent primary anastomosis and fibrin sealing [36]. They conclude that FG sealing protected the primary anastomosis in patients with intra-abdominal sepsis therefore preventing the need for stoma placement.

Cyanoacrylate/ Other categories
No clinical studies have been performed using other types of tissue adhesives.

LOE*	Author/ year	Model	N	Tissue adhesive	Methods	Outcome
-	Li / 2006 71	Rat	360	FG (Guanzhou bio seal)	Ileal anastomosis	+
-	Li / 2007 29	Rat	300	FG (Guanzhou bio seal)	Ileal anastomosis;Incomplete	+
-	Wang / 2009 30	Pig	63	FG (Guanzhou bio seal)	Ileal anastomosis; gunshot wound model	+
-	Park / 2002 31	Dog	18	FG(Greenplast, Tisseel)	Jejunal anastomosis	+
-	Elemen / 2008 32	Rat	96	CA (Pattex)	Ileal anastomosis	+
-	Ensäri / 2010 33	Rat	40	CA (Glubran 2)	Jejunal anastomosis	+
-	Sweeney / 2002 34	Rabbit	24	PEG (Focalseal)	Ileal anastomosisl	+
2b	Wang / 200735	Clinical	48	FG (Guanzhou bio seal)	Ileal anastomosis	+

Table 5. Sealants in anastomosis of the small intestine

Sealants in colorectal anastomosis

Experimental

Fibrin Glue

Several experimental studies on the use of FG on colon anastomosis have been performed. Akgun *et al.* compared FG with an anti-adhesion barrier (hyaluronic acid-carboxymethylcellulose sheet) to investigate its early effects on the rat anastomosis [37]. They concluded that in the first 3 days after surgery FG may protect the anastomosis from leakage. Capitan Morales *et al.* used FG to create sutureless colonic anastomoses in a rat model, with positive results [38]. Girgin *et al.* also report positive effects of the use of FG (Tisseel) as an anastomotic sealant, also in combination with electromagnetic stimulation [39]. In another study the same FG was evaluated in combination with gentamycin [40]. The authors concluded that FG significantly increased ABP and also resulted in fewer adhesions, more fibroblast production and increased neovascularisation. Adding gentamycin did not lead to further improvement of these results. Kanellos *et al.* have performed numerous studies on FG of which the first on its effects around the colonic anastomosis in rats [41]. They found that the FG group had significantly higher ABP compared to the group without sealing, however no significant differences were found in the chosen clinical outcomes or histopathology. In following studies by the same authors, sealing with FG protected anastomotic healing from the adverse effects of 5-fluorocil, interferon-alpha-2a and leucovorin application [43]. Further experimental research has been performed by Giuratrabocchetta *et al.*, who performed a study in ten rabbits to test the effectiveness of a FG (TissuCol) and polyethylene glycol (PEG) sealant (CoSeal) in the prevention of colorectal anastomotic leakage [44]. The authors found no effect of either glue on the ABP; however they did find more fibroblast activity and neoangiogenesis in the Coseal group.

Cyanoacrylate

On the effect of CA glues on colorectal anastomosis, Bae *et al.* performed a rat study in which Histoacryl Blue was used as a sealant around the sutured anastomosis and also in sutureless anastomosis [45]. In the CA groups, more inflammation and healing by secondary intention around the glue, less collagen deposition, lower ABP as well as more stricture formation was reported. Furthermore, Irkorucu *et al.* studied the effect of GluSeal on anastomotic healing of ischemic left colon sutureless anastomosis [46]. No significant differences were found in AL rate, and in the ischemia groups no differences were found in ABP. Kanellos *et al.* performed a rat study testing Dermabond

as an anastomotic sealant [47]. They concluded that the sutureless anastomosis was equal to the sutured one, but that the outcome could be different under more demanding clinical conditions. Kayaoglu *et al.* investigated Glubran 2 around rat anastomoses in either a clean- contaminated or bacterial peritonitis environment [48]. The authors concluded that Glubran 2 glue did not provide any benefits, especially in the group with bacterial peritonitis, and caused increased inflammatory reaction, necrosis and adhesion formation. Nursal *et al.* performed a rat study in which a high-risk colonic anastomosis was created and then sealed with Dermabond [49]. The authors reported that in the late phase of wound healing Dermabond was detrimental to the wound healing process due to the ongoing inflammatory reaction. Ozmen *et al.* used Histoacryl Blue for the creation of a sutureless colonic anastomosis in a rat model and concluded that glue use impaired anastomotic healing [50]. Paral *et al.* compared two types of cyanoacrylate glues (Glubran 2 and Dermabond) for the creation of sutureless sigmoidal anastomoses in a pig model [51]. The authors favored Glubran 2 and concluded that Dermabond elicited more inflammation and fibrosis of the anastomosis as well as more AL. Tingstedt *et al.* showed no benefits of the use of polyanionic bioactive polypeptides in rat model for anastomotic leakage [52].

Other categories

Ustek *et al.* reported that the use of polydione-liposome (PVP-1) hydrogel improved wound healing of the rat colon anastomosis [53]. Another study by Yol *et al.* compared the use of platelet rich plasma (PRP) or glutaraldehyde-albumin glue (BioGlue) [54]. The authors reported that PRP sealing resulted in significantly higher ABP and hydroxyproline levels when compared to the BioGlue and control groups.

Clinical

Fibrin Glue

One clinical trial has been performed to test effectiveness of colorectal anastomotic sealing. In this prospective cohort study Huh *et al.* reported on 223 patients that underwent oncological laparoscopic rectum resection without the use of a defunctioning stoma [55]. In this study the use of FG was not associated with a decrease in AL.

Cyanoacrylate/ Other categories

No clinical studies have been performed using other types of tissue adhesives.

LOE*	Author/ year	Model	N	Tissue adhesive	Methods	Outcome
-	Akgun / 2006 36	Rat	38	FG (TIsseel)	Colonic anastomosis	+
-	Capitan Morales / 2000 44	Rat	105	FG (Tisseel)	Colonic anastomosis	+
-	Girgin / 2009 37	Rat	28	FG (Tisseel)	Colonic anastomosis	+
-	Subhas / 2011 43	Rat	70	FG (Tisseel)	Colonic anastomosis	+
-	Kanellos / 2003 39	Rat	36	FG (TissuCol)	Colonic anastomosis	+
-	Kanellos / 2004 40	Rat	64	FG (TissuCol)	Colonic anastomosis	+
-	Kanellos / 2007 41	Rat	60	FG (TissuCol)	Colonic anastomosis	+
-	Kanellos / 2006 42	Rat	60	FG (TissuCol)	Colonic anastomosis	+
-	Giuratrabocchetta / 2011 38	Rabbit	10	FG(Tissucol)	Colonic anastomosis	+/-
				PEG (CoSeal)		
-	Tingstedt / 200745	Rat	132	FG (Tisseel)	Iliocolic anastomosis	-
-	Bae / 2010 46	Rat	60	CA (Histoacryl Blue)	Colonic anastomosis	-
-	Irkorucu / 2009 48	Rat	40	CA (GluSeal)	Colonic anastomosis	-
-	Kanellos / 2002 47	Rat	40	CA (Dermabond)	Colonic anastomosis	+/-
-	Kayaoglu / 2009 50	Rat	80	CA (Glubran 2)	Colonic anastomosis	-
-	Nursal / 2004 51	Rat	90	CA (Dermabond)	Colonic anastomosis	-
-	Ozmen / 2004 49	Rat	40	CA (Histoacryl Blue)	Colonic anastomosis	-
-	Paral / 2011 52	Pig	12	CA (Glubran 2)	Colonic anastomosis	+ (Glubran2)
				CA (Dermabond)		
-	Ustek / 2005 53	Rat	70	Povidone-liposome (PVP-I)	Colonic anastomosis	+
-	Yol / 2008 54	Rat	30	BioGlue	Colonic anastomosis	+
				PRP (Autologous)		(PRP)
2b	Huh / 2010 55	Clinical	223	FG (Tissucol, Greenplast)	Rectal cancer surgery	+/-

Table 6. Sealants in the colorectal anastomosis.

Discussion

AL remains an important complication in GI surgery. It is a significant cause of morbidity and mortality, necessitating redo operations and increasing length of hospital stay for already weak patients [56-57]. AL occurs in every level of GI surgery. In this review we have addressed recent tissue adhesive research for all levels of GI anastomosis.

Esophageal: the extraperitoneal anastomosis created in the esophagus is associated with a high incidence of AL, ranging from 10 % to 27% [58-59]. The factors involved include poor blood supply to the esophagus, the absence of a protective omentum and the lack of a supporting serosal layer on the esophagus [12]. A limited amount of studies were included in this review, namely two animal studies and two RCT's (level 1b and 3b), only on specific clinical problems (atresia and colon interposition). Although results were positive in these studies, they concentrated only on these specific clinical problems. Sealing of esophageal anastomosis with FG may be helpful in esophageal atresia (level 1b), or colonic interposition (level 3b). Animal research supports the use of sealing end/end esophageal anastomosis with CA or FG, however before clinical use can be justified level 1 evidence is needed.

Gastric/bariatric: in bariatric surgery (laparoscopic) Roux-en-Y gastric bypass ((L) RYGB), staple lines are increasingly being sealed by either staple line reinforcements or glues to protect from staple line dehiscence and bleeding [60]. RYGB dehiscence rates vary from 0.7% to 6% [13-14, 61-62]. In this review we included 4 experimental studies, which all showed that sealing the gastrojejunal anastomosis with FG, CA or BioGlue prevented AL. The majority of evidence was drawn from 9 clinical studies. One level 1b, 7 level 2b and 1 level 3b studies showed that FG sealing of the gastroenteral anastomosis in RYGB and gastric bypass surgery prevented the onset of AL. The use of platelet rich plasma was also helpful in this field, according to one level 4 study. In only 3 studies the examined glue was other than FG, and many glue categories have not yet been tested in gastric/bariatric surgery. Although FG sealing seems helpful in this field, future research should also concentrate on these different categories of glue.

Pancreatic: pancreatic leakage and subsequent fistula formation occurs in 5% to 25% of patients undergoing pancreatico-digestive anastomosis, depending on aetiology and definition used [63]. One level 1b RCT concluded that the use of FG for the

sealing of the PJ did not provide any benefits for the patients. A level 3b retrospective case-control study showed negative results of the use of BioGlue. PEG sealant also was promising in two experimental studies; however no clinical studies have been performed to assess PEG in humans. Based on the ambiguous results derived from the included studies we cannot recommend clinical use of any type of adhesive for the topical sealing of the pancreatico-digestive anastomosis at this time. The included animal studies are however promising and may lead to novel clinical (pilot) studies in due time.

Ileal: small bowel anastomosis is primarily performed after resection for inflammatory disease, after small bowel obstruction, abdominal trauma or as a part of bariatric surgery. In addition, another important indication for ileal anastomosis is closure of defunctioning loop ileostomy, which is associated with AL incidence of 3.0% [3]. All nine included studies, of which only one on humans (level 2b), showed positive effects of anastomotic sealing in this field. Before clinical implementation can take place there is a need for a large scale RCT to provide level 1 evidence.

Colorectal: in colorectal surgery, the reported incidence of anastomotic leakage ranges from 5-15% with a mortality rate of up to 32% [2, 64]. Despite extensive animal research in this field results vary and therefore it is not possible to generalize results per glue type. Of the twenty included studies, 11 showed positive results. However, only one level 2b clinical study reported neutral results of FG sealing. We cannot conclude that any single adhesive may have a beneficial effect on the healing of colorectal anastomosis, preventing AL. This could be due to the anatomical positioning of the colorectum which is partly located extraperitoneally and is thus not accessible to the sealing function of the omentum. Furthermore, ultralow anastomoses also are affected by their lack of perfusion, due to minimal and fragile arterial supply [65]. Along with other known risk factors such as male gender, obesity and a tension anastomosis, the colorectum is a fragile and precarious location for the creation of an anastomosis [2]. Until now research has almost exclusively been performed in animals, and there is little variation in studied glues. The future of glue research in this field will entail a wider palette of tissue adhesives, and more uniformity in animal testing methodology. Afterwards promising results should lead to clinical testing.

The field of tissue adhesives in surgery is relatively new and the adhesive market has changed substantially throughout the years. Due to the great improvements in surgical adhesives, especially in the new millennium, we decided to only include

studies that were published after 2000 in this review. More detailed information on the early period of adhesive research in GI surgery is addressed in several older reviews [4, 66]. Despite all the research that has taken place to date in the field of surgical adhesives it remains difficult to draw concrete conclusions about the effects of the tested glues on each level of anastomosis. The reason for this is that there is too much heterogeneity in used experimental methods between research groups. Looking at the used endpoints, one cannot help but notice great differences between methodology of studies. Most authors use anastomotic bursting pressure (ABP) as a major endpoint, a test which we feel is useful in this field as it reflects the strength of the intact anastomosis. Although popular, this test has however also been scrutinized and it has been said that ABP might not be correlated with the integrity of the anastomosis and clinical outcome [48, 67]. Furthermore, we have seen great differences in ABP test methods with some groups performing the ABP test on intact *in-vivo* colon with air insufflation, others resecting the anastomotic segment first before performing the test with dyed saline or submersion of the segment in water and insufflation with air.

When using glue it is imperative to provide details on glue application; such as the amount of glue used, glue layer thickness/width and the curing time. Based on this review we have seen that only a minority of authors state the abovementioned parameters, which naturally makes repetition of the results difficult if not impossible. Lastly, anastomotic technique should be further standardized to make results more comparable. Especially amount of sutures used for the sutured anastomosis vary greatly per animal model, and in the case of the sutureless (glued) anastomosis there were variations in the use of 'guide' sutures at the (anti)mesenteric edges. Our recommendation would be to standardize methodology of such experimentation.

Another issue in this field is the choice of animal models used for glue testing. As Pommergaard *et al.* show in their recent review there are various animal models for AL [68]. At the moment, we agree with their views and recommend the use of two models, a mouse and a pig model, based on the creation of a technically insufficient anastomosis [69-70]. In this review we have seen, in fact, that the most popular animal model for the creation of anastomosis is the rat. Within this model there are great differences, with some authors 'devitalizing' the wound edges by selective devascularization or by crushing and others making a sufficient anastomosis, with variable amounts of sutures. The use of a standardized animal model is imperative for the comparability of glue research.

In this review we have provided an overview of glue research on different GI anastomotic configurations. Fibrin glue and cyanoacrylate glue seem to be the most popular glues at the moment. Within these categories we noticed that differences in glue formulation have produced contradicting results. In the case of cyanoacrylates the use of shorter chain lengths such as n-butyl-cyanoacrylate tend to give more tissue toxicity and tissue damage based on the degree of exothermic reaction. New cyanoacrylates are becoming less histotoxic, and more flexible than older formulations. Furthermore, results of experiments performed on esophageal and colorectal anastomoses showed more negative outcomes than the other anastomotic levels. Especially in bariatric surgery tissue adhesives tend to provide good results and are being introduced into clinical practice. Colorectal anastomosis has been the subject of glue research in many experimental studies, however results do not uniformly point out an ideal glue candidate for further research.

It is our view that future experimental studies should be more methodologically standardized so that results may be compared to other studies and common conclusions can be made. We feel that glue research for GI anastomosis should also provide a better perspective on the biomechanical mechanisms of adhesiveness in the different anastomotic locations. This may enable the development of adhesives, custom made for the various anatomical locations. This will provide a better understanding of why certain glues tend to be more effective than others, and may provide insight into the next steps of glue development.

Conclusion

The field of tissue adhesives is gaining ground in GI surgery. Despite years of research the 'ideal' adhesive is yet to be found. The use of fibrin glue and cyanoacrylate has been the main focus of glue research for the sealing of GI anastomoses. Using these glues seems effective in protecting the ileal anastomosis and also in gastric/bariatric surgery. Results for sealing esophageal and pancreatico-digestive anastomoses remain inconclusive, as is the case for colonic anastomoses. More (level 1) research is needed to further implement tissue adhesives as anastomotic sealants and new adhesives are needed specifically for the various anatomical locations. Current experimental glue research may benefit from a more systematic approach in which first a sound foundation is built, based on basic adhesiveness mechanisms and inventarisation of existing tissue adhesives.

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2.5 The placement of an emergency stoma

Emergency stoma placement in advanced rectal cancer: a practical guideline
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Submitted Digestive Surgery

Abstract

Emergency stoma placement prior to curative surgery in colorectal cancer is a common procedure, 20% of colorectal cancer patients present themselves with a mechanical bowel obstruction. In this study the extent of stoma malpositioning and the impact on rectal cancer care is described and an algorithm is provided for the placement of a suitable stoma. A prospectively database is maintained. All patients who received surgery for locally advanced rectal cancer or locally recurrent rectal cancer from 1994 to 2010 in our tertiary referral centre were reviewed. All patients who received a stoma prior to curative surgery were included. Patients with recurrent rectal cancer were only included if stomas from primary surgery had been restored. Outcome measures are stoma malpositioning, surgical characteristics and postoperative and stoma related complications. A total of 464 patients were included, 106 patients (22.8%) had a stoma prior to curative surgery. The main indications were defecation related problems (n=16), acute mechanical obstruction (n=27), an intra-operative irresectable tumour (n=13, a pending obstruction prior to neoadjuvant therapy (n=27). In 50 patients (47%) the stoma had to be revised during surgery. No significant differences were found regarding postoperative complications. Almost half of the previously placed emergency stomas were considered inappropriate and had to be revised during definitive surgery for advanced or recurrent rectal cancer. Unfortunately, we were not able to identify an association with postoperative complications due to our heterogeneous population. In order to improve care, an algorithm is proposed for the placement of a suitable stoma.

Introduction

In case of obstructive or symptomatic rectal cancer, the gastro-intestinal surgeon is confronted with the decision on the type and location of the deviating or definitive stoma prior to neo-adjuvant treatment or definitive surgery. The main goal of early or elective stoma placement in these patients is clear: full patients' compliance during neoadjuvant treatment without temporary interruption or delay due to the need for acute diverting stoma placement. Emergency stomas are indicated for complications arising from the tumour itself; e.g. obstruction, incontinence, disabling pain or diarrhoea, fistula and abscess and perforation; and can be necessary to bridge the time between the start of neoadjuvant treatment and final curative surgery. Furthermore, a stoma maybe indicated due to the gastro-intestinal toxicity from the neoadjuvant therapy itself. Neo-adjuvant radiotherapy can induce obstruction due to a radiation induced rectal stricture or tissue oedema and chemotherapy can induce invalidating diarrhoea.[1, 2] With the increased use of neoadjuvant treatment and "liver-first" treatment strategies, the use of bridging stomas will increase. Since up to 20% of colorectal cancer patients present with an acute or pending obstruction, emergency stoma placement is a frequently performed operation.[3]

The type and location of emergency stomas should correspond with the type and location of future necessary deviating or definitive stomas and is predominantly influenced by factors that are known very early in the course of treatment, i.e. the indication, the distance from the anal verge, the local progression of the tumour and the patient status. Although, malpositioned stomas can be restored, revised or replaced during definitive surgery, this exposes the patient to longer operating time, additional adhesiolysis and anastomoses and a higher risk of abdominal complications.

This study was designed to investigate stoma placement prior to neoadjuvant treatment in a tertiary referral centre for locally advanced (LARC) and locally recurrent rectal cancer (LRRC) in the Netherlands. The primary objective is to investigate the role of stoma malpositioning on surgical characteristics; e.g. operating time, blood loss; and postoperative complications.

The indication and the type of stomas were assessed and the consequences during definitive surgery were reviewed. An algorithm to guide surgeons during the decision making process concerning emergency stomas is created in order to standardise stoma placement and to optimise curative surgery in rectal cancer.

Methods

Patients

The Eindhoven Rectal Cancer Unit has been a tertiary referral centre for locally advanced (LARC) and locally recurrent rectal cancer (LRRC). A prospectively database is maintained, containing all patients who received surgery for LARC or LRRC between 1994 and 2010 in our hospital. Locally advanced rectal cancer was defined as a threatened, distance from tumour to fascia < 2mm, (cT3+) or involved mesorectal fascia (cT4) on MR imaging. All patients with LARC who received a diverting stoma prior to primary surgery were selected for further analysis. The decision for an emergency stoma was made in the referral hospital for all referred patients. In case of LRRC, patients were selected for analysis when primary surgery consisted of a low anterior resection (LAR) and any previous stoma had been restored. LRRC patients with an end colostomy due to an APR were excluded. Patient characteristics included gender, age, ASA classification, preoperative T stage based on MRI of the lesser pelvis, type of neoadjuvant treatment, type of chemoradiotherapy scheme and type of surgery. Comorbidity was scored using the Charlson Comorbidity Index.[4]

Stoma location and surgical techniques

Guidelines for stoma type and location in our hospital are summarized below. In general we try to avoid a stoma that has to be revised during definitive tumour resection.

- When a LAR is performed or expected feasible after neo-adjuvant treatment, a right-sided diverting transverse double loop colostomy is created.
- Prior to an expected APR an end sigmoid colostomy is created.
- A right-sided double loop diverting transverse colostomy is created when the type of surgery is unclear. A very low single barrel end sigmoid stoma is an alternative in this situation, since it could still be used as descending limb for an anastomosis during LAR and could be preserved during an APR.
- Stoma placement in the left upper abdomen is avoided. This could compromise adequate mobilisation of the descending colon in case of a future LAR.

Data on stoma location was obtained by studying medical records, investigating records from the referral hospital or by contacting patients by telephone. Stoma malpositioning was defined as a preoperative stoma that had to be repositioned during surgery in order to perform necessary resection or construct a suitable permanent or

diverting stoma. Unfortunately, we were not able to recover data on the decision-making process, regarding stoma type and location.

Statistical analysis

Statistical analyses were performed using the SPSS Statistics 20.0 software (SPSS Inc., Chicago, IL, USA). Intergroup comparisons were analysed using chi-square tests or independent t-test when appropriate. Predictive values were identified using a univariate binary logistic regression or cox regression analysis, as appropriate. A p-value of ≤0.10 was considered statistically significant in the univariate analysis and these values were entered into the multivariate analysis. In multivariate analysis, a p-value of ≤0.05 was considered statistically significant.

Results

Clinical and demographical data

All patients operated upon consecutively between 1994 and 2010, were analysed (n=600). 136 patients operated on before the year 2000 were excluded due to lack of data, 464 remaining patients were analysed. Patient characteristics are shown in Table 1.

	LARC (n=300)	LRRC (n=164)
Gender		
male	176 (59%)	100 (61%)
female	124 (41%)	64 (39%)
Age		
<70 years	218 (73%)	112 (68%)
>70 years	82 (27%)	49 (30%)
mean age in years	64	62
ASA		
I	63 (21%)	34 (21%)
II	220 (73%)	69 (42%)
III	17 (5.7%)	8 (5%)
IV	0	4 (2.4%)
LARC		
cT3	82 (27%)	
cT4	195 (65%)	
missing	23 (7.7%)	
Neoadjuvant treatment		
none	5 (2%)	12 (7.3%)
5x5Gy	26 (12%)	0
LRT	27 (9%)	0
Chemoradiation	221 (74%)	118 (72%)
(Re)irradiation		26 (16%)
Type of surgery		
LAR	145 (48%)	37 (23%)
APR	114 (38%)	44 (27%)
ASR	11 (4%)	28 (17%)
Exenteration	11 (4%)	34 (21%)
Hartmann's procedure	13 (4.3%)	17 (10%)
IORT		
yes	185 (62%)	141 (86%)

Table 1. Patient characteristics. LARC, locallyadvancedrectalcancer; LRRC, locallyrecurrentrectalcancer; 5x5Gy, short-course radiotherapy; LRT, 45-50 Gy in 28 fractions of 1.8-2 Gy; LAR, low anteriorresection; APR, abdominoperinealresection; ASR, abdominosacralresection; IORT, Intraoperativeradiotherapy.

Stoma placement and malpositioning

Figure 1 shows data regarding stoma formation, 106 patients (22.8%) had a preoperative stoma. In 47% of patients a stoma revision was required.

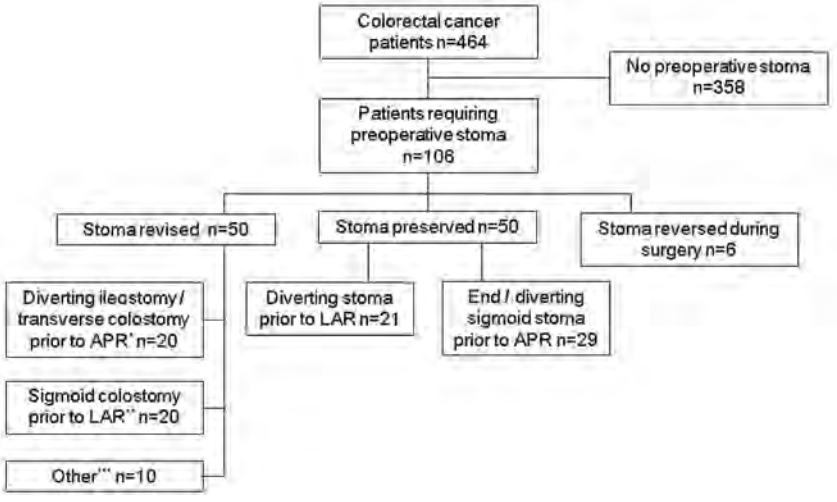

Figure 1. Types of emergency stoma and number of revisions.

* The diverting stoma was reversed during surgery.
** A sigmoid end or loop colostomy was reversed and a diverting ileostomy or transverse colostomy was created.*** Revised sigmoidcolostomy (n=8), malpositioned ileostomy or transverse colostomy (n=2).

The indications for stoma placement are summarized in Table 2.

Indication	**No. of patients** (n=106)
Defecation related problems	
Incontinence and / or diarrhoea	14
Pain	2
Acute bowel obstruction	27
Pending bowel obstruction	27
Fistula and / or abscess	9
Peroperative irresectable tumour	13
Other	8
Missing	6

Table 2. Indications for stoma placement.

Stoma revision was required due to various reasons. In 20 patients (40%) a diverting ileostomy or diverting transverse colostomy was present, but had to be reversed to an end sigmoid colostomy because an APR was performed. In 20 patients (40%) a diverting sigmoid or end colostomy was present which had to be reversed to a temporary stoma, with the creation of a diverting double loop ileostomy or transverse double loop colostomy because a LAR was performed. Other indications for stoma revisions were placement in the midline (n=1, Figure 2), malpositioned left sided ileostomy or transverse colostomy (n=2) or malpositioned sigmoid colostomy (n=8) which had to be revised and repositioned in order to perform adequate surgery. In 6% of patients (n=6), undergoing a LAR, the diverting stoma was closed during surgery without creation of a new diverting stoma.

Figure 2. Stoma malplacement in the midline.

Complication rates

Postoperative complications were scored for all patients, including presacral abscess (PA), anastomotic leakage (AL), wound related complications and general complications. Table 3 illustrates postoperative complications in relation to stoma malpositioning.

	Stoma placement		
	correct (n=69)	**malpositioned (n=31)**	**significance (p)**
Operating time mean in hours (range)	5:24 (2:13-10:36)	5:17 (2:20-10:44)	0,79
Admission to ICU mean in days (range)	1,99 (0-59)	1.13 (0-10)	0,53
Total admission time mean in days (range)	17,2 (5-138)	16.2 (6-79)	0,81
Perioperative bloodloss mean in mL (range)	4998 (50-18.000)	4775 (800-25.000)	0,62
Presacral abscess formation	13 (19%)	6 (19%)	0,95
Anastomotic leakage	5 (5%)	3 (10%)	0,68
Postoperative ileus	16 (23%)	4 (13%)	0,23
Incisional hernia	10 (7%)	2 (6%)	0,25
Stoma complications overall (nr of patients)	8 (12%)	2 (6%)	0,43
necrosis	1 (1,4%)	0 (0%)	0,5
prolapse	4 (6%)	1 (3%)	0,59
herniation	5 (7%)	1(3%)	0,43

Table 3. Postoperative complications.

No significant differences were identified in the development of postoperative complications, in relation to stoma revision or relocation.

Discussion

Our results show that in 23% of all patients with LARC and LRRC, a stoma was created prior to neoadjuvant treatment and subsequent tumour resection. In almost half of these patients (47%), the stoma had to be repositioned or revised during curative surgery in order to perform adequate rectal surgery. Whereas these patients already face extensive, often multivisceral, surgical procedures, these stoma revisions unnecessarily induce longer operating times, an additional stoma site, more adhesiolysis and additional anastomoses. This might expose the patient to increased

morbidity and mortality, including anastomotic leakage (AL), pesacral abscess (PA), peritonitis and incisional herniae.[5-7] Unfortunately, in our series we were not able to identify stoma revision or reversal as a single significant factor associated with the development of postoperative complications. The heterogeneity of our study population and the great variety of performed surgical procedures could be the explanation for this unexpected result. The need for multivisceral dissections beyond the TME planes, including total pelvic exenteration and sacral resection, will primarily influence general characteristics such as operating time, duration of admission and peroperative blood loss. Postoperative complications, including PA and AL, are predominantly influenced by the extend of the resection, the number of anastomosis, the distance of the tumour from the anal verge and patient characteristics, including nutritional status and medication use instead of malpositioned emergency stomas. The effect of other patient and operative characteristics; i.g. sacral resection, multivisceral resection; on postoperative complications and operating time outweigh the influence of stoma malpositioning.

The type of stomas commonly used are the diverting double loop ileostomy (11%) or transverse double loop colostomy (31%); and diverting double loop (17%) or end sigmoid colostomy (28%). As mentioned earlier, no general consensus or evidence-based criteria for stoma placement prior to neoadjuvant therapy or definitive surgery are present in the literature. Factors that influence stoma placement probably include stoma reversibility and stoma related morbidity and mortality and the availability of expertise; but not the type of definitive surgery. In patients undergoing an APR/ASR with a previously created end colostomy, the colostomy site could remain completely untouched. In patients with a diverting colostomy and a so-called mucus fistula, additional take down of the efferent limb was required, leading to oversized abdominal wall defects, higher risk of wound infection and incisional herniae. In some cases the colostomy was easily adapted by stapling the efferent loop, in this case no additional risk is expected. We believe that the incidence of blow out of a blind loop, in case of an end sigmoid stoma for obstruction of a rectal tumour, is very low when the sigmoid loop above the tumour is as short as possible. Especially when neoadjuvant treatment is started shortly after, it does not outweigh the negative aspects of a double barrel sigmoid stoma as mentioned above.

Moreover, 25% of our patients presented with a pending or actual acute mechanical bowel obstruction, in some patients an ileostomy was created (n=3). When an ileostomy is created in case of rectal obstruction, an intact ileocecal valve could lead to inadequate diversion, and is therefore contra-indicated.

A recent questionnaire amongst surgeons showed there are wide variations regarding the indications for stoma placement prior to neoadjuvant treatment.[1] A literature search regarding stoma placement prior to neoadjuvant chemoradiotherapy produced very limited results. Morton published a brief overview on defunctioning stomas in rectal cancer treatment, in which the wide variety in opinions on early stoma formation is discussed but no general advice is given.[1] Two evidence-based studies have been published since. Parnaby et al. reported data on 49 consecutive patients with locally advanced rectal cancer.[2] He concluded that faecal incontinence and the inability to cannulate the tumour at colonoscopy regardless of clinical symptoms are the criteria for early stoma placement, with limited stoma complications and good compliance during neoadjuvant therapy. Patel et al. concluded that routine stoma placement was not required in more than 90% of patients if neoadjuvant treatment was started early, in 85 patients without clinical signs of bowel obstruction.[8] All authors confirmed the lack of evidence and objective criteria regarding the subject.

The stoma type remains controversial. A diverting loop ileostomy is superior to a loop colostomy regarding stoma prolapse, postoperative wound infection and incisional hernia. No significant difference was observed regarding operating time, leakage rates or fistula after stoma reversal.[7, 9, 10] Major complications are reported in up to 9% of patients and reported mortality rates range from 0-2.3% after stoma reversal.[11-13] A diverting ileostomy is significantly associated with the sequelae of a high output stoma.[7] Overall readmission rates for patients with an ileostomy are reported up to 16.9%, with dehydration as the main cause of readmission in 7.2% of patients.[5] Dehydration rates increased up to 29% after neoadjuvant chemotherapy, with a 15% readmission rate.[14] In up to 25% of patients the intended temporary ileostomy will not be reversed,[15] which increases life-time risk of stoma related problems. We consider this; in combination with the high risk of dehydration, especially in a population depending on well timed pre- and postoperative chemotherapy; the quintessential reason not to use an ileostomy. In addition, with an intact ileocoecal valve, an ileostomy does not decompress the obstructed colon when a tumour obstruction is the indication for pre-treatment stoma placement.

In figure 3 we propose a flowchart with advice regarding stoma placement in the emergency situation.

Most and foremost, a simple diagnostic workup should be performed, with assessment of patient and tumour characteristics, in order to optimise the stoma type and location. This includes a digital rectal examination (DRE), where distance of the tumour from the anal verge and tumour size and mobility are assessed. Digital

examination may supply important extra information when on MRI the distant margin is marginal. Involvement of the pelvic floor muscles or tumour growth into the anal sphincter indicates the need for a permanent end colostomy, since an APR is usually inevitable even after neoadjuvant treatment. This includes patients in whom the distal margin on MRI would allow for a LAR. MRI is by far the most important diagnostic modality in preoperative staging in rectal cancer and should be performed to address local tumour growth. Pulmonary and liver metastases should be disseminated by thoracic and abdominal computed tomography (CT). On the basis of these investigations, the surgeon can already anticipate the future definitive surgery in the majority of cases. Because of this, we believe that decision-making on which stoma should be created prior to curative surgery has to be performed by an experienced colorectal surgeon who can decide which type of definitive surgery will be performed.

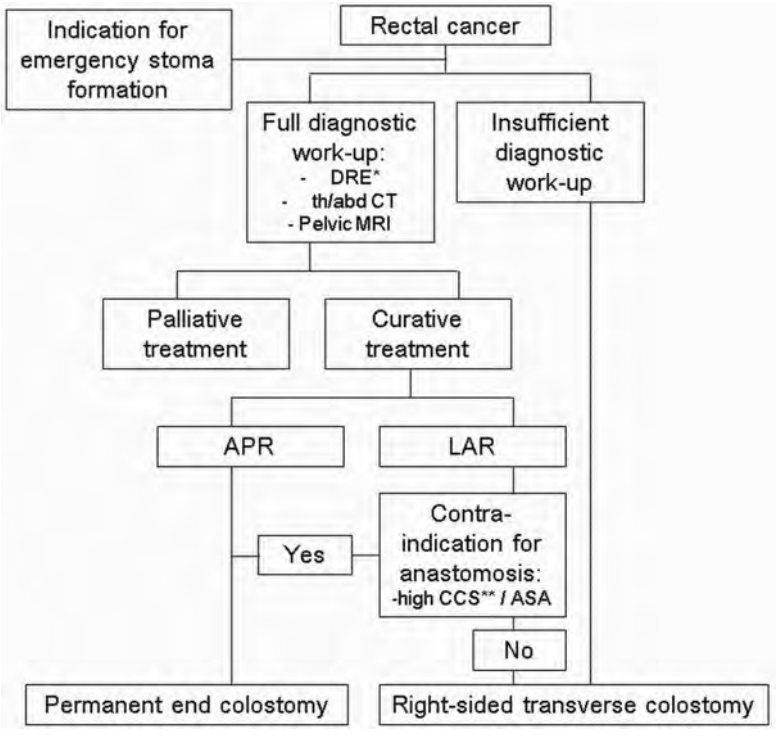

Figure 3. Flowchart with advised emergency stoma placement. * digital rectal examination; ** CharlsonComorbidity Index.

Age, comorbidity and quality of life (QOL) are important factors that influence the type curative surgery and stoma placement should also be guided by these factors. In the elderly patient, mortality rates after anastomotic leakage are reported up to 57%.[16] Therefore the creation of an end colostomy should always be considered in the elderly patient even when a primary anastomosis could be technically acquired. In addition, morbidity and mortality in patients with multiple comorbid conditions or high Charlson Comorbidity Index are negatively affected by postoperative complications. Similar considerations should be made in these patients. In addition,QOL should influence stoma choice, since the presence of a stoma is associated with decreased QOL.[17, 18] Especially in younger patients stoma reversal should always be the goal. A remarkable finding is the fact that QOL in the elderly patient is not always impaired by an end colostomy.[19-21] Moreover, in 20% of elderly patients a diverting stoma created during TME surgery will not be reversed.[22] These findings suggest that elderly patients could benefit from an end colostomy. The patient, and surgeon, should be well informed about these benefits since the decision for an end colostomy will be difficult, even for an elderly patient.

The EURECCA experts concluded that in case of palliative treatment of rectal cancer with a very poor prognosis (expected less than 3 months), due to pulmonary or liver metastases, self-expending metal stenting (SEMS) could be considered, as adjuvant to radiotherapy.[23] In selected cases stent placement could be a safe alternative to a colostomy, but this should always be discussed in a multidisciplinary team meeting.[24, 25] In the curative treatment of rectal cancer, stent placement is inferior to emergency surgery in case of an acute obstruction and is associated with increased morbidity.[26, 27]

Laparoscopic surgery is becoming increasingly important in colorectal cancer surgery. The first randomized studies and Cochrane review show advantages over conventional surgery, including less blood loss, less postoperative pain, faster return of bowel function and shorter hospital stay.[28, 29] The laparoscopic approach to stoma placement has been described decades ago, with reduction of postoperative pain and ileus and reduction of hospital stay.[30] Despite the increasing use of laparoscopic surgery, implementation varies tremendously on a national and European level.[31, 32] Based on current literature no general recommendation can be given regarding open or laparoscopic stoma, the decision should be guided by the surgeons experience with both techniques.

A deviation from the advised flowchart is sometimes necessary due to various reasons: an incomplete diagnostic work up, usually due to practical limitations; uncertainty regarding the feasibility of sphincter preserving surgery; and uncertainty regarding

the downstaging effect of chemoradiotherapy and the influence on the expected type of surgery. In these situations a right-sided diverting transverse colostomy is advised inducing minimal effect on possible curative surgery, leaving the left lower abdomen untouched. If the final operation is an APR, the end sigmoidostomy is the preferred stoma. However, when a LAR has to be performed, care should be taken not to compromise the future surgical field by unnecessary dissections and jeopardizing the afferent loop by malplacement of the stoma, since the length of the remaining colon is crucial for the creation of a distal anastomosis. When the type of future surgery is unclear or still under debate during emergency stoma placement, a low end colostomy could be performed as well, but only by experienced surgeons. Doing so, the limb could be used for future anastomosis or kept in place during LAR and APR respectively. In our institute no mucous fistula are created without any additional blow out risks in our experience. In the 1980s several authors described an increased risk of pelvic sepsis after rectal stump closure in patients undergoing a subtotal colectomy and ileostomy placement.[33, 34] An overview article by Trickett et al., who included similar studies over a 15 year period, on the other hand showed that the creation of a mucous fistula is not associated with a risk reduction regarding postoperative complications.[35] The creation of a mucous fistula is therefore not advised.

Conclusion

Despite the increasing number of patients with early stoma placement prior to neoadjuvant therapy and subsequent tumour resection, neither general consensus nor objective criteria are present in the literature regarding emergency stoma. From our experience the placement of emergency stomas is often performed to alleviate the acute symptoms, but without overseeing the consequences of malplacement and the additional risks for complications during the final surgery. Placement of an emergency stoma is part of the complete treatment of the tumour. We weren't able to find a correlation between stoma malpositioning and postoperative complications, but optimal stoma placement remains a very important part of the patients treatment. Optimally, the use and place of a temporary stoma should be discussed in a multidisciplinary team meeting and should be an integral part of the complete treatment plan. At least the decision should be made by an experienced gastrointestinal surgeon, only after diagnostic workup is complete. The decision should be guided by patient characteristics, including age and morbidity, and should be carefully based on the type of definitive surgery. The proposed guidelines in this paper may be helpful for decision-making even for less experienced surgeons or for those still in training.

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3

Early detection

3.1 Detection of anastomotic leakage using intraperitoneal microdialysis

Identification of anastomotic leakage after colorectal surgery using microdialysis of the peritoneal cavity
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Tech. Coloproctol. 2014 Jan;18(1):65-71.

Abstract

Early detection of colorectal anastomotic leakage (AL) may lead to better outcome. AL may be preceded by change in local metabolism and local ischemia. Microdialysis of the peritoneal cavity is able to measure these changes real-time and is minimally invasive. This study was set up to investigate the role of microdialysis in the early detection of AL after colorectal surgery. 24 Patients were operated for left sided, sigmoid and rectal carcinoma with creation of an anastomosis. Peroperatively a juxta-anastomotical intraperitoneal and subcutaneous microdialysis catheter was placed. From the dialysate levels of lactate, pyruvate, glucose and glycerol were measured every 4 hours during the first 5 postoperative days, mean values and area under the curve (AUC) were calculated. Mortality was 0%, morbidity 38%. In 3 patients AL occurred (17%). In patients with AL postoperative peritoneal lactate levels were 3,2mmol/l (SD 0,9) for patients without AL, compared to 4,4mmol/l (SD 1,5) in case of AL (p = 0,03 for AUC). Intraperitoneal glucose levels were 8,1mmol/l (SD 1,3), compared to 7,8mmol/l (SD 2,2) in the complicated course (ns for AUC). Mean intraperitoneal lactate/pyruvate ratio was 19,2 (SD 3) after colorectal surgery without AL compared to 25 (SD 4,7) in case of AL (ns for AUC). No significant differences were observed between patients that underwent laparoscopic resection and those after open resection. In patients after colorectal surgery AL was preceded by an significant higher AUC and mean value of lactate levels during the first 5 postoperative days. To identify cut off values for clinical use, pooling of data is necessary.

Introduction

Anastomotic leakage (AL) is a major complication after colorectal surgery, which occurs in 3 to 13% of patients [1, 2]. AL after rectum surgery leads to increased morbidity and mortality, many operative and non-operative therapeutical interventions and longer hospitalisation [3-5]. Several studies have identified risk factors for AL after rectum surgery including male sex, low colorectal anastomosis (< 6cm), multiple blood transfusions and long operating-time [5, 6], resulting in a AL risk score [7].

The preventive role of routine draining is among other interventions subject of ongoing investigation [8]. Still, apart from the possibly beneficial effect of draining drain fluid, the fluid itself has a role in the early detection of AL. Where in some recent studies analysis of cytokines in drain fluid seems to help in the early detection of this dreaded complication [9-11], routine measurement of TNF-alpha nor IL-6 in drain fluid enabled a quick diagnosis of AL in an older study by Bertram et al. [12]. Intraperitoneal bacterial colonisation can be measured by quantative cultures or RT-PCR of drain fluid and is positively related with the occurrence of AL [9, 13].

Clinical scoring systems, as described by den Dulk et al., use clinical features as presence or absence of fever, ileus and pain to score patients objectively. These are easily applicable to daily practice and decreased the delay in diagnosis by 2,5 days [14]. Instruments like these prevent doctor's delay and decrease false negative diagnostic imaging, which are major factors of delay in diagnosis [15]. A study by Bellows using non-standardised clinical examination showed that pulmonary and neurological events occur previously to AL and should warn the treating physician [16].

Another method for early detection of AL is routine postoperative measurement of serum level C-reactive protein (CRP). In a study by Ortega-Deballon et al. a cut-off of 125mg/l on postoperative day 4 resulted in a sensitivity of 82% and a negative predictive value of 96% for AL [17]. Welsch et al. showed similar predictive value of 91% for a complicated postoperative course, not just AL, when CRP levels were 140mg/l at day 4 [18]. Another study showed correlation of AL with a prolonged postoperative elevation of CRP [19].

The drawback of all these parameters is their ability only to detect overt systemic disturbances in a later phase without detecting preceding local ischemia, disintegration of cells and confined peritonitis. Furthermore large indwelling intraperitoneal drains are considered limitative and leave scars. Daily clinical scoring has the disadvantage of a low probability of detection resulting in decreased motivation. Therefore, the minimally invasive method of intraperitoneal microdialysis seems promising as detection technique, since it measures ischemia and changes in metabolism locally

and real-time [20, 21], by the use of a small 0,9mm double lumen catheter. At the tip of this catheter a semi permeable membrane enables diffusion of small size molecules as lactate, glucose and glycerol (cut-off 20kDa) intraperitoneally. In a few small previous studies, intraperitoneal microdialysis has shown promising results in detecting postoperative complications after colorectal surgery [22-25]. This prospective study was designed to compare values of intraperitoneal microdialysis in patients with AL to patients without AL after open and laparoscopic colorectal surgery.

Materials and Methods

Patients who underwent planned open or laparoscopic left sided hemicolectomy, sigmoid or rectum resection for resectable colorectal carcinoma, or stenosing diverticulitis were included. All patients were >18years old, <ASA4 and gave informed consent prior to the operation. The local ethical committee approved this study.

In microdialysis of the peritoneal cavity and subcutaneous fat, a physiological salt solution (NaCl 147 mmol/L, KCl 4 mmol/L, CaCl2 2.3 mmol/L, T1 perfusion fluid, CMA, Solna Sweden) was pumped (CMA 106 MD Pump, CMA, Solna, Sweden) with a constant speed of 0.3 L/min through a semi permeable membrane. The solution was equilibrated with the surrounding tissue fluid. The intraperitoneal catheter (Figure 1A, CMA 62 Gastrointestinal MD Catheter, CMA, Solna, Sweden) was placed transabdominally during the last stage of the operation in the direct proximity of the anastomosis. For open and laparoscopic surgery this was performed by introducing a splittable tunnelling needle to transduce the microdialysis catheter. In laparoscopic surgery extra care was taken not to touch the distal membrane. A second catheter (Figure 1B, CMA60 MD Catheter, CMA, Solna, Sweden) was placed in the subcutaneous fat of the abdominal wall serving as reference.

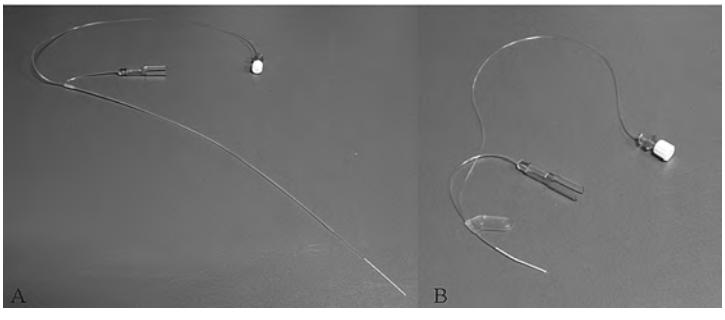

Figure 1. A. CMA 62 catheter for intraperinoneal application. B. CMA 60 for subcutaneous use. Both catheters have a double lumen shaft, a connector to the CMA 106 pump (not depicted) and a connector for the sample tubes. Note the 3 cm long semipermeable tip at the end of both catheters.

Before placement, the catheters were flushed with perfusate so that no air was trapped in the lumen of the catheter. The subcutaneous catheter was placed at least 5cm from the laparotomy- or laparoscopy wounds. All catheters were fixed with a single non-resorbable suture. A sterile dressing protected both catheters. The outgoing dialysate was stored in a small airtight receptacle that was removed from the catheter every 4hrs, starting at 0:00hr of the first postoperative day during 96hrs. Samples were processed in a batch using a CMA600-analyser (CMA 600 MD Analyser, CMA, Solna, Sweden) directly after the patient was discharged.

In the sample values for lactate, pyruvate, glycerol and glucose were measured. The lactate/pyruvate ratio (L/P-ratio) is an indicator for hypoxia, whereas decreased glucose levels indicate increase in metabolism. When local ischemia progresses cells are broken down and due to lipolysis glycerol is released.

Patients were treated according standard postoperative protocol of enhanced recovery and microdialysis values were not used clinically. Every day patients were physically examined, including temperature, heart rate, mean arterial blood pressure and haemoglobin saturation. According to our local postoperative protocol, during the first 3 postoperative days plasma CRP-levels were determined. In case of a suspected abdominal complication, diagnostic and/or therapeutical steps were undertaken according to current local standards. If an AL was diagnosed, the time of diagnosis was recorded as well as findings during re-operation. AL was defined according to the grading system of Rahbari et al.
For glucose, lactate, pyruvate, glycerol and L/P-ratios the area under the curve (AUC) was calculated for the first 4 postoperative days and used for statistical analysis. Mann-Whitney test for unpaired samples was used. $P < 0.05$ was considered statistically significant.

Results

Forty-five patients met inclusion criteria during the study period. Data of 24 patients could finally be used for evaluation, since 12 refused to participate and in 9 patients technical failure was encountered. Eighteen patients were operated laparoscopically, of which 4 were converted to open surgery, 6 had open resection. Conversions

occurred in an early phase of the operation in all 4 patients, therefore, for analysis, these are considered as open procedures.
Twenty-one patients were exempt from AL, but in 5 of them other complications were observed, amongst which were pneumonia, superficial wound infection, prolonged postoperative ileus, delirium and congestive heart failure. Three patients (3/24, 12%) were diagnosed with AL at postoperative day 4, 5, 42 respectively. Patient characteristics are shown in Table 1.

	No leakage (n = 21)	**Leakage (n = 3)**
Sex (male / female)	15 / 6	1 / 2
Age (years)	68	69
ASA classification		
I	7	-
II	10	2
III	4	1
Indication		
Malignancy	18	1
Benign	3	2
Type of operation		
Leftsided colectomy	3	-
Sigmoidresection	9	2
LAR	8	1
HR	1	-
Type of procedure		
Laparoscopic	14	-
Open	4	2
Converted	3	1
Hospital admission		
Days	7,1	21,7
Other complications		
Pneumonia	1	-
Woundinfection	1	-
Prolonged postop ileus	1	-
Evisceration	-	1

Table 1. Patient characteristics. LAR = Low anterior resection. HR = Restoration of continuity after Hartmann's procedure.

All AL were objectified by abdominal CT scan and confirmed by re-operation or endoscopy. The severity of AL was grade 3 according to Rahbari et al. in all patients and mortality was 0% [28].

Clinically, patient 1 developed tachycardia at the second postoperative day and CRP level was 298mg/l, there was no sign of abdominal pain. At day 4 the patient developed sepsis and CT showed AL, which necessitated reoperation and admittance to the ICU. At reoperation an abscess was found at the site of the anastomosis, showing a small leakage. No signs of anastomotical ischemia were present. Patient 2 developed fever at 48hr after primary operation and had an acute abdominal evisceration at the third postoperative day. During reoperation no signs of AL were observed. Two days later (5th postoperative day) the patient developed fever again, while CRP level was 235mg/l, the abdomen being distended and painful. A CT-scan was indicative for AL, which was confirmed during reoperation the same day. The anastomosis did not appear ischemic. Patient 3 was discharged from the hospital on POD 12 after reversal of a colostomy that was placed previously due to perforated diverticulitis. Intraoperatively, iatrogenic bladder injury occurred. At POD 27 the patient was readmitted with fever and signs of colovaginal fistula. This was confirmed by CT and endoscopy, which showed a large pelvic abscess partially draining through the dorsal vaginal wall. After conservative treatment failed, reoperation followed at POD 94 and confirmed the aforementioned findings. The anastomosis, which was semicircular dehiscent, was broken down and did not show macroscopic signs of ischemia.

In the uncomplicated course after colorectal surgery mean intraperitoneal glucose levels were 8.1mmol/l (SD 1.3), compared to 7.8mmol/l (SD 2.2) in the complicated course. AUC for patients with AL was not significantly different from patients without AL ($p = 0.6$). For the subcutaneous samples glucose levels were 7.4 (SD 1.5) and 7.4 (SD 1.5) for patients without and with a AL respectively. Mean intraperitoneal lactate levels were 3,2mmol/l (SD 0.9) for patients without AL, compared to 4.4mmol/l (SD 1.5) for patients who developed AL, showing significant different AUCs for patient with and without AL ($p = 0.03$) (Figure 2a and b).

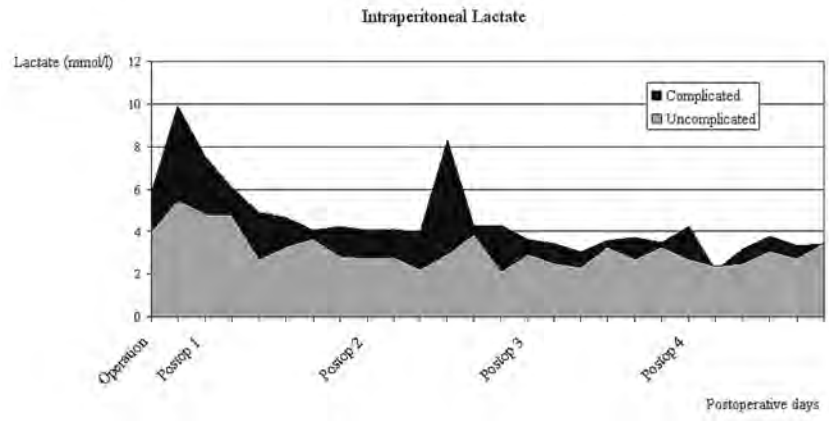

Figure 2A. Mean intraperitoneal lactate levels for patients with and without leakage. AUC was significantly different (p=0,03) for the first 4 postoperative days.

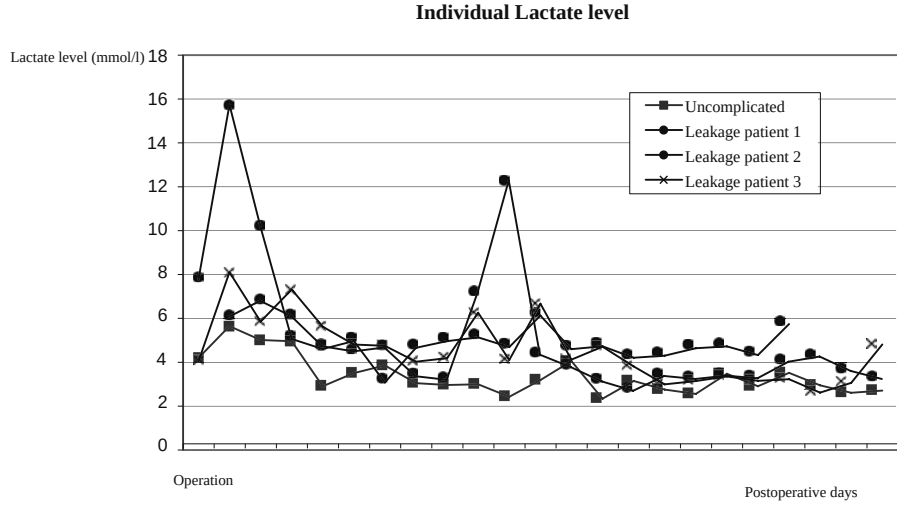

Figure 2B. Individual intraperitoneal lactate levels for patients with AL compared to the mean value of patients without a leakage.

Subcutaneous microdialysis showed a mean lactate level in patients without AL of 2mmol/l (SD 0.6), compared to a level of 3mmol/l (SD 1.2) in patients without AL. Mean intraperitoneal lactate/pyruvate ratio was 19.2 (SD 3) after colorectal surgery without AL compared to 25 (SD 4.7) in case of AL. The AUC for patients with AL

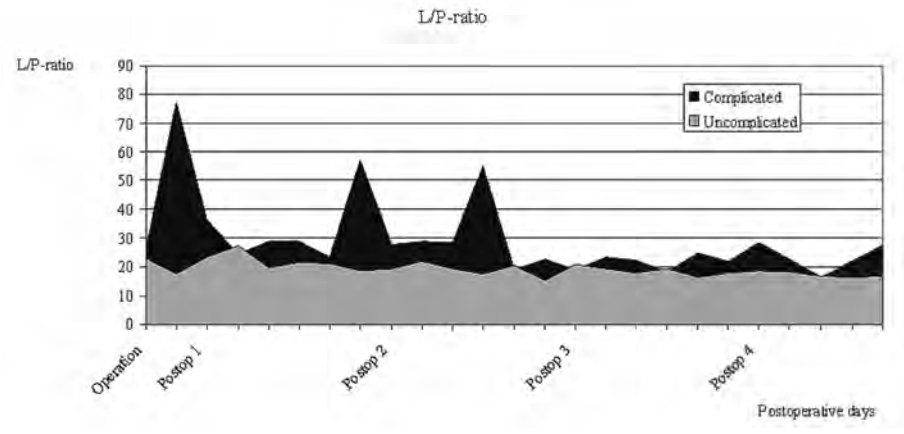

Figure 3. Mean lactate/pyruvate-ratios for patients with and without leakage. Area under the curve was not significantly different.

Subcutaneously mean LP-ratio was 14 (SD 3.9) and 17.7 (SD 4.2) for patients without and with AL. In the group of patients that was operated laparoscopically and did not develop AL, mean intraperitoneal glucose levels were 7.2mmol/l (SD 2.7mmol/l) compared to 9.1mmol (SD 3.1mmol/l) for open surgery. AUCs were not significantly different between these groups (p = 2.4). Mean intraperitoneal lactate levels were higher in laparoscopic patients (Laclap: 3.5mmol/l, SD 1.8; open: 2.7mmol/l, SD 1.2) but the difference in AUCs was not significant (p = 0.5). Intraperitoneal pyruvate, glycerol and LP-ratio were not significantly different after laparoscopic and open surgery (Pyrlap: 165.5micromol/l, SD 67.8micromol/l, Pyropen: 151.1micromol/l, SD 47.9micromol/l, AUC p = 1.0; Glycerollap: 179micromol/l, SD 64.2micromol/l, Glycerolopen: 153.6,micromol/l, SD = 53.7micromol/l, AUC p=1.0; LP-ratiolap: 21.4, LP-ratioopen: 18, AUC p = 0.35). All parameters for subcutaneous microdialysis did not show any difference between open and laparoscopic surgery.

Two patients developed an early AL after 4dys (patient 1) and 5dys (patient 2) respectively. Figure 4 shows curves for intraperitoneal L/P ratio in during the first 4 days for these individual patients. A clear peak can be seen for both patients at 48hrs and 32hrs respectively.

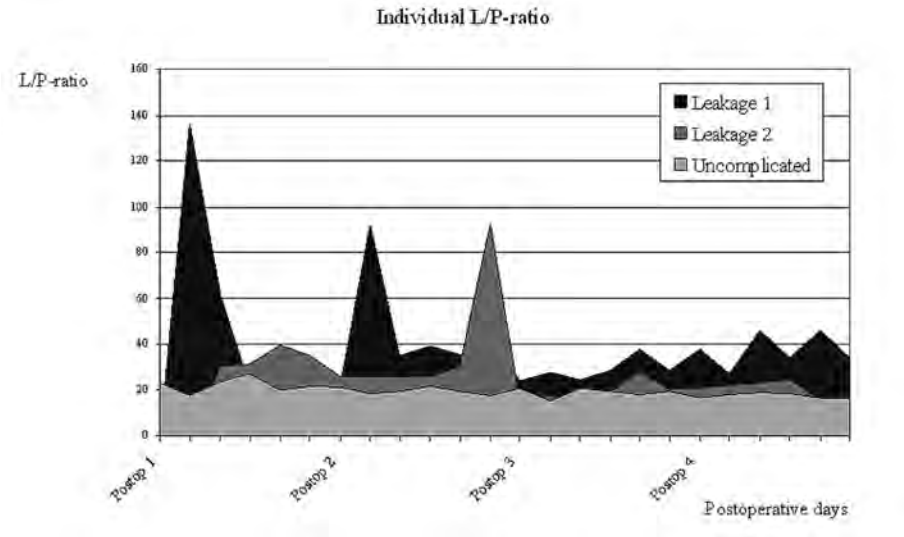

Figure 4. Individual lactate/pyruvate-ratios for leakage patient 1 and 2 compared to the mean of lactacte/pyruvate-ratio of the uncomplicated group.

CRP levels were measured daily during the first three days postoperatively. differences were observed in mean daily values (day 0 CRPuc 5.3mg/l, CRPal: 45mg/l; day 1 CRPuc 81mg/l, CRPal 88mg/l; day 2 CRPuc 154mg/l, CRPal 206mg/l; day 3 CRPuc 136mg/l, CRP al 217mg/l) but the difference in AUC (p = 0,12) did not reach significance (Figure 5).

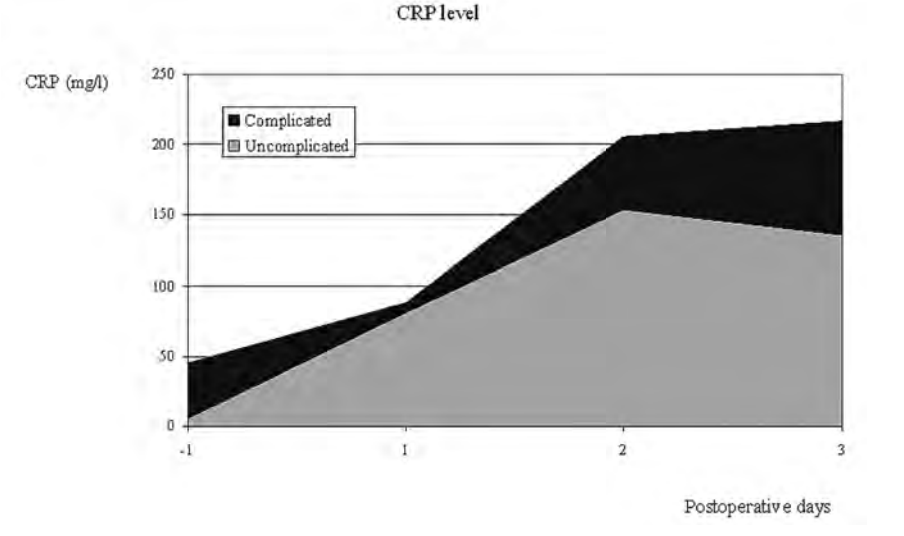

Figure 5. CRP levels preoperatively and 3 days postoperatively of patients with and without a leakage. AUC's were not significantly different.

Preoperatively CRP level in patient 2 was 127mg/l. This patient was operated electively on a diverticular stricture and peroperatively an abscess in the subcutaneous fat was drained, being the only focus of infection.

Discussion

AL is the most feared complication after colorectal surgery occurring after a mean of 12 days postoperatively [26]. Since early detection of AL might lead to a better outcome, many authors have focussed on this topic. Microdialysis is a minimally invasive method to detect changes in carbohydrate metabolism in the tissue directly surrounding the tip of the catheter and has been described for intraperitoneal use in few publications. This study shows that lactate levels in patients who develop AL after left sided colectomies, sigmoid and rectum resections are significantly higher during the first days after surgery, compared to patients that had an uncomplicated course. This finding corresponds with previous research by Ellebaek Pedersen et al. who found elevated levels of lactate prior to AL after rectum resections [22]. In this study AL was also related to a decrease in intraperitoneal glucose levels, which in our study was not observed. A reason for this could be the small group size of patients with AL and the variations in clinical presentation. Another study by Horer et al showed an elevated intraperitoneal L/P-ratio and decreased intraperitoneal glycerol levels in patients developing AL. In our study, both patients with an early AL showed a peak in L/P-ratio prior to the diagnosis of AL. Lactate levels increase in case of hypoxia by fermentation of pyruvate and by hyper metabolism due to inflammation, thus an elevated lactate level and L/P-ratio can be observed under these circumstances. In AL both of these processes might be present, although there is no consensus on what is the underlying pathophysiology [10, 27, 28]. Our findings support the hypothesis that ischemia of the anastomosis compromises its healing in most cases of AL. Contradictory to this hypothesis is that the anastomosis did not appear ischemic during reoperation.

CRP level is increased in the presence of inflammation and reaches a peak after 48hrs. In this study, uncomplicated surgery caused an elevation in CRP precisely according to this pattern. One patient with an early AL had a subcutaneous abscess during primary operation, therefore obscuring the interpretability of the postoperative samples. Other studies with larger sample size have investigated the value of CRP measurement in the detection on AL and found that a failure of decreasing plasma levels after day 2 or a level of >125mg/l at day 4 are indicative for inflammatory

complications [17, 18]. Since the routine CRP measurement was terminated after day 3, all the patients with AL met up with the first criterium.
In a study by Gianotti et al. on the influence of pneumoperitoneum in laparoscopic resections on the pO_2 of the colon wall an increased pO_2 in laparoscopic patients was found [29]. Another study by Pascual showed that the inflammatory response, measured by interleukins of peritoneal fluid postoperatively after laparoscopic or open colectomy, is higher in patients after open surgery [30]. In our study, patients who were operated laparoscopically showed no differences in intraperitoneal microdialysis compared to patients of the open group. Since the intraperitoneal catheter was placed right next to the anastomosis, samples reflect local metabolism of this area. Our findings suggest that local metabolism is not influenced by the operative technique.
Intraperitoneal microdialysis is a costly technique and requires full cooperation from nursing staff and patients. Often, technical failure cause early cessation of sampling. In this study this occurred in 9 patients, varying from iatrogenic damage to the catheter or air entrapment in the catheter to erroneous preliminary removal of the catheter by either the patient or nursing staff. Although other techniques for early detection of AL like clinical scoring systems and plasma CRP measurement also have their drawbacks, these methods are applied easily, being cheap and superior in terms of higher sensitivity and specificity as yet. In this study microdialysis samples were batch-analyzed but can also be analyzed bedside at any preferred frequency. A drawback of the current study is its small sample size, due to this, no cut-off values could yet be established for intraperitoneal microdialysis for the earliest possible detection of AL. Since our findings correspond with the limited previous research, the next step for further development of microdialysis as a method for early detection of AL is represented by a meta analysis of all data so far and is currently being worked on.

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3.2 Review of literature on the early detection of anastomotic leakage

Prediction and diagnosis of anastomotic leakage after colorectal surgery: a systematic review of literature

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Abstract

Although many studies have focused on the preoperative risk factors of anastomotic leakage after colorectal surgery (CAL), postoperative delay in diagnosis is common and harmful. This review provides a systematic overview of all available literature on diagnostic tools used for CAL. A systematic search of literature was undertaken using Medline, Embase, Cochrane and Web-of-Science libraries. Articles were selected when a diagnostic or prediction tool for CAL was described and tested. Two reviewers separately assessed the eligibility and level of evidence of the papers. 69 Articles were selected (clinical methods: 11, laboratory tests: 12, drain fluid analysis: 12, intraoperative techniques: 22, radiology: 16). Clinical scoring leads to early awareness of probability of CAL and reduces delay of diagnosis. CRP measurement at POD 3-4 is helpful. CAL patients are characterized by elevated cytokine levels in drain fluid in the very early postoperative phase in CAL patients. Intraoperative testing using the air leak test allows intraoperative repair of the anastomosis. Routine contrast enema is not recommended. If CAL is clinically suspected, rectal contrast-CT is recommended by a few studies. In many studies a "no-test" control group was lacking, furthermore no golden standard for AL is available. These two factors contributed to a relatively low level of evidence in the majority of the papers. This paper provides a systematic overview of literature on the available tools for diagnosing CAL. The study shows that colorectal surgery patients could benefit from some diagnostic interventions that can easily be performed in daily postoperative care.

Introduction

Anastomotic leakage is the most frequent major adverse event after colorectal surgery and remains a large burden for patients and surgeons[1]. Despite evolutions in stapling techniques and operation modalities, incidence of anastomotic leakage after colorectal surgery (CAL) has not decreased over the last decade[1 2]. In the abundant literature on CAL, figures on incidence vary widely, most probably because many studies did not apply the unequivocal definition of CAL that has been available since 2010[3 4]. Clinical signs of CAL before the fifth postoperative day (POD) are uncommon, and most studies described a mean POD of 8 days for CAL to become clinically apparent. However, some studies even show that CAL is diagnosed at mean POD 12[5 6]. Short-term morbidity and mortality, as well as detrimental long-term effects, such as permanent stoma, might be reduced if CAL is detected and treated in an early phase[7]. Many studies have focused on preoperative risk factors, such as age, sex, neoadjuvant therapy, emergency surgery and distance to the anal verge, and should enable an estimation of risk of postoperative CAL[8-11]. Despite this caution, delay in diagnosis is common and has been described to be caused by false negative radiological investigation and intervening weekends[12]. This study was designed to provide colorectal surgeons with a systematic review of the predictive value of the diagnostic techniques for detection of CAL that are currently described in literature.

Methods

Search methods

A systematic search of literature was undertaken using Medline, Embase, Cochrane and Web-of-Science libraries. No limitations for year of publication were applied. Search terms were: anastomosis, leakage, dehiscence, colorectal, rectum, resection, anterior resection, diagnosis, sensitivity, specificity, prediction, forecasting, monitoring. The search was restricted to publications in English and French. Full search syntax is shown in Addendum and was carried out lastly on 15 October 2012. All references in eligible articles were screened for additional publications. Articles were retrieved according to the Preferred Items for Reporting of Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Study selection

Articles were selected if a diagnostic tool or prediction model for CAL was described and tested, preferably using a reference. Furthermore, definition of CAL was required. If an article described more than one diagnostic tool, it was included for all the tools that were addressed, with the exception of the technique serving as reference / golden standard.

Studies were excluded if they reported on risk prediction of other complications than CAL. The included anastomosis were ileo-colic, colo-colic, colorectal and colo-anal. Total coloproctectomy with ileal pouch anal anastomosis was excluded since etiology, diagnosis and treatment are very different from the types of anastomosis mentioned before. Moreover, studies on risk factors for CAL and randomized trials studying treatment modalities were excluded, as were presentations, experimental studies, narrative reviews and letters to the editor.

Data extraction

For all eligible studies, a standard data extraction form was filled in and the following data were extracted: study design, number of patients, percentage of clinically important CAL, diagnostic tool and main results. If published, sensitivity, specificity, positive predictive value and negative predictive value were noted, or, if possible, calculated. If stated, the POD of CAL diagnosis was recorded. Furthermore, two authors (F.D., Z.W.) separately determined the level of evidence for validation studies according to the Levels of Evidence 2011 from the Centre for Evidence Based Medicine. In case of inconsistencies, agreement was accomplished by discussion.

Results

The abstracts of a total of 859 articles were screened separately by 2 authors (F.D., Z.W.) for eligibility. Of these article, 771 were excluded, either for being written in a different language than French and English (n = 25), or for description of preoperative risk factors for CAL (n = 90), or due to irrelevance (n = 308), or because they described a patient cohort or randomized trial or experimental studies, or for other reasons than early detection of CAL (n = 348). This resulted in 88 articles, 18 of which were excluded after full text examination, either for being a narrative review (n = 3), or abstract (n = 11), or due to irrelevance (n = 4).

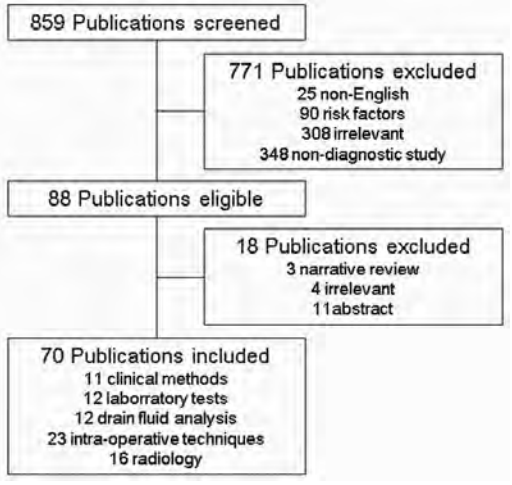

Figure 1. PRISMA-chart for included articles. Two articles could be included in two subgroups.

The remaining 70 articles were included and subdivided into 5 groups, according to type of method used. Two studies were included in two different groups, some studies related to more than one diagnostic tool from one category.

Clinical methods: Eleven articles focused on clinical methods, such as the value of physical examination (n = 1), the correlation between clinical symptoms and CAL (n = 5), the application of CAL risk scores (n = 2) or the direct postoperative prediction of the risk of CAL by the surgeon (n = 3)

Laboratory tests: Twelve articles related to the correlation between CAL and postoperative levels of cytokines (n = 1), C-reactive protein (CRP, n = 10) or coagulation parameters (n = 1).

Drain fluid analysis: Twelve articles related to diagnosis of CAL by analysing peritoneal drain fluid, in one case using two different methods in one study. The articles focussed on macroscopic findings of drain production (n = 2) or on drain fluid analysis of cytokine levels (n = 6), lipopolysaccharides levels (n = 1) or lysozym levels (n = 1). One article addressed the topic of intramucosal pH-measurement, and two articles focused on microdialysis of the peritoneal cavity.

Intra-operative techniques: Twenty-three articles investigated the correlation between preoperative assessment of the anastomosis and CAL, using one or more of the following techniques: air/methylene blue leak test (ALT, n = 13), intraoperative endoscopy (IOE, n = 4), Doppler ultrasound (n = 2), tissue oxygen tension measurement (n = 1), intraoperative inspection of marginal artery bleeding (n = 1), laser fluorescence angiography (LFA, n = 1) and near infra-red/visible light spectroscopy (n = 2).

Radiology: Sixteen studies evaluated the accuracy of one or more of the following radiological techniques in detecting CAL: computer tomography (CT, n = 7), water-soluble contrast enema (WSCE, n = 11) and plain X-ray (n = 2).

Clinical methods

Table 1 gives an overview of the main results of the eleven included studies. Three studies described direct postoperative CAL risk prediction by the surgeon. Two studies described direct postoperative assessment by the surgeon as valuable[13 14]. Karliczek et al. prospectively studied subjective assessment of the risk of CAL by the surgeon directly after surgery[15]. Low predictive values were found, with a sensitivity of 62% and a specificity of 52% for low rectal anastomosis.

Five studies analysed the postoperative clinical course of patients with CAL in comparison to patients with an uncomplicated course. Two retrospective studies noted that occurrence of respiratory and neurological disorders often precede CAL after colonic surgery (odd's ratio 2.8 and 5.3 respectively)[16 17]. One prospective study noted that cardiac disorders preceded CAL in 40% of 22 patients with CAL[18]. A small study reported no differences in heart rate variability between patients with and without CAL[19]. In a prospective study by Nesbakken et al., the postoperative assessment of the patient by the surgeon was reported to have high specificity and low sensitivity (91% and 50% respectively)[20]. Tang et al. investigated the value of digital rectal examination (DRE) in assessing CAL before stoma closure, and found a sensitivity of 98,4% [21].

Author	Type of study	Loe	n(CAL/ non-CAL)	Colorectal/ rectum	Stapled/ handsewn anastomosis	Study subject/tool		Se	Sp	PPV	NPV	ROC	Main outcome
Dekker et al[22]	Pro	3b	10/121	Colorectal	?	Leakage score		-	-	-	-	0.95	OR = 1.74 for leakage score predictive of CAL
den Dulk et al[23]	Pro	2b	21/223	Colorectal	Both	Leakage score		-	-	-	-	-	Delay of treatment reduced from 4 d to 1.5 d
Sutton et al[18]	Pro	3b	22/398	Colorectal	?	Clinical symptoms		0.33	0.97	0.59	0.93		Over 40% of patients with cardiac event has CAL
Haase et al[19]	Pro	4	mrt-40	Colorectal	?	Clinical symptoms		-	-	-	-	-	No difference in heart rate variability between CAL and non-CAL
Ghariani et al[17]	Retro	3b	23/314	Colon	?	Clinical symptoms		-	-	-	-	-	Respiratory, neurological disorders and bloating precipitate CAL
Bellows et al[16]	Retro	3b	25/311	Colorectal	?	Clinical symptoms	Respiratory symptoms	0.52	0.84	0.22	0.95	-	Respiratory, neurological disorders and abdominal pain and distension precipitate CAL
							Neurology symptoms	0.24	0.97	0.4	0.94	-	
							Abdominal pain and distension	0.52	0.83	0.21	0.95	-	
Nesbakken et al[20]	Pro	3b	mei-56	Rectum	?	Clinical symptoms	Daily assessment by surgeon	0.50	0.89	0.5	0.89	-	50% of CAL is silent
Tang et al[21]	Pro	3b	10/195	Rectum	Both	Digital rectal examination		0.98	-	-	-	-	As valuable as WSCE before stoma closure
Pettigrew et al[13]	Pro	3b	28/113	Colorectal and general	?	Risk prediction by surgeon		0.38	0.91	0.56	0.82		Highest predictive value for postop surg assessment
Makela et al[14]	Retro	3b	44/88	Rectum	Both	Risk prediction by surgeon		-	-	-	-	-	In 86% of pts with > 3 risk factors CAL occurs
Karliczek et al[15]	Pro	3b	26/191	Colorectal	?	Risk prediction by surgeon	High anastomosis	0.38	0.46	-	-	-	Low predictive value for prediction of CAL by surgeon
							Low anastomosis	0.62	0.52	-	-	-	

Table 1. Clinical methods

Author	Type of study	Loe	n(CAL/ non-CAL)	Colorectal/ rectum	Stapled/ handsewn anastomosis	Study subject/ tool	Cut-off value	Se	Sp	PPV	NPV	ROC	Main outcome	OnsetCAL (POD)
Slotwinksi et al[29]	Pro	3b	feb-16	Colorectal	?	sTNF-R1, IL-1RA/-6/-8/-10, CRP	-	-	-	-	-	-	TNF higher at POD 1 in CAL	?
Iversen et al[30]	Pro	3b	17/341	Colorectal	Both	s-Fibrin, TAT-complex, PT-f1/-2	-	-	-	-	-	-	PT-f1/-2, TAT-complex, s-Fibrin higher at POD 1/2 in CAL	7
Woeste et al[25]	Retro	3b	26/342	Colorectal	Both	CRP	-	-	-	-	-	-	CRP higher from POD 3 to POD 7 in CAL	8,7
Warschkow et al[24]	Meta	3a	?/1832	Colorectal	Both	CRP	135 mg/L at POD 4	0.680	0.830	0.560	0.89	-	CRP < 135 mg/L at POD 4 discharge is safe	?
Kornerin et al[24]	Retro	3b3	18/231	Colorectal	Both	CRP	190 mg/L at POD 3	0.820	0.730	-	-	0.820	Persisting elevation of CRP is indicative for CAL	8
Mackayin et al[24]	Pro	3b3	5/160	Colorectal	?	CRP	145 mg/L at POD 4	0.850	0.860	0.610	0.96	-	CRP > 145 mg/L at POD 4 is highly predictive for CAL	?
Ortegain et al[24]	Pro	3b3	21/133	Colorectal	Both	CRP	125 mg/L at POD 4	0.820	0.960	-	-	-	CRP > 125 mg/L at POD 4 discharge is not safe	6
Welschin et al[24]	Pro	3b3	22/961	Rectum	Staples	CRP	140 mg/L at POD 3	0.802	0.812	0.862	-	-	Persisting elevation of CRP is indicative for CAL	8
Warschkowinet al[24]	Retro	3b3	89/1115	Colorectal	?	CRP	143 mg/L at POD 4	0.750	0.710	0.190	0.97	-	Use CRP as screening at POD 4	9
Platt et al[26]	Pro	3b	26/454	Colorectal	Both	CRP	190 mg/L at POD 3	0.772	0.802	-	-	0.892	CRP at POD 3 is useful for predicting CAL	6,8
Matthiessen et al[27]	Pro	3b	sep-33	Rectum	?	CRP	-	-	-	-	-	-	CRP higher from POD 2 in CAL	8
Almeida et al[28]	Retro	3b	24/149	Colorectal	?	CRP	140 mg/L at POD 3	0.780	0.860	-	-	-	CRP sign higher from POD 2 in CAL	7

Table 2. Laboratory tests

Two Dutch authors developed and applied leakage scores for the detection of CAL. One risk score prospectively combined preoperative and intraoperative items and yielded a twofold higher score in patients with CAL than in patients without CAL[22]. For postoperative clinical course assessment, a standardized leakage score was developed by den Dulk et al[23] attributing points to certain clinical factors, nutritional status and biochemic findings, thus identifying high risk patients. It facilitated the diagnosis of CAL at POD 6, as opposed to POD 8 in a historical control group.

Laboratory tests

Twelve studies investigated the correlation between postoperative levels of CRP and CAL as shown in table 2. Six of them were included in a meta-analysis of 1832 patients by Warschkow et al. [24], which did not focus solely on CAL but on all postoperative infectious complications. In all studies, CRP-levels were elevated several days before the diagnosis of CAL was established. Slotwinski and colleagues reported higher levels of soluble-TNF-receptor at POD 1 in patients who developed CAL after colorectal surgery[29]. Iversen et al. studied levels of markers of coagulation and fibrinolysis in patients with CAL showed elevated levels 5-6 PODs before clinical onset of CAL compared to patients without leakage.

Drain fluid analysis

Table 3 shows twelve studies on drain fluid analysis. Six out of twelve studies investigated cytokine levels after colorectal surgery, mainly focussing on IL-6, IL-10 and TNF-α. In 4 of these studies, patients after colorectal surgery who developed CAL at POD 5-20 had elevated cytokine levels from POD 1 onwards[31-34]. One study reported the same phenomenon, but the onset of increased cytokine levels was POD 3[35]. Another study did not find a relation between CAL and levels of IL-6 and TNF-α [36]. In two studies describing the technique of microdialysis, local signs of ischemia were measured before CAL became clinically apparent in some patients, although both studies also describe patients with CAL who showed no preceding abnormal microdialysis values [33 37]. Macroscopic changes in drain production were examined by Tsujinaka et al. [38]. Of 21 patients with CAL, 15 had previous changes in drain content, while other clinical signs were not obvious. Likewise, Eckmann et al. found that 80% patients that developed CAL after rectum resection had changes in drain fluid aspect[39]. In a small study, intraperitoneal levels of lipopolysaccharides were elevated from POD 3 in patients with CAL, while CAL was only clinically evident at mean POD 6,7 [40]. By contrast, lysozyme activity was not correlated with clinical CAL in another small study [41].

Drain fluid analysis								
Author	**Type of study**	**Loe**	**n (CAL /non-CAL)**	**Colorectal/ rectum**	**Stapled/ handsewn anastomosis**	**Study subject/tool**	**Main outcome**	**Onset CAL (POD)**
Bertram et al [36]	Pro	4	3/28	Colorectal	?	Cytokines	No correlation between IL-6, TNF-alpha and CAL	5.3
Herwig et al[34]	Pro	3b	12/24	Colorectal	?	Cytokines	IL-6 and TNF-alpha elevated from POD 1 in CAL	5.8
Yamamoto et al[35]	Pro	3b	7/90	Colorectal	Stapled	Cytokines	IL-1beta, IL-6, TNF-alpha elevated from POD 3 in CAL	5,8
Ugras et al[32]	Pro	3b	4/34	Colorectal	Both	Cytokines	IL-6, IL-10, TNF-alpha elevated from POD 1 in CAL	6
Fouda et al[31]	Pro	3b	8/56	Rectum	Both	Cytokines	IL-6, IL-10 elevated from POD 1 in CAL, TNF-alpha elevated from POD 2 in CAL	6
Mattiessen et al[33]	Pro	3b	7/23	Rectum	?	Microdialysis, cytokines	L/P-ratio elevated at POD 5/6 in CAL; IL-6, IL-10, TNF-alpha elevated from POD 1 in CAL	Early CAL: 6 Late CAL: 20
Ellebaek et al[37]	Pro	3b	4/50	Colorectal	?	Microdialysis	Mean L/P-ratio higher in CAL,	Early CAL: 5-10 Late CAL: 20
Tsujinaka et al[38]	Pro	3b	21/196	Rectum	Both	Drainproduction	15/21 Patients with CAL had changes in drain content	7
Eckmann et al[39]	Retro	3b	30/306	Rectum	Stapled	Drainproduction	80% of leakages were indicated by drain, 40% of which prior to clinical symptoms	?
Millan et al[40]	Pro	3b	6/90	Colorectal	Stapled	Intramucosal pH	Intramucosal pH < 7.28 on POD1 increases risk of CAL 22 fold	?
Junger et al[41]	Pro	3b	3/22	Colorectal	Both, biodegradable ring	LPS	Excretion of LPS and LPS concentration is higher at POD 3 in CAL	6,7
Miller et al[42]	Pro	2b	2/42	Rectum	Stapled	Lysozym activity	No correlation between lysozyme activity and CAL	?

Table 3. Drain fluid analysis

Intraoperative techniques

Table 4 demonstrates the studies on intraoperative techniques to detect CAL. Eleven studies on peroperative leak tests were evaluated[42-52]. Although these tests facilitate intraoperative repair of the anastomosis or creation of faecal diversion in case of air leakage or methylene blue leakage, postoperative leakage rates were not reduced to 0%. A study by Beard, reported on 18 intraoperative anastomotic corrections, leading to CAL in 3 patients in the "test"-group, compared to 10 patients with CAL in the "no test"-group. As with the air leak test, colonoscopy, performed in 6 studies, led to intraoperative correction of the anastomosis for reasons of leakage and bleeding[51 53-57]. All studies reported low incidences of CAL, although no study compared intraoperative colonoscopy to no intraoperative control. Two studies comparing routine intraoperative colonoscopy to selective use of this technique showed no benefit of routine application of this technique[55 57]. For assessing local anastomotical blood flow, multiple techniques have been described. Ambrosetti et al. studied the use of Doppler intraoperatively at the site of the anastomosis, enabling correction of the anastomosis in 10 of 200 patients, leading to CAL in 2 (1%)[58]. Vignali et al. found that reduced microperfusion at the rectal stump, during creation of a colorectal anastomosis, measured by laser Doppler increased the risk of CAL[59]. In a study by Kudszus et al. intraoperative laser fluorescence angiography (LFA) led to 28 intra-operative corrections, an absolute reintervention rate of 4% and reduced hospital stay[60]. Hirano et al. studied the application of near infrared spectroscopy of the anastomosis. In their small study, perianastomotic StO_2 < 60 mmHg was measured in patients who developed CAL[61]. In a similar study by Karliczek, using visible light spectroscopy, changes in perianastomotic pO_2 before and after creation of the anastomosis had a significant correlation with CAL[62]. One study showed that reduced pO_2 in perianastomotic tissue was predictive for CAL, although cut-off values for routine clinical application were lacking [63].

Author	Type of study	Loe	n(CAL/ non-CAL	Colorectal/ rectum	Stapled/ handsewn anastomosis	Test	Testper-formed	Test +	Intra-operative correction	CAL test+	Test -	CAL test-	Test not per-formed	CALtest not per-formed	Mainoutcome
Beard et al[43]	Pro	1b	13/145	Colorectal	Both	ALT	73	18	18	3	55	0	70	10	ALT and preop-erative repair reduce risk of AL
Davies et al[44]	Pro	3b	4/33	Rectum	?	ALT	33	6	6	1	27	3	-	-	LT helpful to reduce leakage rate
Dixon et al[45]	Retro	3b	2/202	Rectum	Both	ALT	119	5	5	0	114	0	-	-	Leaks were avoided
Gilbert et al[46]	Retro	3b	1/21	Colorectal	Handsewn	ALT	21	5	5	1	16	0	-	-	ALT facilitates IOR
Lazorthes et al[47]	Pro	3b	3/82	Colorectal	Stapled, doughnut complete 68	ALT	68	0	0	0	68	3	-	-	High NPV for ALT
					Stapled, doughnut incomplete 14		14	4	4	0	10	0	-	-	
Ricciardi et al[48]	Retro	3b	48/998	Colorectal	Both	ALT	825	65	65	5	760	29	173	14	ALT for leftsid-ed anastomosis
Schmidt et al[49]	Pro	3b	68/933	Rectum	Both	ALT	260	47	42	5	213	22	36	4	Risk of AL is unrelated to ALT
Wheeler et al[50]	Pro	4	7/102	Colorectal	?	ALT	99	21	21	2	85	2	-	-	LT facilitates IOR
Yalin et al [51]	Po	3b	1/23	Colo-rectal	Stapled	ALT	21	5	5	1	16	0	-	-	LT facilitates IOR
Griffith et al[54]	Pro	4	2/60	Colorectal	Stapled	ALT	60	11	11	0	49	2	-	-	ALT facilitates IOR
Sakanoue et al[55]	Pro	3b	4/70	Rectum	?	ALT	35	2	2	0	33	0	35	4	Useful for intraopera-tive decision making

Smith et al[53]	Pro	4	7/229	Colon	Both	ALT	229	16	16	0	213	7	-	-	After IOR no CAL occurred
Lanthaler et al[56]	Pro	3b	6/122	Colorectal	Stapled	IOE	73	5	5	0	68	4	49	2	ALT prevents early leak
Li et al[57]	Pro	3b	2/244	Rectum	Stapled	IOE	107	11	11	0	96	0	137, 30 IOC1	2/137, 1/30	Routine IOE and selective IOE equal results
Shamiyeh et al[58]	Pro	3b	7/253	Rectum	Stapled	IOE	85	2	2	0	83	1	253	4	Routine IOE does not reduce CAL
Ishihara et al[52]	Pro	4	1/73	Rectum	Stapled	IOE and ALT	73	4	4	0	69	1	-	-	ALT recommended
Ambrosetti et al[59]	Pro	4	2/200	Colorectal	Both	Doppler ultra-sound									Doppler facilitates IOR
Vignali et al[60]	Pro	3b	8/55	Colorectal	Stapled	Laser doppler	-	-	-	-	-	-	-	-	Reduction in microperfusion increases risk of CAL
Kudszus et al[61]	Retro	3b	22/402	Colorectal	Both	LFA	201	28	28	8	-	-	201	15	LFA reduces reoperation rate for AL, most prominent in handsewn
Hirano et al[62]	Pro	4	1/20	Colorectal	?	Near infrared spectroscopy									StO2 < 60% in CAL
Novell et al[64]	Pro	3b	275	Colorectal	Both	Observation of marginal artery bleeding									Pulsatile flow: lower incidence CAL
Sheridan et al[65]	Pro	3b	5/50	Colon	?	Tissue pO2measurement									Reduced anastomotic pO2 predictive CAL
Karliczek et al[63]	Pro	3b	14/77	Colorectal	?	Visible light spectroscopy									pO2 could predict CAL

Table 4. Intraoperative techniques

Radiology

Sixteen studies evaluated several imaging modalities for the detection of CAL. Seven studies in this review used computer tomography (CT) for the detection of CAL[20,67,68,73,75,77,78]. A prospective study by Nesbakken et al. reported a 94% accuracy for 5 patients with CAL out of 56 patients who had received rectum resection[20]. Similarly, Eckman et al. concluded that CT detected 29 of 30 leaks in a group of 305 patients after stapled rectum resection, although no data were presented on the specificity of the technique[76]. Gouya et al. even reported an excellent 100% sensitivity and specificity. However CT will only show leakage of intraluminal contrast at the site of the CAL in 10% of the patients[67]. Improved results are achieved with the detection of associated features such like pericolic/pelvic fluid collections[78]. Presacral abnormalities, commonly described as caused by leakage, were found in 70% of the patients without clinical anastomotic leakage[68].

Eleven studies investigated the value of the water-soluble contrast enema in determining CAL, mostly after rectum resection, both in the postoperative phase and before closure of deviating ileostomy[20 65-74]. All studies described a high degree, in one case even up to 41%[71], of asymptomatic radiological leakage that resolved without therapeutical intervention. In addition, no study performed contrast enemas in the very early postoperative phase (< POD 5) due to the potential risk of complications so that, when performed at POD 7-8, a clinical leakage concurred with radiological leakage[75]. For these reasons, most studies concluded that routine application of WSCE at POD 7-8 did not contribute to clinical decision-making or to early detection. In the presence of clinical signs suggestive for CAL, a study by Nesbakken described an accuracy of 93% for WSCE in the detection of CAL[20]. Doeksen et al. reported a high specificity and positive predictive value of 94% and 91% respectively, with an interobserver variability of 14%[66].

Two studies investigated the value of plain X-ray. One of these studies reported that increase of subdiafragmatical free air after POD5 increased the likelihood of CAL[78]. The other study, by Williams et al., reported that the finding of staple line disruption on plain X-ray was suggestive for CAL[75].

Author	Type of study	Loe	n(CAL/ non-CAL)	Colorectal/ rectum	Stapled/ handsewn anastomosis	Study tool	Se	Sp	PPV	NPV	Main outcome
Eckmann et al[77]	Retro	3b	30/306	Rectum	Stapled	CT	-	-	-	-	29 of 30 CAL detected by CT
Power et al[78]	Retro	3b	17/50	Colorectal	?	CT	0.30	0.90	0.58	0.74	Peri-anastomotic located fluid containing air found in CAL
Gouya et al[75]	Retro	3b	10/195	Rectum	?	CT	-	-	1.00	1.00	CT has role in predicting CAL
DuBrow et al[68]	Retro	3b	35/75	Rectum	?	CT	-	-	-	-	30% of pts with CAL have presacral abnormalities
Nicksa et al[73]	Retro	4	36 CAL	Rectum	?	CT	0.12	-	-	-	Low percentage true positives
Doeksen et al[67]	Retro	3b	68/429	Colorectal	?	CT	0.54	0.78	0.68	0.66	Interobserver variability 10%
Nesbakken et al[20]	Pro	3b	5/56	Rectum	?	CT	0.57	1.00	-	-	94% accuracy of CT for detection of CAL
Severini et al[74]	Retro	3b	12/175	Rectum	?	WSCE	-	-	-	-	2 CAL out of 78 positive WSCE, low predictive value
Hoffmann et al[70]	Retro	3b	5/51	Colorectal	Both	WSCE	0.20	0.85	0.13	0.91	WSCE not recommended for routine use
Markham et al[72]	Retro	3b	1/136	Rectum	Handsewn	WSCE	1.00	0.57	0.02	1.00	WSCE no contribution to surgical management
Kalady et al[71]	Retro	3b	8/211	Rectum	?	WSCE	0.88	1.00	1.00	0.99	WSCE does not provide additional information
Akyol et al[66]	Pro	3b	12/233	Colorectal	Both	WSCE	0.52	0.87	0.30	0.94	WSCE provides little useful clinical information
Haynes et al[69]	Retro	3b	14/117	Colorectal	Both	WSCE	0.71	0.86	0.42	0.96	WSCE not recommended for routine use
Gouya et al[75]	Retro	3b	10/195	Rectum	?	WSCE	-	-	1.00	0,98	WSCE is recommended for routine use
Nicksa et al[73]	Retro	4	36 CAL	Rectum	?	WSCE	0.88	-	-	-	WSCE superior to CT
Doeksen et al[67]	Retro	3b	68/429	Colorectal	?	WSCE	0.68	0.94	0.91	0.76	Interobserver variability 13%
Nesbakken et al[20]	Pro	3b	5/56	Rectum	?	WSCE	0.60	1.00	-	-	93% accuracy of WSCE for detection of CAL
Williams et al[76]	Retro	4	10/31	Rectum	Stapled	X-ray	0.90	1.00	1.00	0.95	Staple line dehiscence in 9/10 patients with CAL
Tang et al[79]	Pro	4	2/64	Colorectal	?	X-ray	-	-	-	-	Increase free air after POD 5 higher chance CAL

Table 5. Radiology

Discussion

In this paper, all available evidence on the diagnostic tools for detection of CAL was systematically reviewed, according to the guidelines of the Oxford Centre of evidence based medicine. Diagnostic techniques were appraised for their ability to predict or detect clinically relevant CAL, since this is relevant in daily care for patients directly after colorectal surgery. Early intervention in abdominal sepsis is essential as is shown by the Surviving Sepsis Campaign, emphasizing on source identification and surgical control when possible[78].

Many studies report data on asymptomatic or radiological CAL. However, these data were not included in this review, since asymptomatic CAL, if detected, will be left untreated as a rule. Furthermore, it has a poor correlation with clinically relevant CAL. Theoretically; asymptomatic CAL might prove to be important if the oncologic outcome is studied, since equivocal literature is available showing a higher percentage of local recurrence after CAL[80-82]. To this date, however, the role of asymptomatic CAL in local recurrence is unknown.

All eligible studies were separately evaluated by two investigators, and a level of evidence was assigned to each of them. Overall, the level of evidence was considered low. This was due to factors that coincide with the problem of CAL. First, in the field of the diagnosis of CAL, no definition of CAL is available, nor is a golden standard[3]. Such a golden standard cannot even be found in relaparotomy during which faecal discharge at the site of the anastomosis is established, since many patients are treated for CAL without direct visualization of the anastomosis during reoperation. Secondly, a major cause of the low level of evidence is the fact that many studies lack a non-test group. Finally, guidelines to determine the level of evidence differ between diagnostic studies and their therapeutic counterparts. Publication bias and reporting bias in particular were estimated to be low, since the primary search yielded many studies with negative results and small numbers of subjects.

Much research has been done on the early detection of leakage after ileoanal pouch reconstruction following total colectomy for inflammatory bowel disease. These studies were excluded from this review, since they comprise more extensive surgery, different types of leakage, other types of pouch failure and different therapy modalities.

Clinical methods

Clinical factors are objective and easily available for risk prediction. A few problems, however, occur if surgeons rely solely on clinical factors. First, the influence of individual factors is not exactly known. Secondly, by the time signs of septicaemia occur; patients will be in a worse clinical state at the onset of an often prolonged and onerous therapeutic course. Subjective prognosis of leakage at the moment of finishing the anastomosis was proven to have a limited prognostic value[15]. Objective measurements might be of greater prognostic value, as shown by the Colon Leakage Score, in which the presence of objective risk factors leads to a higher score representing a higher chance of CAL[22]. This leakage score was based on previously identified risk factors and to our knowledge is the first to translate all available literature on risk factors for CAL into an instrument that can easily be implemented in daily practice. In a cohort of 233 patients, using a historical control group of 1066 patients, den Dulk et al. developed a similar score system for postoperative clinical evaluation of the colorectal patient. When a high score is found, computer tomography using rectal contrast is warranted. Although this promising method has shown to reduce delay in diagnosis, no information was provided on the prognostic value of this risk score, nor did the study mention the number of CT-scans and concomitant negative results In a study on tracking of surgical site infections (SSI), van Ramshorst et al. found that protocolled tracking yields a higher reported incidence of SSI than self-reported detection[83]. We believe that this finding could be applied to the protocolled detection of CAL as described above, as it contributes to increased awareness and early detection.

Little is known about the value of physical examination in relation to CAL, except that digital rectal examination has at least the same prognostic value for low anastomosis as contrast enema prior to stoma reversal.

Laboratory tests

Many investigators have studied the behaviour of CRP during the subclinical phase of CAL. CRP has the capacity to rise quickly after the onset of an inflammatory stimulus, reaching its highest serum level within 48 hours. Since it has a short halftime of around 19 hours, a drop in CRP corresponds well with the removal of the stimulus. Most studies investigating CRP used cut-off values of around 120 – 190 mg/L at POD 3-4, and all studies in this review showed a reasonable predictive value of CRP for CAL. Drawbacks of all studies described in this review is that the number of included patients per study is rather small and that none of these studies

provide a protocol that structurally describes the postoperative clinical examination, the clinical state of the patients during postoperative follow-up and the type of CAL (i.e. faecal peritonitis, juxta-anastomotic abscess, rectovaginal fistula). Despite these drawbacks, we believe that these studies have indeed shown that measurement of CRP is of great importance in detecting CAL in the preclinical phase.
Other laboratory tests like coagulation factors and cytokines show a correlation with occurrence of CAL, but they have been studied sparsely. Since no parameters for their predictive value can be calculated from the available data, there is no basis for incorporating them in the standard postoperative lab tests.

Drain fluid analysis

In this review, the results for cytokine levels in peritoneal drain fluid, as biomarkers for local infection, seem promising. In most studies cytokine levels were elevated from POD 1 in patients with CAL compared to patients without CAL. This finding suggests an early onset of local infection in patients with CAL, or at least a more prominent postoperative reaction in this group. It is hypothesised that cytokines are directly elevated postoperatively and will normalise unless infectious complications occur. Most frequently investigated cytokines are interleukin (IL)-1, 6, 10 and tumour necrosis factor-a (TNF-a).
Although routine drainage after colorectal surgery does not seem to prevent CAL and is omitted in enhanced recovery programs, two studies showed that changes of drain production occur frequently and before clinical symptoms. These interesting findings might justify the routine placement of a drain for the first postoperative days as an indicator for CAL.
Two studies on intraperitoneal microdialyis show, by retrospectively analysing of peritoneal microdialysis samples, that CAL was preceded by changes in local lactate/pyruvate ratio. Although these findings are promising, patient numbers were too low to compute predictive values and cut-off values. Future research should elucidate if prospective, real-time analysis actually leads to early detection and determine whether this technique is cost effective.
For intramucosal pH monitoring, as a measure for mucosal hypoperfusion and subsequent hypoxia, data are limited but promising. The same holds for measurement of lipopolysaccharides, integral components of normal gut flora, and measurements of lysozym in drain fluid, since the studies investigating these biomarkers did neither lead neither to confirmation of these techniques nor to a re-evaluation.

Intra-operative techniques

Except for one, all studies evaluating the air / methylene blue leak test (ALT) confirm the importance of this simple intervention. Although not completely eliminating the occurrence of CAL, ALT allows intraoperative revision of the anastomosis, is easy to perform and has a high negative predictive value. Understandably, no studies have been performed that relate a positive ALT without intraoperative repair to CAL. All valuable studies, those that use a no-test control group, show a lower percentage of CAL in the group in which ALT was performed; in two out of four papers this difference was significant.

Intraoperative endoscopy (IOE) can, apart from direct visualisation of CAL, be of diagnostic and therapeutical importance if the location of the tumour or of additional lesions is unknown or if anastomotic bleeding occurs. More recently, the routine application of IOE has been studied in comparison to selective IOE. No favourable results in occurrence of CAL were described for routinely performed IOE compared to selective IOE. Apart from the mentioned benefits of IOE, no data are available on the superiority of IOE compared to ALT for intraoperative diagnosis of anastomotic dehiscence. Thus, ALT seems to be favourable to IOE since it is faster, easier and cheaper.

Some authors have attempted to relate anastomotic perfusion parameters to anastomotic leakage. Except for one, all studies are case controlled without reference and have not been repeated. It has not led to clear cut-off values for any of these techniques that seem not very practical in daily current practice. At least one cohort study with a good reference is needed before clinical implementation.

Radiology

As far as CT with rectal contrast is concerned, only 7 studies could be included. These studies showed large differences in methodology and lacked generally applied definitions. These differences between several studies, especially in CT criteria for CAL, resulted in equivocal results. Intestinal contrast leakage is not regularly depicted with CT in patients with CAL. However CT can accurately depict the associated features of anastomotic leakage such like pericolic/pelvic fluid collections and free air. When these additional criteria were used the accuracy improved dramatically with accuracies varying from 80-100%[20,75,77].

All six studies that were performed on the subject of WSCE over the last two decades concluded that there is no place for routine application of WSCE. In these studies, WSCE did not have a consistently high positive predictive value, and other techniques, such as digital rectal examination in low rectal anastomosis, appeared to

provide at least equal results. Furthermore due to the potential risk of complications no study performed contrast enemas in the very early postoperative phase. This means that, when performed at POD 7-8, clinical CAL concurred with radiological leakage[75]. In addition, radiologic signs of CAL do not correlate with clinical CAL and frequently do not require any form of treatment. Another drawback of WSCE is that the rectally administered contrast has been diluted and there may be not enough remaining pressure to induce contrast leakage in more proximal anastomoses[73].
Two older studies describe how plain X-rays can be used in assessment of intra-abdominal free air and staple line integrity in the diagnosis of CAL[75,78]. Although sometimes helpful, modern techniques offer the surgeon much more detailed information on the extend of CAL compared to plain X-rays.

Conclusions

Many studies have been performed in the field of diagnosis of CAL. Many lack a no-test control group and reference; therefore the general level of evidence is relatively low. The air leak test is recommended for intraoperative assessment of CAL. When a leakage score system is used intraoperatively, peroperative preventive measures can be taken. When using a clinical algorithm postoperatively, delay in diagnosis of CAL might be reduced. CRP measurement should be part of postoperative laboratory routine at least at POD 3 and 4, since due to a high negative predictive value patients with an uncomplicated course can be identified. Cytokine measurement among other measurements of peritoneal drain fluid is promising and could justify the routine placement of a juxta-anastomotic drain, while peritoneal microdialysis might develop as minimally invasive peritoneal "smart"-drain. When clinical signs are present, CT with rectal contrast is recommended. CT cannot only to detect CAL but also can be used as a therapeutic instrument for percutaneous drainage of a pericolic/pelvic abscess. We believe that this review reaffirms the importance of early detection of colorectal anastomotic leakage and that it offers colorectal surgeons an overview on easily applicable diagnostic tools to improve early detection.

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4

Treatment

4.1 Incidence, risk factors and treatment of anastomotic leakage after surgery for advanced rectal cancer

Anastomotic leakage and presacral abscess after advanced rectal cancer surgery: Incidence, risk factors and treatment
Vermeer TA, Orsini RG, Daams F, Nieuwenhuijzen GA, Rutten HJ.
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Abstract

Despite improvements in surgical techniques, anastomotic leakage (AL) and presacral abscess (PA) after rectal cancer surgery are still a major concern for the colorectal surgeon. In this study, incidence, prognosis and treatment was assessed. All patients operated on in our institute, from 1994 until 2011, for curative resectable locally advanced rectal cancer (LARC, T3+/T4M0) were included. Morbidity was scored using the Clavien-Dindo classification. Prognostic factors were analysed using univariate binary logistic regression. A total of 517 patients were included after a low anterior resection (LAR, n=219) or abdominoperineal resection (APR, n=232). AL occurred in 25 patients (11.4%) and 50 patients (9.7%) developed a PA. Univariate analysis identified intraoperative blood loss ≥4500cc (p=0.038) and the era of surgery; patients operated on before the year 2005 (p=0.042); as risk factors for AL. The timing interval, time between last day of neo-adjuvant treatment and surgery, <8 weeks is significantly associated with the development of PA (p=0.010). In our study population of LARC patients we found an incidence of 9.7% PA and 11.4% AL, with a 12% mortality rate for AL, which comparable to surgery in general colorectal cancer. Increased intra-operative blood loss and surgery prior to the year 2006 are associated with AL. Increased intra operative blood loss and an interval between neoadjuvant (chemo)radiation and surgery <8 weeks increases the risk of PA formation. This emphasizes the positive effect of a prolonged timing interval, in addition to the improved oncological outcome, as published by numerous authors.

Introduction

In the last few decades many changes have been made in the perioperative treatment, surgical techniques and general patient care, which have greatly improved oncological outcome and overall survival in locally advanced rectal cancer (LARC).(1-6) Despite these changes, complication rates are still high in some series and anastomotic leakage (AL) and the development of a presacral abscess (PA) is a major concern for the colorectal surgeon.(7-12) AL is a predominant cause of short- and long-term morbidity and a prolonged hospital stay with mortality rates ranging between 0.6-22% in a recent review.(8, 12)

In the general population male sex, preoperative radiation, preoperative low serum albumin levels, prolonged duration of surgery, increased blood loss, COPD and a low anastomosis are considered risk factors for anastomotic failure.(10, 13-17) Age, co-morbidity and the number of postoperative complications are significantly associated with mortality and worse outcome after colorectal surgery in elderly patients.(17) Leakage rates are similar in younger and elderly patients according to the data from the Dutch TME-trial, but mortality due to AL in elderly patients (>75 years) is reported up to 57% compared to 8.2% in younger patients (<75 years).(18)

Short-term morbidity associated with AL includes pneumonia, deep venous thrombosis (DVT), pulmonary embolism, CVA, surgical site infections, sepsis and PA formation.(15, 19) In addition, long-term morbidity includes the formation of a persistent PA or sinus, creation of a permanent stoma, preservation of a diverting stoma and abdominal herniae.(20, 21) Known risk factors for the development of PA are short-term neoadjuvant radiotherapy, ASA classification and tumour size, but studies regarding the incidence and prognostic factors of PA are scant.(21, 22)

There is a wide incidence range for AL in the current literature with incidences up to 53%.(23) A recent review by the International Study Group of Rectal Cancer (ISGRC) reported an incidence range of 3-23%.(24) Variations in surgical techniques and patient selection influence the reported incidence of AL, but the main reason for the wide incidence range found in the literature is the lack of an international definition and grading system regarding AL. However, a clear difference in the incidence of AL is made between a proximal anastomosis, ranging between 5-12cm, with an incidence from 2-4% and a more distal anastomosis, with an incidence between 6-12%. (12, 16, 24-26) Due to improvements in neo-adjuvant treatment and surgical techniques, there is an increase in patients with a distal colo-anal anastomosis, subsequently increasing the incidence of AL and PA.

In 2010, the International Study Group of Rectal Cancer (ISGRC) proposed an

international uniform definition and grading system for AL, since the lack of a definition contributes to various results in recent literature.(24) Anastomotic leakage was defined as " a communication between the intra- and extraluminal compartments owing to a defect in the integrity of the intestinal wall at the anastomosis between the colon and rectum or the colon and anus". The ISGRC concluded that any abscess on the anterior side of the anastomosis should be regarded as an AL, thus making no difference between both conditions. The definitions used in our series, which are supported by different authors, make a clear distinction between both conditions, defining a PA as an abscess on CT-scan positioned on the anterior side of the sacrum without signs of AL such as extravasation of enteral contrast on CT-scan, faecal generalised peritonitis or a palpable defect in the anastomosis.(21, 27)
This study is conducted to investigate the incidence, prognosis and treatment of AL and PA in LARC patients with the use of a clear definition and a clear distinction between these two complications. Furthermore, risk factors regarding AL and PA were assessed.

Methods

Patients

As a national referral centre for LARC and locally recurrent rectal cancer our Hospital has gained a lot of experience in the treatment of rectal cancer. In this retrospective study, only patients with LARC were included, which was defined as a threatened (cT3+) or involved mesorectal fascia (cT4) on MR imaging. All patients who received curative, non-laparoscopic, surgery for primary rectal cancer between 1994 and 2010 were included in the study and are maintained in prospective database. Co-morbidity was scored using the Charlson Co-morbidity Index.(28) Patients with metastatic disease at presentation (cM1) were excluded.

Neo-adjuvant treatment and timing interval

During the study period, different types of neo-adjuvant treatment strategies have been used: 5x5Gy, long-term radiotherapy and different types of chemoradiation schemes. Chemoradiation schemes differed in the type of chemotherapy used. The type of neo-adjuvant treatment depended on the protocols or trials used by the referral hospitals or the Catharine Hospital at the time of inclusion. Details about the different chemoradiation schemes and their influence on survival are described

elsewhere.(29) The timing interval was defined as the interval in weeks between the last day of neo-adjuvant treatment and the day of surgery. The duration of the timing interval in LARC has changed over the last decade and was influenced by the accepted consensus at the time of surgery, practical considerations, the degree of acute toxicity due to neo-adjuvant treatment which required a delay of surgery or the need for acute oncologic resection.

Postoperative complications

Postoperative complications were registered for all patients. A PA was defined as an abscess on the anterior side of the of the sacrum without extravasation of enteral contrast on CT-scan or signs of generalised peritonitis due to AL. AL was defined as an extravasation of enteral contrast on CT-scan, the presence of a PA in combination with a defect in the anastomosis on palpation or the presence of faecal peritonitis when performing a laparotomy. All patients had grade B or C AL according to the ISGRC grading system.(24) Complications were scored using the Clavien-Dindo classification of surgical complications.(30) Postoperative complications, including AL, were scored within 30-days after surgery. For PA formation and sinus formation no time limit was set since it is routinely diagnosed >30 days after surgery. Data on PA and AL were obtained by studying medical records, investigating records from the referral hospital or by contacting patients by telephone.

Conservative treatment of AL and PA consisted of treatment with antibiotics. Surgical drainage of PA was performed in the operating theatre, either pararectal, transvaginal or through the perineal wound if possible, or by relaparatomy depending on type of surgery performed and the location of the abscess.

Statistical analysis

Statistical analyses was performed using the SPSS Statistics 20.0 software (SPSS Inc., Chicago, IL, USA). Intergroup comparisons were analysed using chi-square tests or independent t-tests when appropriate. Follow-up was calculated as the time from the day of surgery to death or the date of last contact. Predictive values were identified using a binary logistic regression, as appropriate. A p-value of ≤0.05 was considered statistically significant.

Results

General patient characteristics are given in Table 1. A total of 517 patients were included in the study. The median interval between neo-adjuvant treatment and surgery was 9 weeks (range 1-31 weeks), with a mean of 9.2 weeks. Twenty-five patients developed AL after undergoing a LAR (n=219), 13 men (52%) and 12 women (48%), with an overall incidence of 11.4%.

	All patients	Anastomotic leakage	Presacral abscess
	n=517	n=25*	n=50
Gender			
male	319 (62%)	13 (52%)	33 (66%)
female	198 (38%)	12 (48%)	17 (34%)
Age			
<70 years	376 (73%)	18 (72%)	38 (76%)
>70 years	141 (27%)	7 (28%)	12 (24%)
ASA			
I	103 (20%)	2 (8%)	9 (18%)
II	388 (75%)	21 (84%)	40 (80%)
III	25 (4.8%)	2 (8%)	1 (2%)
IV	1 (0.2%)	0	0
cT			
cT3	187(36)	9 (36%)	20 (40%)
cT4	330 (64%)	16 (64%)	30 (60%)
Neoadjuvant treatment			
none	9 (1.7%)	0	1 (2%)
5x5Gy (1)	11 (2.1%)	0	0
LRT (2)	85 (16%)	6 (24%)	9 (18%)
Chemoradiation	409 (79%)	19 (76%)	40 (80%)
Chemoradiation scheme			
capecitabine	101 (20%)	5 (20%)	11 (22%)
CORE (3)	145 (28%)	3 (12%)	19 (38%)
other	144 (28%)	10 (40%)	8 (16%)
Type of surgery			
LAR	219 (42%)	24 (96%)	15 (30%)
APR	232 (45%)	0	24 (48%)
ASR (4)	27 (5.2%)	0	5 (10%)
Exenteration (5)	18 (3.5%)	1 (4%)	4 (8%)
Hartmann's procedure (6)	21 (4.1%)	0	2 (4%)

Table continued

	All patients	Anastomotic leakage	Presacral abscess
	n=517	n=25*	n=50
IORT (7)			
yes	374 (72%)	20 (80%)	38 (76%)
Radicality			
R0	454 (88%)		
Intraoperative blood loss			
median in mL (range)	2000 (50-25000)	2100 (100-13000)	3000 (300-20800)
Year of operation			
1994-2005	246 (48%)	17 (68%)	24 (48%)
2006-2010	271 (52%)	8 (32%)	52 (%)
Timing interval (8)			
<8 weeks	168 (32%)	8 (32%)	22 (44%)
>8 weeks	207 (40%)	13 (52%)	12 (24%)
Total CCS (9)			
0	403 (78%)	17 (68%)	35 (70%)
1	74 (14%)	6 (24%)	12 (24%)
2	20 (3.9%)	2 (8%)	2 (4%)
3	16 (3.1%)	0	0
4	3 (0.6%)	0	0
5	1 (0.2%)	0	1 (2%)

Table 1. Patient characteristics. 1. 25 Gy in 5 fractions of 5 Gy; 2. 45-50 Gy in 28 fractions of 1.8-2 Gy; 3. CORE: capecitabine and oxaliplatin; 4. Abdminosacral resection; 5. En bloc excision of adjacent organs and adjacent structures of the pelvis in case of tumour infiltration; 6. A LAR resection including an end colostomy; 7. Intraoperative radiotherapy; 8. Interval in weeks between last days of neo-adjuvant treatment and surgery; 9. CCS: Charlson Comorbidity Score; *Only patients after LAR were included in the analysis (n=219).

Three patients died as a direct result of AL during primary admission, with a mortality rate of 12%. Of these patients, two were aged >75 years and were ASA III. Additional surgery was required in 18 patients (Figure 1); dismantling of the anastomosis was required in seven patients, with creation of an end colostomy, and a new anastomosis was created in two patients. In a further two patients, a diverting stoma was created as treatment for AL, while in all other patients a diverting stoma was created during primary surgery. Surgical drainage was required in seven patients. In 72% of patients (n=18), a relaparatomy was required for adequate treatment of AL.

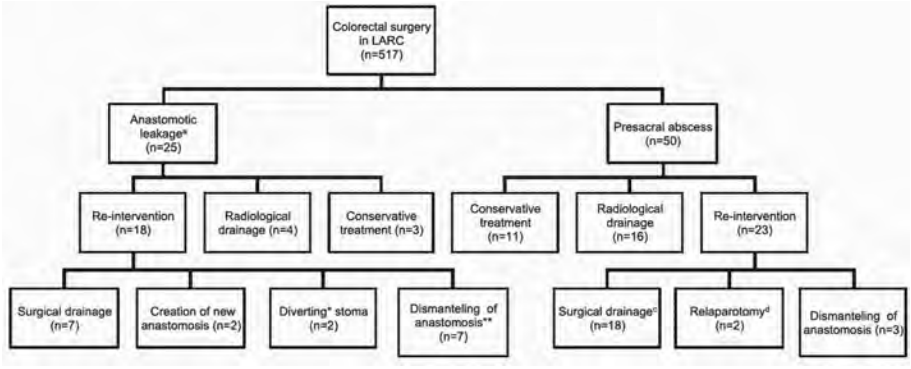

Figure 1. Treatment of anastomotic leakage and presacral abscess. a. A low anterior resection was performed in 219 patients; b. creation of new anastomosis; c. 2 patients after Hartmann's procedure; d. drainage of the abscess through laparotomy * indicates death of 1 patient.

Fifty patients developed a PA after surgery (n=517), 33 men (66%) and 17 women (34%), with an overall incidence of 9.7%. No patients died as a direct result of a PA within 30 days of surgery. Additional surgery was required in 23 patients (Figure 1): in 4% of patients (n=2) with PA a relaparatomy was performed for treatment of acute illness; when including chronic sinus or abscess formation a late relaparatomy was performed in 10% of patients with PA.

The overall short-term co-morbidity incidence in our population, regarding AL and PA, was 14.5%.

Long-term results

Long-term results regarding stoma reversal and sinus formation are shown in Figure 2.

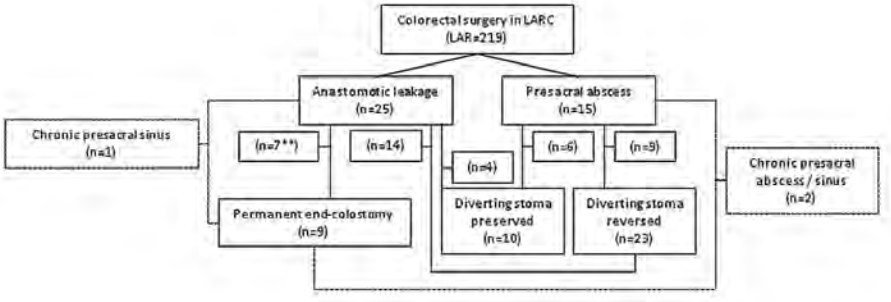

Figure 2. Long term results and stoma status at the time of follow-up. ** Indicates death of 1 patient. Dotted line indicates surgery due to chronic morbidity > months after primary surgery.

After a LAR (n=219), nine patients still had a permanent end-colostomy after long-term follow-up, either due to AL or chronic presacral sinus or abscess formation (12%). In ten patients, the diverting stoma was not reversed due to AL or PA (13.3%). Stoma reversal was complicated by AL in five patients resulting in the creation of a diverting stoma (n=3) and a permanent stoma (n=2). Eight patients developed a chronic presacral sinus with a chronic abscess cavity, which required surgical intervention. After AL and PA, six (24%) and two (8.3%) patients, respectively, developed a chronic presacral sinus. Treatment of these chronic presacral sinus consisted of the creation of a diverting stoma (n=3), relaparatomy with debridement of the presacral cavity and closure of the sinus (n=2) and dismantling of the anastomosis and APR (n=3). Multiple interventions were needed in 63% (n=5) of the patients with a chronic sinus.

Risk factors

Risk factor analysis for development of AL identified the era of surgery, as a risk factor for AL in the univariate analysis. (data not shown)

Patients operated on between 1995-2005 had a significant increased AL rate, (OR 2.44, p=0.04), compared to patients operated on between 2006-2010. The median intraoperative blood loss for all patients was 2000cc (range 50-25000cc). Increased intraoperative blood loss, at a cut-off value of ≥4500cc, was significantly associated with AL (OR 2.41, p=0.04).