Similar analyses were performed for PA formation (data not shown). The univariate analysis showed an increased risk of PA formation with increased intraoperative blood loss, at a cut-off value of ≥3000cc (OR 2.19, p=0.010). A timing interval <8 weeks (n=168), versus >8 weeks (n=207), was significantly associated with increased PA formation (OR 2.66, p=0.01). The type of neo-adjuvant treatment; chemoradiation, long-course radiotherapy and short-course radiotherapy; was not identified as a significant risk factor for the development of a PA.

Co-morbidity was scored extensively for all patients: the Charlson Co-morbidity Index (CCS) is shown in Table 1. All patients who died due to AL within 30-days of surgery (n=3) had a low total CCI ≤2, but all patients suffered from additional co-morbid conditions which are not included in the Charlson Co-morbidity Score. No risk factor analysis for co-morbidity, including COPD and DM, and total CCS and the development of AL or PA was performed due to the lack of power in these groups.

Discussion

Anastomotic leakage after colorectal surgery in cancer patients is a frequently observed complication with a high morbidity rate; AL has been associated with increased local recurrence and decreased survival.(31-33) Therefore, AL is one of the most feared complications for the colorectal surgeon, especially in patients with LARC, since this kind of surgery requires more distal anastomosis and often multivisceral resections. Determining the risk factors for the development of AL is essential for a patient tailored treatment. Tumour characteristics, neo-adjuvant treatment, type of surgery, creation of a diverting stoma and many other variables are important in pre- and peri-operative decision-making. Despite multiple studies regarding risk factors, no general consensus on patient selection and high-risk patients has been established. One of the main drawbacks of studies regarding AL is the lack of a universal definition. In 2001, Bruce et al. published a systematic review regarding the definition and classification of AL, resulting in 17 different general terms and 19 grading terms.(34) This results in high inconsistency regarding incidence, treatment, risk factors and prognosis in the different studies. The proposed international definition for AL by the International Study Group of Rectal Cancer makes no clear distinction between AL and PA. According to our experience, a clear distinction between both conditions should be made for several reasons. A PA alone does not

indicate anastomotic failure. PA is frequently seen in patients after an APR and could indicate peri-operative spill or an infected haematoma. In our study, relaparatomy was required for adequate treatment in 4% compared to 72% of patients, for PA and AL, respectively, indicating that both conditions are different entities. A large series by Damrauer et al. supports that a clear definition leads to a more accurate incidence, a more tailored treatment and reduction of treatment delay.(19) Age, co-morbidity and postoperative complications are key factors in morbidity and mortality after colorectal surgery.(17, 18) Risk factor analyses for the development of AL, identified the era of surgery as a risk factor for AL. Perioperative care en surgical techniques have dramatically improved during the period of this study. Patients operated on after the year 2005 are treated according to modern standards, which is a possible explanation for the decrease of AL rates over time. PA formation was divided equally over the inclusions period, and the chance over time did not significantly influence PA formation.

Intraoperative blood loss is associated with development of AL and PA at different cut-off points, ≥4500cc and ≥3000cc respectively. Two previous series have associated intraoperative blood loss and AL, in a low-risk patient population with colorectal cancer, with a cut-off point of >100 and 200mL.(15, 16) In our high-risk population, with locally advanced rectal cancer patients and extended resections, a higher in cut-off point is found. More active peroperative resuscitation and postoperative Intensive Care treatment with active control of patient status and circulation might be an explanation for this increased cut-of point in these high-risk patients.

Literature regarding PA formation is very scant. The association between intraoperative blood loss and PA formation has not yet been described. Increased blood loss and perioperative spill could lead to an infected presacral hematoma. Subsequently a PA can form due to this increased blood loss.

Neoadjuvant short-course radiotherapy has been associated with PA formation.(21) In our series, a timing interval < 8 weeks is significantly associated with PA formation, independent of the type of neoadjuvant treatment.

In our series, only LARC patients were included and therefore short-course radiotherapy was only administered in 11 patients. Long-course radiotherapy and chemoradiation in combination with a short timing interval (<8 weeks) were both significantly associated with the development of PA. The type of chemotherapy used is not associated with development of PA. These findings suggest that radiotherapy and subsequent tissue changes might be the cause of the increased risk of abscess formation, which supports the findings by Van der Vaart et al. in 2006.(22) The use

of IORT is not significantly associated with the development of PA in our series. Seventy-two percent (n=374) of patients received IORT, which might explain the lack of significance. The narrow and well-directed field of radiation during IORT might be another explanation for why no association with abscess formation was found.

Recent studies have shown that an interval ≥8 weeks between chemoradiation and surgery is safe and associated with a higher rate of pathological complete response (pCR), decreased local recurrence and improved survival outcomes.(35-38) In combination with our findings, a timing interval between neoadjuvant treatment and surgery of more than 8 weeks is also advised to decrease the risk of PA formation.

The high mortality rates after AL in the elderly colorectal cancer patient and the finding that 20% of diverting stomas in elderly patients will not be reversed underline the fact that the creation of a permanent end colostomy has to be considered in elderly patients.(18) Especially in case of additional comorbidity or poor physical status.(17) A recent previous study showed that the quality of life in elderly patients with colorectal cancer is not impaired by a permanent stoma.(39) In addition, stoma reversal is associated with high complication rates, up to 30% in our series, exposing the elderly to further increased mortality.(12, 40, 41)

In our series, the incidence of COPD in patients with AL was 1.7 times higher than in our entire population, a finding which is in line with earlier findings suggesting that COPD is associated with increased postoperative morbidity in colorectal surgery. (17) The incidence of diabetes mellitus (DM) in patients with PA is 2 times higher than in our entire population, suggesting that patients with DM are at increased risk of postoperative abscess formation.

Efficient drainage is the most important step in the treatment of any abscess. Many different techniques for the drainage of a PA are described in literature. Transvaginal or transrectal drainage, including transanastomotic drainage, performed either with or without ultrasound guidance, are frequently used techniques.(21, 42, 43) The effectiveness of percutaneous abscess drainage is well established using different types of assistance including ultrasound, CT-scan or MRI, depending on abscess characteristics.(44) In our experience, the presence of a PA is not a clear indicator of anastomotic integrity and transanal drainage of the PA through the anastomosis is not recommended. An alternative and frequently used technique in our institute is pararectal drainage, and drain placement, with a 5-10mm trocar, leaving the anastomosis intact. After an APR, transperineal drainage can be performed using this technique without the need for ultrasound guidance. It is a relatively easy and short

procedure and therefore a recommended first step in the treatment of PA. To our knowledge, no literature on the use of this technique is currently available.
The incidence of chronic presacral sinus formation and its prognosis is not well established. Chronic presacral sinus formation is reported in up to 36% of patients who develop AL after a LAR, with the need for often multiple surgical interventions in about 50% of patients.(20) In our population of LARC patients, the results are similar, indicating that it is primarily related to the incidence of PA and AL and not patient or tumour characteristics.
To our knowledge this study is one of the largest series regarding information about PA and AL in LARC patients treated in a single institution. Many clinically relevant variables were scored with a low prevalence of missing values. Limitations of this study are based on its retrospective character. The report on minor complications, including conservatively treated AL or PA, could be underestimated due to a lack of documentation. In addition, as a referral centre for LARC, some patients are transferred to the referral hospital after the operation, which could lead to an underestimation of short- and long-term complications. However, we believe that the underestimation of complications was kept to a minimum by the accurate studying of medical records, contact with referral hospitals and general practitioners and direct contact with patients by telephone and validated questionnaires.

Conclusion

We found an overall incidence of 11.4% for anastomotic leakage and 9.7% for presacral abscess in locally advanced rectal cancer patients receiving curative surgery. The incidence of these complications is acceptable in our high-risk population with a relatively high number of very low anastomosis and multivisceral resections. Increased Intraoperative blood loss is significantly associated with AL and PA formation and patients operated on prior to the year 2006 have an increases risk of AL. The interval between the last day of neo-adjuvant treatment and surgery <8 weeks is significantly associated with the development of presacral abscess. An increased timing interval (>8 weeks) is advised since it is significantly associated with an increased number of pCR and improved oncological outcome, as published by various authors, and it reduces the risk of PA formation, as published in the current series. A universal and internationally used definition for these complications is important and consistency is needed since it is an essential measurement for the quality of surgery.

References

1. Vauthey JN, Marsh RW, Zlotecki RA, Abdalla EK, Solorzano CC, Bray EJ, et al. Recent advances in the treatment and outcome of locally advanced rectal cancer. Annals of surgery. 1999;229(5):745-52; discussion 52-4.
2. Bosset JF, Collette L, Calais G, Mineur L, Maingon P, Radosevic-Jelic L, et al. Chemotherapy with preoperative radiotherapy in rectal cancer. The New England journal of medicine. 2006;355(11):1114-23.
3. MacFarlane JK, Ryall RD, Heald RJ. Mesorectal excision for rectal cancer. Lancet. 1993;341(8843):457-60.
4. Valentini V, Coco C, Picciocchi A, Morganti AG, Trodella L, Ciabattoni A, et al. Does downstaging predict improved outcome after preoperative chemoradiation for extraperitoneal locally advanced rectal cancer? A long-term analysis of 165 patients. International journal of radiation oncology, biology, physics. 2002;53(3):664-74.
5. Cunningham D, Atkin W, Lenz HJ, Lynch HT, Minsky B, Nordlinger B, et al. Colorectal cancer. Lancet. 2010;375(9719):1030-47.
6. Aklilu M, Eng C. The current landscape of locally advanced rectal cancer. Nature reviews Clinical oncology. 2011;8(11):649-59.
7. Karanjia ND, Corder AP, Bearn P, Heald RJ. Leakage from stapled low anastomosis after total mesorectal excision for carcinoma of the rectum. The British journal of surgery. 1994;81(8):1224-6.
8. Enker WE, Merchant N, Cohen AM, Lanouette NM, Swallow C, Guillem J, et al. Safety and efficacy of low anterior resection for rectal cancer: 681 consecutive cases from a specialty service. Annals of surgery. 1999;230(4):544-52; discussion 52-4.
9. Eriksen MT, Wibe A, Norstein J, Haffner J, Wiig JN, Norwegian Rectal Cancer G. Anastomotic leakage following routine mesorectal excision for rectal cancer in a national cohort of patients. Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland. 2005;7(1):51-7.
10. Matthiessen P, Hallbook O, Andersson M, Rutegard J, Sjodahl R. Risk factors for anastomotic leakage after anterior resection of the rectum. Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland. 2004;6(6):462-9.
11. Kruschewski M, Rieger H, Pohlen U, Hotz HG, Buhr HJ. Risk factors for clinical anastomotic leakage and postoperative mortality in elective surgery for rectal cancer. International journal of colorectal disease. 2007;22(8):919-27.
12. Huser N, Michalski CW, Erkan M, Schuster T, Rosenberg R, Kleeff J, et al. Systematic review and meta-analysis of the role of defunctioning stoma in low rectal cancer surgery. Annals of surgery. 2008;248(1):52-60.
13. Rullier E, Laurent C, Garrelon JL, Michel P, Saric J, Parneix M. Risk factors for anastomotic leakage after resection of rectal cancer. The British journal of surgery. 1998;85(3):355-8.
14. Suding P, Jensen E, Abramson MA, Itani K, Wilson SE. Definitive risk factors for anastomotic leaks in elective open colorectal resection. Archives of surgery. 2008;143(9):907-11.
15. Telem DA, Chin EH, Nguyen SQ, Divino CM. Risk factors for anastomotic leak following colorectal surgery: a case-control study. Archives of surgery. 2010;145(4):371-6; discussion 6.
16. Leichtle SW, Mouawad NJ, Welch KB, Lampman RM, Cleary RK. Risk factors for anastomotic leakage after colectomy. Diseases of the colon and rectum. 2012;55(5):569-75.
17. Shahir MA, Lemmens VE, van de Poll-Franse LV, Voogd AC, Martijn H, Janssen-Heijnen ML. Elderly patients with rectal cancer have a higher risk of treatment-related complications and a poorer prognosis than younger patients: a population-based study. European journal of cancer. 2006;42(17):3015-21.
18. Rutten HJ, den Dulk M, Lemmens VE, van de Velde CJ, Marijnen CA. Controversies of total mesorectal excision for rectal cancer in elderly patients. The lancet oncology. 2008;9(5):494-501.
19. Damrauer SM, Bordeianou L, Berger D. Contained anastomotic leaks after colorectal surgery: are we too slow to act? Archives of surgery. 2009;144(4):333-8; discussion 8.
20. van Koperen PJ, van der Zaag ES, Omloo JM, Slors JF, Bemelman WA. The persisting presacral sinus after anastomotic leakage following anterior resection or restorative proctocolectomy. Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland. 2011;13(1):26-9.

21. Veenhof AA, Brosens R, Engel AF, van der Peet DL, Cuesta MA. Risk factors and management of presacral abscess following total mesorectal excision for rectal cancer. Digestive surgery. 2009;26(4):317-21.

22. van der Vaart MG, van der Zwet WC, Arends JW, Eeftinck Schattenkerk M, Eddes EH. Rectal carcinoma treated with short-term preoperative radiotherapy followed by abdominoperineal resection. Significantly more presacral abscesses with absence of local recurrence. Digestive surgery. 2006;23(3):173-7; discussion 7-8.

23. Bardini R, Asolati M, Ruol A, Bonavina L, Baseggio S, Peracchia A. Anastomosis. World journal of surgery. 1994;18(3):373-8.

24. Rahbari NN, Weitz J, Hohenberger W, Heald RJ, Moran B, Ulrich A, et al. Definition and grading of anastomotic leakage following anterior resection of the rectum: a proposal by the International Study Group of Rectal Cancer. Surgery. 2010;147(3):339-51.

25. Guenaga KF, Matos D, Wille-Jorgensen P. Mechanical bowel preparation for elective colorectal surgery. The Cochrane database of systematic reviews. 2011(9):CD001544.

26. Akbarshahi H, Andersson B, Norden M, Andersson R. Perioperative nutrition in elective gastrointestinal surgery--potential for improvement? Digestive surgery. 2008;25(3):165-74.

27. Hyman N, Manchester TL, Osler T, Burns B, Cataldo PA. Anastomotic leaks after intestinal anastomosis: it's later than you think. Annals of surgery. 2007;245(2):254-8.

28. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. Journal of chronic diseases. 1987;40(5):373-83.

29. Martijnse IS, Dudink RL, Kusters M, Vermeer TA, West NP, Nieuwenhuijzen GA, et al. T3+ and T4 rectal cancer patients seem to benefit from the addition of oxaliplatin to the neoadjuvant chemoradiation regimen. Annals of surgical oncology. 2012;19(2):392-401.

30. Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD, et al. The Clavien-Dindo classification of surgical complications: five-year experience. Annals of surgery. 2009;250(2):187-96.

31. Walker KG, Bell SW, Rickard MJ, Mehanna D, Dent OF, Chapuis PH, et al. Anastomotic leakage is predictive of diminished survival after potentially curative resection for colorectal cancer. Annals of surgery. 2004;240(2):255-9.

32. McArdle CS, McMillan DC, Hole DJ. Impact of anastomotic leakage on long-term survival of patients undergoing curative resection for colorectal cancer. The British journal of surgery. 2005;92(9):1150-4.

33. den Dulk M, Marijnen CA, Collette L, Putter H, Pahlman L, Folkesson J, et al. Multicentre analysis of oncological and survival outcomes following anastomotic leakage after rectal cancer surgery. The British journal of surgery. 2009;96(9):1066-75.

34. Bruce J, Krukowski ZH, Al-Khairy G, Russell EM, Park KG. Systematic review of the definition and measurement of anastomotic leak after gastrointestinal surgery. The British journal of surgery. 2001;88(9):1157-68.

35. de Campos-Lobato LF, Geisler DP, da Luz Moreira A, Stocchi L, Dietz D, Kalady MF. Neoadjuvant therapy for rectal cancer: the impact of longer interval between chemoradiation and surgery. Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract. 2011;15(3):444-50.

36. de Campos-Lobato LF, Stocchi L, da Luz Moreira A, Geisler D, Dietz DW, Lavery IC, et al. Pathologic complete response after neoadjuvant treatment for rectal cancer decreases distant recurrence and could eradicate local recurrence. Annals of surgical oncology. 2011;18(6):1590-8.

37. Habr-Gama A, Perez RO, Proscurshim I, Nunes Dos Santos RM, Kiss D, Gama-Rodrigues J, et al. Interval between surgery and neoadjuvant chemoradiation therapy for distal rectal cancer: does delayed surgery have an impact on outcome? International journal of radiation oncology, biology, physics. 2008;71(4):1181-8.

38. Tulchinsky H, Shmueli E, Figer A, Klausner JM, Rabau M. An interval >7 weeks between neoadjuvant therapy and surgery improves pathologic complete response and disease-free survival in patients with locally advanced rectal cancer. Annals of surgical oncology. 2008;15(10):2661-7.

39. Orsini RG, Thong MS, van de Poll-Franse LV, Slooter GD, Nieuwenhuijzen GA, Rutten HJ, et al. Quality of life of older rectal cancer patients is not impaired by a permanent stoma. European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology. 2013;39(2):164-70.

40. Rondelli F, Reboldi P, Rulli A, Barberini F, Guerrisi A, Izzo L, et al. Loop ileostomy versus loop colostomy for fecal diversion after colorectal or coloanal anastomosis: a meta-analysis. International journal of colorectal disease. 2009;24(5):479-88.

41. Sharma A, Deeb AP, Rickles AS, Iannuzzi JC, Monson JR, Fleming FJ. Closure of defunctioning loop ileostomy is associated with considerable morbidity. Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland. 2013;15(4):458-62.

42. Alexander AA, Eschelman DJ, Nazarian LN, Bonn J. Transrectal sonographically guided drainage of deep pelvic abscesses. AJR American journal of roentgenology. 1994;162(5):1227-30; discussion 31-2.

43. McGahan JP, Wu C. Sonographically guided transvaginal or transrectal pelvic abscess drainage using the trocar method with a new drainage guide attachment. AJR American journal of roentgenology. 2008;191(5):1540-4.

44. Khurrum Baig M, Hua Zhao R, Batista O, Uriburu JP, Singh JJ, Weiss EG, et al. Percutaneous postoperative intra-abdominal abscess drainage after elective colorectal surgery. Techniques in coloproctology. 2002;6(3):159-64.

4.2 Treatment of anastomotic leakage

Treatment of Colorectal Anastomotic Leakage: Results of a Questionnaire amongst Members of the Dutch Society of Gastrointestinal Surgery
Daams F, Slieker JC, Tedja A, Karsten TM, Lange JF.
Digestive Surgery 2012;29(6):516-21

Abstract

Anastomotic leakage after colorectal surgery is correlated with considerable morbidity and mortality. Although many studies focus on risk factors and detection, studies on the treatment strategy for colorectal anstomotic leakage are scarce. A national questionnaire amongst 350 members of the Dutch Society for Gastrointestinal Surgery was undertaken on the current treatment of colorectal anastomotic leakage. The response was 40% after two anonymous rounds. 27% Of the respondents states that a leaking anastomosis above the level of promontory should be salvaged in ASA1-2 patients less than 80 years old, for ASA3 and/or >80y this percentage is 7,3%. For an anastomosis under the promontory 50% of the respondents chooses preserving the anastomosis for ASA1-2 compared to 17% for ASA3 and/or >80y. In ASA1-2 patients with a local abscess after a rectum resection without protective ileostomy 31% of the respondents will create an protective ileostomy, 40% breaks down the anastomosis to create a definite colostomy, in ASA3 and/or >80y 14% of the respondents creates a protective ileostomy and 63% a definitive colostomy. In ASA1-2 patients with peritonitis after a rectum resection with deviating ileostomy 31% prefers a laparotomy for lavage and repair of the anastomosis, 25% for lavage without repair and 36% of the respondents prefers to break down the anastomosis. When the patient is ASA3 and/or> 80y 13% prefers repair, 9% a lavage and 74% breaking down the anastomosis. This questionnaire shows that in contrast to older people more surgeons make an effort to preserve the anastomosis in younger people.

Introduction

Anastomotic leakage after colorectal surgery (CAL) is a major complication with a reported incidence of 2,8 to 12,3% [1, 2]. It leads to increased morbidity (extended hospital stay, re-operation, permanent enterostomy and higher recurrence rates for carcinoma) and even up to 7% mortality [3, 4]. Many studies describe risk factors for CAL [5, 6], several studies describe prevention methods [7, 8], and some describe diagnostic procedures for early detection [9-12], but only a few studies have described treatment options for CAL [13-15]. In treating patients with anastomotic leakage many factors should be considered before engaging a therapeutic strategy, such as patient age, co-morbidities, level of anastomosis, delay after primary operation, presence of abdominal sepsis, degree of anastomotical dehiscence. Definitions of type of leakage are not univocal [16] and although recently the International Study Group of Rectal Cancer proposed a clinical grading, this is not widely used in literature nor in daily clinical practise [17]. Prospective randomised studies on treatment are difficult to design due to the lack of a golden standard and due to logistic problems. To overcome these problems Phitayakorn et al. used a Delphi-round to establish a treatment algorithm for CAL [18]. In their study, the authors came to a consensus among 43 experts on colorectal surgery and radiology. The current study was undertaken simultaneously and describes the results of a questionnaire amongst all members of the Dutch Society of Gastrointestinal Surgery. Its goal is to reflect the surgical decision making when facing CAL.

Material and methods

A written questionnaire was developed by the investigators containing multiple-choice questions on treatment strategies in colorectal anastomotic leakage based on clinical cases. The questionnaire can be found in Table 1. The cases were formulated to measure the effect of certain patient factors on the strategy of the surgeon treating CAL. Patient factors included anastomotic leakage above or below the level of the promontory, the percentage of anastomotical dehiscence, a primary operation with or without deviating ileostomy, ASA-classification 1-2 or >3. A few definitions were stated in advance, such as that an anastomosis cranially to the promontory was considered to be any anastomosis after right or left sided colectomy and sigmoid resection. In this article referred to as intraperitoneal. An anastomosis caudally to the promontory was considered any anastomosis after rectum resection and is referred to as extraperitoneal. Small bowel anastomosis was not subject to the questionnaire nor

was the ileoanal anastomosis. Furthermore a small leak was defined as <30% of the circumference, a large leak was defined as >30%. The questionnaire was sent to all members of the Dutch Society of Gastrointestinal Surgery (NVGIC) by mail. At the time of sending the questionnaire this society has 347 members, of which 53 were not practising colorectal surgery. The remaining 294 members were invited to answer the questionnaire in 2 anonymous rounds. Data were analysed by 1 investigator, who was blinded for the identity of the respondent.

Results

Response rate was 40 % (137/294) over 2 anonymous rounds.

General considerations

Prior to any intervention, 54% of the responding surgeons wants to be informed on the extend of anastomotical dehiscence. A majority of 72% believes that a preplanned, patient-centred strategy in treating CAL leads to a better outcome than when no strategy is followed. When a deviating enterostomy is created 61% of the respondents creates an ileostomy and 39% a colostomy.

Level of anastomosis

Twenty-seven percent of the respondents assume that a leaking anastomosis cranially to the level of the promontory can be preserved in ASA 1-2 patients, younger than 80 years old. For patients ASA =/> 3 and/or older than 80 years old this percentage is only 7 %. When the anastomosis is caudally to the level of the promontory 50% of the respondents will preserve the anastomosis in ASA 1-2 patients and 17% for ASA =/> 3 and/or >80 years old.

Local abscess

In ASA 1-2 patients with a local abscess with a major anastomotic leakage (>30 % circumferential dehiscence) after rectum resection without deviating ileostomy 60% of the respondents choose a anastomosis-sparing treatment, 40% break down the anastomosis and create a permanent colostomy. In ASA =/> 3 and/or > 80 years old these percentages are 37% and 63% respectively.

Questionnaire

1 When treating a patient with CAL, would you like to be informed on the extend of leakage?
a yes
b no

2 In your opinion, would a preplanned strategy improve outcome compared to ad hoc decisionmaking?
a yes
b no

3 A deviating ileostomy is preferable above a deviating colostomy.
a true
b false

4a When an intraperitoneal anastomosis is leaking in an ASA 1-2, <80 year patient, this anastomosis should be preserved
a true
b false

4b When an intraperitoneal anastomosis is leaking in an ASA 3, >80 year patient this anastomosis should be preserved
a true
b false

5a When an extraperitoneal anastomosis is leaking in an ASA 1-2, <80 year patient this anastomosis should be preserved
a true
b false

5b When an extraperitoneal anastomosis is leaking in an ASA 3, >80 year patient this anastomosis should be preserved
a true
b false

6a A local abscess as a presentation of a major leakage in an ASA 1-2 , < 80 year patient after rectal resection without deviating ostomy, should be treated by
a drainage of the abscess,
b relaparotomy, drainage of the abscess, deviating ileostomy
c relaparotomy, drainage of the abscess, repair of the anastomosis,
d relaparotomy, drainage of the abscess, repair of the anastomosis, deviating ileostomy
e relaparotomy, drainage of the abscess, breakdown of the anastomosis and permanent colostomy

6b A local abscess as a presentation of a major leakage in an ASA 3 , >80 year patient after rectal resection without deviating ostomy, should be treated by
a drainage of the abscess,
b relaparotomy, drainage of the abscess, deviating ileostomy
c relaparotomy, drainage of the abscess, repair of the anastomosis,
d relaparotomy, drainage of the abscess, repair of the anastomosis, deviating ileostomy
e relaparotomy, drainage of the abscess, breakdown of the anastomosis and permanent colostomy

7a Faecal peritonitis from a minor leak in an extraperitoneal anastomosis with deviating ileostomy in an ASA 1-2, <80 year patient should be treated by
a relaparotomy for lavage and drainage
b relaparotomy for lavage and drainage, repair of anastomosis
c relaparotomy for lavage, breakdown of anastomosis

7b Faecal peritonitis from a minor leak in an extraperitoneal anastomosis with deviating ileostomy in an ASA 3, >80 year patient should be treated by
a relaparotomy for lavage and drainage
b relaparotomy for lavage and drainage, repair of anastomosis
c relaparotomy for lavage, breakdown of anastomosis

Table 1. Questionnaire

General peritonitis

In ASA 1-2 patients with overt faecal peritonitis with a small (<30% circumferential) dehiscence after rectum resection with a deviating ileostomy, 25% of the respondents carry out a laparotomy for peritoneal wash-out, 31% add anastomotical repair to this and 36% break down the anastomosis in addition to peritoneal wash-out. In a patient that is ASA 3 and/or > 80 years old, these clinical conditions render these numbers 9%, 13% and 74% respectively (Figure 1).

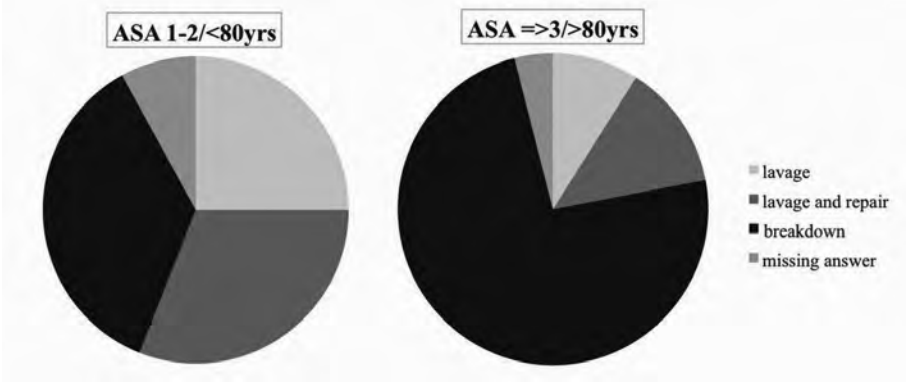

Figure 1. Results for treatment in case of fecal peritonitis and<30% circumferential dehiscence of the anastomosis. Left: distribution of answers of respondents in patients < 80 years old and ASA < 3. Right: in patients > 80 years old and ASA >/= 3.

Discussion

This study shows that surgeons are in some extend influenced by patient factors and surgical factors when treating a patient with CAL. Some general considerations should be taken in mind when the results are valued.

This questionnaire was performed amongst the members of the Dutch Society of Gastrointestinal Surgery, with a response rate of 40%. Although this percentage could lead to selection bias, the response-rate is similar to other nationwide questionnaires [19] and given the absolute number of 139 returned questionnaires it is unlikely that there is a strong response bias.

This study was undertaken before the International Study Group of Rectal Cancer offered a definition of CAL. Therefore, definitions used for the present study are not internationally accepted. Nevertheless, our definitions were constructed based on clinical experience and are in our opinion applicable to the daily surgical practice.

This lack of standardisation could be an explanation for the heterogeneity of the answers of the respondents. Other factors could be the different patient population and type of hospital of the individual surgeons. Since our questionnaire was fully anonymous, no further clarification could be given on these topics. Furthermore, it can be hypothesised that some surgeons are not led by the proposed factors as age, ASA-score, location of anastomosis and therefore treat all patients uniformly in the case of CAL. Moreover other factors as primary disease, immune status and timing after primary operation could be of interest in decision making, although these factors were not the scope of this article.

Patient factors

This study shows that the majority of the responders believes that treatment according to a personalised strategy that incorporates these patient factors leads to improved outcome. In designing a treatment strategy for CAL, patient factors are the most important input. Studies have shown that co-morbidities as diabetes, renal insufficiency, and age are on one hand, amongst others, independent risk factors for CAL [20], but are also negative predictors for secondary peritonitis as well [21]. Contrastingly, other studies show no increased risk of complication in elderly [22, 23]. This study shows that age and higher ASA score do influence the surgeon, leading to a tendency to preserve the anastomosis in younger patients and breakdown the anastomosis in older patients. Surgeons might have the conception that an anastomosis sparing strategy might imply multiple reoperations, radiological interventions and delayed ICU-admittance. As this leads to a serious burden for the patient's health status and require an enormous mental effort of the patient and family, it should be conserved for younger and fitter patients. Next to this, prior to endorsing a treatment, doctors and patients should be fully committed to its accomplishment.

Surgical factors

Leakage of an intraperitoneal anastomosis is believed to be less common than after extraperitoneal anastomosis [24]. The presentation of anastomotic dehiscence varies largely from local abscesses and pelvic sepsis as a result of extraperitoneal leakage to overt abdominal sepsis as a sign of intraperitoneal leakage. Both localisation and presentation of the leak are important factors when a treatment strategy is planned. In our study, this is shown by the fact that 50% of the surgeons chooses to preserve the anastomosis when it occurs as a localised extraperitoneal abscess in ASA 1-2 patients, compared to 27% of the surgeons when the anastomosis is intraperitoneal.

Possibly surgeons apply other techniques for local control of extraperitoneal abscesses like radiological drainage, marsupialisation and endosponge. Although these new techniques seem promising, they also have their back draws [25, 26]. These options were not offered in our questionnaire, since it is considered common surgical practice to treat a minor leak with an adjacent abscess with radiological drainage with or without diversion.

Local repair of a leaking anastomosis was condemned in the literature, until some support of anastomotical preservation appeared [13, 27]. Wind et al. showed that of 25 patients that were re-operated for CAL, 11 were treated with preserving the anastomosis, without any sign of recurrence of leakage[27]. In contrast to this, Rickert et al. recently have shown that re-leakage occurred in 5 of 9 patients in which repair was attempted [14]. In the same study a complete re-do of the anastomosis was successful in 84% of the patients (2/12). In a retrospective study by Ruggiero et al. for 21 out of 32 patients with CAL a conservative treatment strategy was designed. In just 3 (14%) of these patients a laparotomy was needed since clinical condition worsened [28]. The current study shows that preserving the anastomosis is considered an option by 56% of the surgeons in young patients with peritonitis. When the patient's status permits it and repair is attempted, a new anastomosis with diversion should be considered.

In a retrospective study by Paliogiannis et al. early leakages (median 3.6 postoperative days) were treated more aggressively and had a greater dehiscence than leakages that became clinically apparent after a median time of 5.6 days [29]. Furthermore, the authors found that late leakage had a milder clinical course than early leakage. When leakages appear even later, surgeons might be more reluctant to operate since dense adhesions could hamper safe dissection. Timing of leakage and reoperation after the primary operation was not a factor in the questionnaire, nevertheless for aforementioned reasons it should be taken in consideration when treating CAL.

Peritonitis due to anastomotic leakage leads to significant mortality of 6-20% [30]. Treatment of faecal peritonitis is multidisciplinary and requires the utmost commitment of all that are involved. Some studies provide guides for the surgeons when planning the surgical aspects of the treatment of abdominal sepsis. The RELAP-trial has shown that an on demand strategy for the indication of relaparotomy does not lead to increased morbidity and mortality compared to planned relaparotomy, while reducing negative laparotomies and costs significantly [30]. Studies on management of anastomotic leaks show large variations in surgical procedures, with breakdown of anastomosis as single most performed operation [14, 32]. A recent retrospective

study by Fraccalvieri et al. showed that anastomosis-sparing treatment by drainage and diverting loop ileostomy leads to low morbidity and mortality and high stoma reversal rates, compared to breakdown of the anastomosis [33]. These results seem to pave the way for a randomized trial in order to rule out selection bias.

Simultaneous to this study, Phitayakorn et al. performed a Delphi-round among a group of specialists, producing an algorithm for the treatment of AL [18]. In their study patient factors include localisation of leak, extend of anastomotical dehiscence, presence and extend of abdominal sepsis, presence of diversion. The algorithm contains a useful combination of surgical and radiological treatment options. At several key-points in the decision-making, such as to repair or breakdown the anastomosis at relaparotomy, the authors' algorithm leaves space for individualisation. The present study offers the current opinion amongst colorectal surgeons on those critical moments when patient characteristics are considered. It shows that patient characteristics contribute to the decision-making as young healthy patients tolerate an aggressive operative strategy in contrast to elderly patients in whom a more conservative therapy is chosen.

Concluding, this study shows that Dutch colorectal surgeons tend to preserve the anastomosis in non-septic young patients, whereas the anastomosis is broken down in older patients and/or abdominal sepsis as a rule. This study emphasizes the need for a multicentre randomized trial comparing these two strategies in colorectal anastomotic leakage.

References

1. Alves, A.M., et al., Antibody response in mice immunized with a plasmid DNA encoding the colonization factor antigen I of enterotoxigenic Escherichia coli. FEMS Immunol Med Microbiol, 1999. 23(4): 321-30.
2. Yeh, C.Y., et al., Pelvic drainage and other risk factors for leakage after elective anterior resection in rectal cancer patients: a prospective study of 978 patients. Ann Surg, 2005. 241(1): 9-13.
3. Walker, K.G., et al., Anastomotic leakage is predictive of diminished survival after potentially curative resection for colorectal cancer. Ann Surg, 2004. 240(2): 255-9.
4. Eriksen, M.T., et al., Anastomotic leakage following routine mesorectal excision for rectal cancer in a national cohort of patients. Colorectal Dis, 2005. 7(1): 51-7.
5. Matthiessen, P., et al., Risk factors for anastomotic leakage after anterior resection of the rectum. Colorectal Dis, 2004. 6(6): p. 462-9.
6. Biondo, S., et al., Anastomotic dehiscence after resection and primary anastomosis in left-sided colonic emergencies. Dis Colon Rectum, 2005. 48(12): 2272-80.
7. Jesus, E.C., et al., Prophylactic anastomotic drainage for colorectal surgery. Cochrane Database Syst Rev, 2004(4): p. CD002100.
8. Tan, W.S., et al., Meta-analysis of defunctioning stomas in low anterior resection for rectal cancer. Br J Surg, 2009. 96(5): 462-72.
9. Eckmann, C., et al., Anastomotic leakage following low anterior resection: results of a standardized diagnostic and therapeutic approach. Int J Colorectal Dis, 2004. 19(2): p. 128-33.
10. Komen, N., et al., Anastomotic leakage, the search for a reliable biomarker. A review of the literature. Colorectal Dis, 2008. 10(2): p. 109-15; discussion 115-7.
11. den Dulk, M., et al., Improved diagnosis and treatment of anastomotic leakage after colorectal surgery. Eur J Surg Oncol, 2009. 35(4): p. 420-6.
12. Matthiessen, P., et al., Is early detection of anastomotic leakage possible by intraperitoneal microdialysis and intraperitoneal cytokines after anterior resection of the rectum for cancer? Dis Colon Rectum, 2007. 50(11): p. 1918-27.
13. Watson, A.J., et al. Salvage of large bowel anastomotic leaks. Br J Surg, 1999. 86(4): 499-500.
14. Rickert, A., et al., Management and outcome of anastomotic leakage after colonic surgery. Colorectal Dis, 2010. 12(10 Online): e216-23.
15. Verlaan, T., et al., Early, minimally invasive closure of anastomotic leaks: a new concept. Colorectal Dis, 2011. 13 Suppl 7: 18-22.
16. Bruce, J., et al., Systematic review of the definition and measurement of anastomotic leak after gastrointestinal surgery. Br J Surg, 2001. 88(9): 1157-68.
17. Rahbari, N.N., et al., Definition and grading of anastomotic leakage following anterior resection of the rectum: a proposal by the International Study Group of Rectal Cancer. Surgery, 2010. 147(3). 339-51.
18. Phitayakorn, R., et al., Standardized algorithms for management of anastomotic leaks and related abdominal and pelvic abscesses after colorectal surgery. World J Surg, 2008. 32(6): 1147-56.
19. Slieker, J.C., et al., Bowel Preparation Prior to Laparoscopic Colorectal Resection: What Is the Current Practice? J Laparoendosc Adv Surg Tech A, 2011.
20. Cong, Z.J., et al., Influencing factors of symptomatic anastomotic leakage after anterior resection of the rectum for cancer. World J Surg, 2009. 33(6): 1292-7.
21. McGillicuddy, E.A., et al., Factors predicting morbidity and mortality in emergency colorectal procedures in elderly patients. Arch Surg, 2009. 144(12):1157-62.
22. Pelloni, A., Colorectal surgery in patients over 80 years old. Hepatogastroenterology, 2012. 59(113): p. 120-3.
23. Reissman, P., et al. Outcome of laparoscopic colorectal surgery in older patients. Am Surg, 1996. 62(12): 1060-3.
24. Platell, C., et al., The incidence of anastomotic leaks in patients undergoing colorectal surgery. Colorectal Dis, 2007. 9(1): 71-9.

25. Brehant, O., et al., Stapled marsupialisation of chronic low rectal anastomotic sinuses. Int J Colorectal Dis, 2009. 24(10): 1233-7.
26. Arumainayagam, N., M. Chadwick, and A. Roe, The fate of anastomotic sinuses after total mesorectal excision for rectal cancer. Colorectal Dis, 2009. 11(3): 288-90.
27. Wind, J., et al., Laparoscopic reintervention for anastomotic leakage after primary laparoscopic colorectal surgery. Br J Surg, 2007. 94(12): 1562-6.
28. Ruggiero, R., et al., Post-operative peritonitis due to anastomotic dehiscence after colonic resection. Multicentric experience, retrospective analysis of risk factors and review of literature. Ann Ital Chir. 2011 Sep-Oct; 82(5):369-75.
29. Paliogiannis, P., et al., Conservative management of minor anastomotic leakage after open elective colorectal surgery. Ann Ital Chir, 2012. Jan-Feb; 83(1): 25-8.
30. Alberts, J.C., A. Parvaiz, and B.J. Moran, Predicting risk and diminishing the consequences of anastomotic dehiscence following rectal resection. Colorectal Dis, 2003. 5(5): 478-82.
31. van Ruler, O., et al., Comparison of on-demand vs planned relaparotomy strategy in patients with severe peritonitis: a randomized trial. JAMA, 2007. 298(8): 865-72.
32. Alves, A., et al., Management of anastomotic leakage after nondiverted large bowel resection. J Am Coll Surg, 1999. 189(6): 554-9.
33. Fraccalvieri, D., et al., Management of colorectal anastomotic leakage: differences between salvage and anastomotic takedown. Am J Surg, 2011 May 18

5

Quality of Life

5.1 Quality of life 10 years after anastomotic leakage

Longterm Quality of Life after anastomotic leakage following colorectal surgery. A multicentre, case-matched cohort
F. Daams, J vd Broek, D. Hogerzeil, K de Valk, T.M. Karsten, J.J. Scheepers, P.G. Doornebosch, E.J.R. de Graaf, J.F. Lange.
Submitted Colorectal Disease

Abstract

In order to investigate the long term effects of clinical anastomotic leakage after colorectal surgery (CAL) on surgical outcome and Health Related Quality of Life, this multicentre, case-controlled study was set up. Patients after CAL (group A; n = 49) were matched with patients without CAL (group B; n = 96) for sex, type of surgery, indication, time after surgery and hospital. Surgical outcome was scored in a standardized fashion, HRQoL was assessed by the SF 36, EORTC-QLQ-C30, EORTC-C29, EQ-5D-5L and the Body Image Scale. Although there was no difference in all cause mortality after a follow up of 10 years after surgery (44.6% in group A; 38.3% in group B; p = 0.097), reoperations, complications other than CAL, permanent stomas and scars were more frequent in group A. Using the SF-36, group B scored higher in the Physical Component Scale compared to group A (PCS group A: 42.1; group B: 46.3; $p < 0.05$). The EQ-5D-5L showed a significant difference between both groups when the VAS-score was compared between both groups (VAS group A: 69.9 vs group B: 77.2; $p < 0.05$). The index value for the 5 dimensions did not differ between both groups. Mean Body Image scores were significantly higher in group A (BIS group A: 8.9 vs group B: 4.8; $p < 0.01$). This difference was even more pronounced when patients with a stoma were not included in both groups (BIS group A_{st-}: 9.6 vs group B_{st-}: 4.3; $p < 0.05$). Cancer patients group A (group A_c: n = 22) scored significantly worse than cancer patients in group B (group B_c: n = 66) in the Global Health Score (GHS) and the Functional Score (FS) of the EORTC questionnaires. These results show detrimental effects on aspects of HRQoL for patients after colorectal anastomotic leakage even after 10 years, compared to patients after uncomplicated colorectal surgery. Understanding these poor patient reported outcomes and objective surgical outcomes should raise awareness of the treating surgeon for their patient's functional and emotional vulnerability even many years after this dreadful complication

Introduction

Clinical anastomotic leakage (CAL) is reported in 7,5% of patients after colorectal resection over the last years in the Netherlands[1]. Short-term consequences of this complication may include sepsis, multiple organ failure, reoperations, necessity of a permanent stoma and ultimately even death[2]. It is hypothesized that, next to these detrimental short-term results of CAL, long-term aspects of Health Related Quality of Life (HRQoL) are negatively influenced by CAL as well. A few studies have been performed to investigate long term HRQoL after complicated colorectal resections[3-9]. However, their results are difficult to interpret since most of these studies are of inadequate power or lack a control group. Furthermore, different durations of follow up and different investigated aspects of HRQoL render these studies incomparable. Therefore, this case-controlled study was designed to extensively investigate the effect of CAL on long-term surgical outcome and patient reported HRQoL in patients after colorectal resection using widely used and accepted questionnaires.

Methods

A total of 3771 Patients had a colorectal resection with anastomosis or restoration of continuity after Hartman's procedure in the period between 1997 and 2007. All of them were operated in one university hospital and two regional teaching hospitals in the Southwest of the Netherlands and were over 18 years old. Eligible living patients after CAL (Group A) were matched with control patients (Group B) in a 1:2 ratio, matching sex, type of surgery, indication, follow up after surgery and hospital. Both groups were contacted by telephone and invited to visit the outpatient clinic. After informed consent, medical files were examined in a standardized fashion; patients were subject to a short physical examination and completed the HRQoL questionnaires. For both groups, the following items were recorded: sex, age, medical history (both medical and surgical), indication, perioperative therapy, type of surgery, type of anastomosis, deviating stoma. CAL was considered a leakage for which the patient had to be reoperated (Grade C according to classification by Rahbari et al.) [10]. The local medical ethical committees approved of the study protocol.

Surgical outcome

In order to evaluate surgical outcome, items such as type and number of other complications than CAL, number and type of reoperations were registered. Physical examination included recording of the number and size of scars, presence of stoma, presence of incisional and/or parastomal hernias.

Questionnaires

The Dutch version of the SF-36 was used to measure HRQoL in terms of functional health and wellbeing. This generic survey is based on 8 health domains, which together form two summary components: the Physical Component Summary (PCS) and the Mental Component Summary (MCS). Data was transformed to a norm based score in which 50 was the average score (SD = 10). Additionally to the SF-36, general patient reported HRQoL was measured by the EQ-5D-5L [11]. This 2-paged questionnaire consists of 5 questions that cover 5 health domains (Mobility, Self-care, Usual Activities, Pain/discomfort and Anxiety/depression). Each domain has 5 levels: no problems, slight problems, moderate problems, severe problems and extreme problems. Furthermore a visual analogue scale reflects the patient self-reported health. Data from the 5 domains were translated according to the EuroQol Group's translation guidelines. For the oncology patients in this cohort, specific HRQoL questionnaires for cancer patients were used; the EORTC QLQ-C30 and the colorectal extension EORTC-C29 [12]. Data obtained from these questionnaires were linearly transformed to a scale from 0 to 100. A high score for the general health and functional domain resembles a good patient reported quality of life, whereas a high score on the symptom scale represent poor outcome. The Body Image Score (BIS) was used, since abovementioned questionnaires lack specific self-image and body estimation domains. The score covers a 0 to 30 range, in which 30 represents the highest appreciation of body image. For this questionnaire a subgroup analysis was performed for patients with and without stoma, or patients that previously had a stoma.

Statistics

For all questionnaires, missing values were excluded from the domain score, when more than half of the domain was completed. When more than half of the values were missing, the domain was excluded. All calculations were carried out using SPSS 19 (2010, SPSS inc, IBM). Student T-test, Chi-square and Mann-Whitney test were used for the appropriate values comparing Group A and B, Kruskall-Wallis was used comparing >2 subgroups. P-level of <0.05 was considered significant.

Results

A total of 177 Patients had CAL, requiring reoperation (177/3771 (4.7%)). A total of 1456 patients died between the operation and start of this study in 2012 (79 of 177 (44.6%) in group A; 1377 of 3783 (38.3%) in group B; p = 0.097). Of 98 eligible patients with CAL, 49 patients (group A) consented to participating in this study and were matched with 96 non-leakage controls (group B). Table 1 shows the baseline characteristics of both groups. Group A consisted of younger patients and fewer patients had cancer compared to group B. Other variables as sex, BMI, smoking, comorbidities, type of surgery, deviating stomas were equally distributed over both groups.

		Group A	%	Group B	%	p-value
age		62.5 yrs		67.5 yrs		0.025
sex						
	male	26	56.5	66	68.8	0.071
	female	23	50.0	30	31.3	
indication						
	benign	27	58.7	30	31.3	0.007
	malignant	22	47.8	66	68.8	
perioperative therapy						
	radiotherapy	2	9.1	16	24.2	0.218
	chemotherapy	8	36.4	12	18.2	0.076
type of surgery						
	restoration of Hartman	2	4.3	3	3.1	0.113
	right-sided colectomy	12	26.1	24	25.0	
	left-sided colectomy	6	13.0	7	7.3	
	sigmoid resection	13	28.3	39	40.6	
	anterior resection	15	32.6	24	25.0	
initial deviating stoma						
	yes	6	13.0	9	9.4	0.578
	no	43	93.5	87	90.6	
follow up		9.8 yrs		9.7 yrs		0.924

Table 1. Patient characteristics

Surgical outcome

In Table 2 surgical outcome parameters are shown. There was no difference in all cause mortality almost 10 years after surgery. Reoperations, complications other than AL, permanent stomas and scars were more frequent in group A. Although scars were larger in group A, there was no difference in incidence of clinical relevant incisional hernia at the time of this study.

		Group A	%	Group B	%	p-value
complications*						
	number / patient	0.69		0.3		0.002
	classification**					
alive at follow up						
number of reoperation***		3.3		0.36		<0.001
stoma						
	reversed stoma	8	16	8	8	
	permanent stoma	19	39	3	3	<0.001
incisional hernia		8	16	17	18	0.494
scars						
	number / patient	2.51		1.42		<0.001
	length (cm)	27.9		23.4		0.001
	width (cm)	3		1.4		<0.001

Table 2. Surgical outcome. * = complications during primary admission other than CAL, ** = according to the Clavien-Dindo classification, *** = by definition + 1 for group A

Health Related Quality of Life

Patient reported outcome measured by the SF-36 is shown in Figure 1. Missing score percentage was 0.21%. The scores for the Physical Component Scale were higher in group B compared to group A (PCS group A: 42.1 vs group B: 46.3; $p < 0.05$). The score for the Mental Component Scale was not significantly different between both groups.

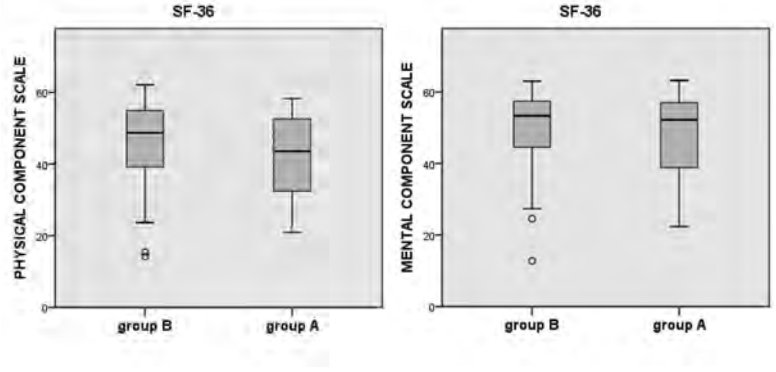

Figure 1. Boxplots of SF36 outcomes for physical component scale (group A: 42.1, group B: 46.3; $p < 0.05$) and mental component scale (group A: 48.2, group B: 50.3; $p = 0.23$)

The EQ-5D-5L (Figure 2) showed a significant difference between both groups when the VAS-score was compared between both groups (VAS group A: 69.9 vs group B: 77.2; $p < 0.05$). The index value for the 5 dimensions did not differ between both groups. Of the items 0.69% were missing.

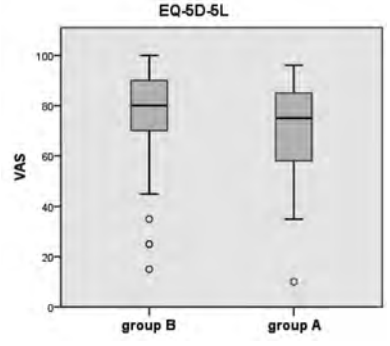

Figure 2. Boxplot for Visual Analogue Score according to the EQ-5D-5L (group A: 69.9, group B: 77.2; $p < 0.05$).

The Body Image Scale (Figure 3) had 1.2% missing values. Mean scores were significantly higher in group A (BIS group A: 8.9 vs group B: 4.8; $p < 0.01$). When the subgroup of patients without a stoma was analysed, a difference was observed between patients from group A without a stoma compared to patients in group B without a stoma (BIS group A_{st-}: 9.6 vs group B_{st-}: 4.3; $p < 0.05$).

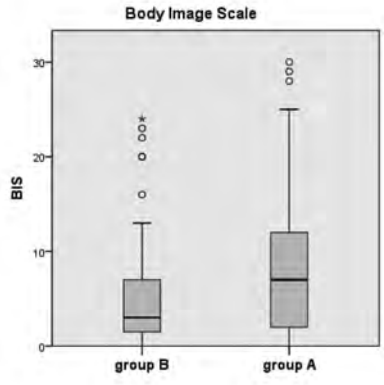

Figure 3. Boxplot for scores of both groups according to the Body Image Scale (group A: 8.9, group B: 4.8; $p < 0.01$).

Cancer patients in both groups (group A_c: n = 22, group B_c: n = 66) completed the EORTC-QLQ-C30 and C29 supplement for colorectal cancer patients with missing values in 0.1% and 1.2% respectively. As depicted in Figure 4, regarding Global Health Score (GHS), group A_c scored significantly worse than group B_c (GHS group A_c: 70.4 vs group B_c: 81.2; $p < 0.05$). Group A_c showed a significant lower score for the Functional Score (FS) in the EORTC-C29 compared to group B (FS group A_c: 69.0 vs group B_c: 82.8; $p < 0.05$). All other scores resembled a favourable outcome for group B, but none of these reached significance.

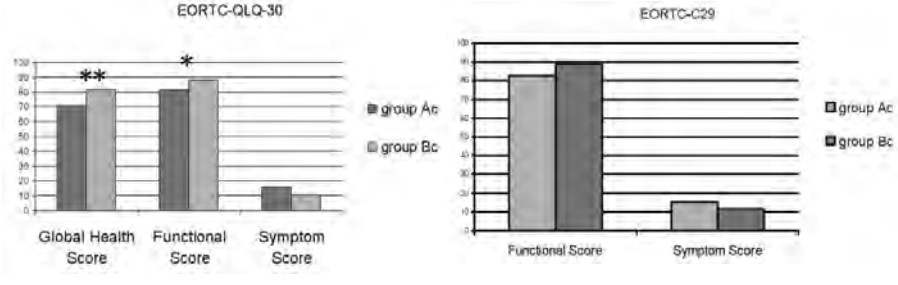

Figure 4. EORTC-QLQ-30 and -C29 outcome for subgroup of cancer patients. * = significant difference for Global Health Score (group Ac: 70.4, group Bc: 81.2; $p < 0.05$). ** = significant difference for Functional Score (group Ac: 69.0, group Bc: 82.8; $p < 0.05$)

Discussion

This study shows that for CAL-survivors after restorative colorectal surgery surgical outcome is worse and many aspects of quality of life are significantly reduced. Where other studies have previously provided data on short term outcome, this study confirms sustained detrimental effects of CAL even after 10 years.

Survival was not significantly different between the two cohorts, a finding which is comparable to the data by Lee et al. In that study the overall survival was 80.2% for non-leakage patients, compared to 64.9% (p = 0.170) for patients after CAL. Other parameters for surgical outcome showed significantly worse results for patients after CAL. Both creation of a stoma as part of treatment of CAL was more frequent and the restoration of continuity occurred less often in group A, corresponding to findings of other authors, who identified CAL as independent negative risk factor for stoma reversal [13 14]. Patients in group A showed more and larger scars than group B, but at this point in time no increased incidence of incisional hernia. This latter finding is in contrast to the finding by Bensley et al who identified multiple reoperations as independent risk factor for subsequent incisional hernia in a large cohort [15]. Possibly our study population was too small to produce a similar significant difference.

Health Related Quality of Life

When general items of HRQoL were compared between both groups, group A scored significantly worse in the Physical Component Scale of the SF-36. This finding almost 10 years after primary surgery is comparable to reports of reduced short term HRQoL as published by Marinatou et al. [5], who performed a case matched study on short term HRQoL after colorectal resections in which 25 patients after CAL scored lower on emotional and social functional domains as well as general HRQoL compared to 50 patients without CAL.

However a small but well designed study by Riss et al. showed no differences in fecal incontinence, constipation, sexual functioning and general HRQoL after a median follow-up of 107 months, although urinary incontinence was significantly impaired in patients after CAL [9]. Another study reported worse mental component scores using the SF-36 questionnaire over three years after rectum resection for patients after CAL compared to non-leakage patients [7].

For subjective QoL, as scored by the EQ-5D-5L VAS, the patient-reported HRQoL in group A was worse than in group B. This subjective assessment did not match the overall index-value that was based on five questions on five different domains. To our knowledge this is the first report on long term HRQoL measured by the EQ-5D-5L in colorectal surgery patients in both uncomplicated cases as well as after CAL.

For estimation of the effect of CAL on patient body estimation the Body Image Scale was used, showing worse scores for patients after CAL. This could be explained by the higher number of patients with a stoma in group A. However, when a subgroup was analysed in which patients with a stoma were excluded from the analysis, group A still showed worse scores than group B (data not shown). As patients with low body image are prone to depression, even after 10 years treating doctors should be aware of this risk in patients after CAL, both with or without stoma [16].

When cancer survivors were separately analysed using cancer specific questionnaires EORTC-QLQ-30 and colorectal surgery extension EORTC-C29, group A_c scored significantly worse than group B_c on the domain of general health and colorectal function. Next to being significantly different the absolute difference between the group's mean scores is also clinically relevant [17], moreover since many studies report normalisation of patient reported HRQoL over time. This might be the result of actual improved patient reported HRQoL but response shift might also play a role [18]. Decreased general health might lead to reduced physical activity which is also associated to higher somatisation [19]. Arndt and co-workers found that although functional problems and symptoms are reported more frequent in older patients, younger patients report lower scores compared to their healthy contemporaries three years after the diagnosis of colorectal cancer[20]. Recently a paper was published in which patients in the CLASSIC-trial either after open or laparoscopic colorectal resection were analysed for HRQoL after 3, 6, 18 and 36 months using the EORTC QLQ-C30, -CR38 and EQ-5D questionnaires[6]. Those that suffered complications (wound infections, cardiopulmonary complications, CAL, etc) scored significantly less on domains of Physical and Social Function, Role Functioning, Body Image, Mobility, Self-care and Pain/Discomfort. According to our study these short term HRQoL results seem to sustain after 10 years. However, age plays an important role as for survivors of colorectal cancer after ten years, younger patients seem to have consistent lower scores for some domains (role, cognitive, emotional and social functioning, bowel dysfunction and fatigue), while older patients score even lower than younger patients[21]. This finding reinforces our results, given that the mean age in our study was lower in the CAL group.

Although no preoperative baseline data was obtained in our study population, the matched control group provides a valuable comparison of our results. Particularly, due to the long interval between primary surgery and this study we have selected a subgroup of survivors, improving comparability between these two groups.

In conclusion, our results show detrimental effects on aspects of HRQoL for patients after colorectal anastomotic leakage even after 10 years, compared to patients after uncomplicated colorectal surgery. Knowledge of these worse patient reported outcomes and objective surgical outcomes could raise awareness of the treating surgeon for their patient's functional and emotional vulnerability even many years after this dreadful complication.

References

1. Bakker IS, Grossmann I, Henneman D, Havenga K, Wiggers T. Risk factors for anastomotic leakage and leak-related mortality after colonic cancer surgery in a nationwide audit. *Br J Surg* 2014;101(4):424-32.
2. Eckmann C, Kujath P, Schiedeck TH, Shekarriz H, Bruch HP. Anastomotic leakage following low anterior resection: results of a standardized diagnostic and therapeutic approach. *Int J Colorectal Dis* 2004;19(2):128-33.
3. Lim M, Akhtar S, Sasapu K, Harris K, Burke D, Sagar P, et al. Clinical and subclinical leaks after low colorectal anastomosis: a clinical and radiologic study. *Dis Colon Rectum* 2006;49(10):1611-9.
4. Bittorf B, Stadelmaier U, Merkel S, Hohenberger W, Matzel KE. Does anastomotic leakage affect functional outcome after rectal resection for cancer? *Langenbecks Arch Surg* 2003;387(11-12):406-10.
5. Marinatou A, Theodoropoulos GE, Karanika S, Karantanos T, Siakavellas S, Spyropoulos BG, et al. Do anastomotic leaks impair postoperative health-related quality of life after rectal cancer surgery? A case-matched study. *Dis Colon Rectum* 2014;57(2):158-66.
6. Brown SR, Mathew R, Keding A, Marshall HC, Brown JM, Jayne DG. The Impact of Postoperative Complications on Long-term Quality of Life After Curative Colorectal Cancer Surgery. *Ann Surg* 2013.
7. Ashburn JH, Stocchi L, Kiran RP, Dietz DW, Remzi FH. Consequences of anastomotic leak after restorative proctectomy for cancer: effect on long-term function and quality of life. *Dis Colon Rectum* 2013;56(3):275-80.
8. Mongin C, Maggiori L, Agostini J, Ferron M, Panis Y. Does anastomotic leakage impair functional results and quality of life after laparoscopic sphincter-saving total mesorectal excision for rectal cancer? A case-matched study. *Int J Colorectal Dis* 2014.
9. Riss S, Stremitzer S, Riss K, Mittlbock M, Bergmann M, Stift A. Pelvic organ function and quality of life after anastomotic leakage following rectal cancer surgery. *Wien Klin Wochenschr* 2011;123(1-2):53-7.
10. Rahbari NN, Weitz J, Hohenberger W, Heald RJ, Moran B, Ulrich A, et al. Definition and grading of anastomotic leakage following anterior resection of the rectum: a proposal by the International Study Group of Rectal Cancer. *Surgery* 2010;147(3):339-51.
11. EuroQol--a new facility for the measurement of health-related quality of life. *Health Policy* 1990;16(3):199-208.
12. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993;85(5):365-76.
13. den Dulk M, Smit M, Peeters KC, Kranenbarg EM, Rutten HJ, Wiggers T, et al. A multivariate analysis of limiting factors for stoma reversal in patients with rectal cancer entered into the total mesorectal excision (TME) trial: a retrospective study. *Lancet Oncol* 2007;8(4):297-303.
14. Floodeen H, Lindgren R, Matthiessen P. When are defunctioning stomas in rectal cancer surgery really reversed? Results from a population-based single center experience. *Scand J Surg* 2013;102(4):246-50.
15. Bensley RP, Schermerhorn ML, Hurks R, Sachs T, Boyd CA, O'Malley AJ, et al. Risk of late-onset adhesions and incisional hernia repairs after surgery. *J Am Coll Surg* 2013;216(6):1159-67, 67 e1-12.
16. Sharpe L, Patel D, Clarke S. The relationship between body image disturbance and distress in colorectal cancer patients with and without stomas. *J Psychosom Res* 2011;70(5):395-402.
17. Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. *J Clin Oncol* 1998;16(1):139-44.
18. Barclay-Goddard R, King J, Dubouloz CJ, Schwartz CE. Building on transformative learning and response shift theory to investigate health-related quality of life changes over time in individuals with chronic health conditions and disability. *Arch Phys Med Rehabil* 2012;93(2):214-20.
19. Chambers SK, Lynch BM, Aitken J, Baade P. Relationship over time between psychological distress and physical activity in colorectal cancer survivors. *J Clin Oncol* 2009;27(10):1600-6.
20. Arndt V, Merx H, Stegmaier C, Ziegler H, Brenner H. Restrictions in quality of life in colorectal cancer patients over three years after diagnosis: a population based study. *Eur J Cancer* 2006;42(12):1848-57.
21. Jansen L, Herrmann A, Stegmaier C, Singer S, Brenner H, Arndt V. Health-related quality of life during the 10 years after diagnosis of colorectal cancer: a population-based study. *J Clin Oncol* 2011;29(24):3263-9.

6

Discussion and future perspectives, summary and curriculum vitae

6.1 Discussion and future perspective

Translation

All previous research performed in the field of CAL has yet not led to radically decreased CAL rates. Designing a study investigating a particular surgical technique, tissue adhesive or other surgical interventions to improve anastomotic healing, some difficulties have to be overcome. Firstly, since many risk factors for CAL exist, no single variable that is subject of a particular study, will greatly influence the leakage rate. Secondly, since the chance of leakage is around 8%, many patients need to be enrolled in an adequately powered study to demonstrate a clinically significant decrease in CAL rates. In the experimental setting, no dramatic reduction in leakage has been reported by investigations during the last few years. Would there have been a promising new technique than, apart from the abovementioned obstacles, few aspects of experimental research of CAL and its translation to the human setting need to be addressed. First of all, currently there is no good anastomotic leakage model in an adequately sized species. Although Komen et al. created a validated leakage model in mice, the size of this species does not allow to reproduce similar colon anastomosis between different animals[1]. In addition this, this type of anastomosis is not comparable to those in humans, since inverting the colonic edges is difficult in mice and the ratio between colon diameter, sutere size, bite size and intersuture distance is completely different. When the etiology of CAL is considered, for leakage to occur in animals, particularly in rats, there needs to be a significant defect in the anastomosis. Little, contained leakages and abscesses are frequently adequately covered by a fibrotic reaction. For this reason, CAL could only occur due to an iatrogenic anastomotic defect, which, in humans, comprises a minority of the causes of CAL. On the other hand, in mice CAL will almost always directly lead to death, rendering the leaking anastomosis unfit for biomechanical and pathological analysis. Another aspect is the lack of robust translatable outcome measures. Although informative, objective and comparable biomechanical parameters, such as bursting pressure, do not always correlate to leakage. Secondly, pathological investigation could reveal adequate anastomotic healing even when is leakage is present, depending on the location of the histological section. Probably the single most important outcome measurement of CAL in animals is observation during reoperation.

The following is likely to hold for anastomotic healing in mammals: the more similar the species is to humans, the more similar anastomotic healing will occur. Consequently, the ideal animal model would be a primate or pigmodel. Ethical objections and cost however (higher species, amount of animals needed i.e.) demand a smaller species, making the rabbit or rat the most appropriate[2]. Our research-

group has recently validated a rat model for anastomotic leakage, which reproduced standard leakage rates between 44 and 50%. Standardization of the models used for investigation of anastomotic technique and anastomotic sealing is very important for enhancing comparability of outcomes, techniques and products.

Influence of ischemia

During the creation of a colorectal anastomosis, the appearance of local ischemic colonic edges induced by sutures might encourage the surgeon to increase the distance between sutures. This thesis investigated the effect of very small intersuture distance on anastomotic healing in mice and rats. It was concluded that sutures induced minimal necrosis and that closely placed sutures do not negatively influence anastomotic healing. This was concluded after the observation that two days after creation of the anastomosis, ischemia is seen sporadically in pathologic sections, while around well-apposed colonic edges a fibrotic cap appears on the serosal side of the anastomosis, similar to callus formation in fractures. This cap forms an interstitial matrix in which myofibroblasts migrate and collagen is disposed. When the anastomotic edges are well apposed and inverted, this cap is minimally influenced by bowel content. When balancing between appropriate apposition and inversion of the anastomosis versus local suture induced ischemia, the former factors should therefore be considered more important.

In contrast to local ischemia, regional ischemia is a previously investigated independent predictor of CAL. Regional ischemia can be measured by visible light or near infrared spectroscopy but can also be preoperatively estimated by the calciumscore.

Sealing

Most tested bioglues for colorectal use are fibrin glue (FG) and cyanoacrylate (CA). Were FG had good results in experimental rat studies, CA studies using rat and pig models did not consistently show benefits for the use of CA. One clinical trial, using FG on anastomosis after low anterior resection, did not show a significant difference between the patients with FG and controls. Following these data, bioglues at the currently are not recommended for the sealing of colorectal anastomosis. A recent review on CA however, provided new insights in factors that could distort outcome of these glue studies. These factors included type of model, inverting vs everting anastomosis and suture bite size.

Another group of sealants, autologue fibrin sealant, might play an important role due to improved biocompatibility, applicability and co-delivery of antibiotics and stem cells. Studies should be undertaken to explore these potential benefits. Standardization of models is of crucial importance since it should lead to better comparison of data in this field and could lead to translation to the human setting.

Centralisation

In the last decade, much debate has finally led to centralisation of complex, low volume surgery. Colorectal surgery, due to the prevalence of colorectal cancer, is still being practised in the majority of Dutch hospitals, albeit in varying numbers. In 2011 the Dutch Surgical Colorectal Audit reported a percentage of CAL of 8,7. This percentage of CAL does not differ between high and low volume hospitals (> or < than 130 colorectal resections / year) in the Netherlands[3]. A Cochrane review by Archampong et al. showed that high volume surgeons in high volume hospitals have favourable outcome in terms of lower operative mortality[4]. The volume load of the individual surgeon contributed more to this benefit than the volume load of the hospital. Based on 3 studies, the odds ratio for CAL was 0,86 in favour of high volume hospitals, but this was not significant[5]. In summary, contrary to other outcome parameters, centralisation has not proved to reduce anastomotic leakage rates after colorectal surgery. Persistent auditing however remains important and has potential benefits. Recently in the Netherlands data from the colorectal audit have been used to identify underperformers on postoperative mortality and morbidity. Subsequently, data of these hospitals are reviewed and analysed for causing factors. Simultaneously, overperformers could be invited to share their methods and protocols.

High rate of diversion stoma

A large meta-analysis over 11.429 patients by Tan et al. on the use of defunctioning stomas in low anterior resections for prevention of CAL, showed a risk ratio of 0,39 in favour of patients with a defunctioning stoma[6]. This and other results have led to the increasing use of defunctioning stomas during the last decade. However, a recent paper by Snijders et al. puts the benefit of a stoma in a chronological perspective[7]. During the pas few years, the increase of stoma placement has led to a parallel increase in stoma-related morbidity and major and minor complications of stoma reversal[8]. As mentioned before, during this increase of defunctioning stomas, the national CAL rate was not reduced during the past few years. Proper estimation of risk of leakage is therefore important to identify patients in whom the reduction in risk by the

formation of a stoma outweighs stoma-related morbidity. Dekker et al. developed a scoring system, the Colon Leakage Score, that showed to be a good predictor of CAL[9]. Although promising, this system should still be prospectively validated. Thereafter multicenter implementation of this scoring system could facilitate comparison between high-risk patients with a deviating stoma and undeviated low risk patients.

Early detection and treatment

Early recognition and intervention in sepsis have been long advocated by the Surviving Sepsis Campaign, since every hour of delay in onset of treatment increases mortality with 7,6% [10]. Thus, when CAL is a potential cause of sepsis, highly sensitive diagnostics and quick intervention must be warranted. Double-contrast CT seems to be the most reliable diagnostic tool, although false positive and negative results and interobeserver variability have been described[11]. In the future, "smart"drains that have the ability to detect local signs of infection or other biomarkers could play a role in minimally invasive monitoring of anastomotic healing. A recent promising finding seems to be the routine postoperative detection of lipopolysaccharide-binding protein in drainfluid, since multivariate analysis showed that early increased values are significantly correlated to the occurrence of CAL in the following days[12]. Since an increasing number of colorectal resection are being carried out laparoscopically (40% in the Netherlands in 2011), early relaparoscopy is relatively easy to perform and could serve as an attractive alternative diagnostic tool when CT is contraindicated or inconclusive. Studies have been undertaken recently in which both diagnostic as therapeutical benefits of relaparoscopy are described retrospectively and in small numbers[13 14]. Broad implementation is still awaited.

The clinical presentation of CAL varies from asymptomatic to overt peritonitis and sepsis. Next to this, there seems no correlation between the size of the anastomotic defect and the clinical presentation. Both variables contribute to the fact that definition of CAL is difficult and many different definitions exist. Due to this inconsistency, no studies have been undertaken in which was randomized for different treatment strategies. However, for both colonic and rectal anastomotic leakage, anastomosis-saving techniques have been described and many surgeons put an effort in preserving the anastomosis in case of leakage especially in young otherwise healthy patients[15]. When consensus on definition of leakage could be established, as is attempted by Rahbari and coworkers for the rectal anastomosis, the next step could be made towards a multicenter study in which patients are stratified according to the grade of CAL[16]. Although helpful for comparing data and research, the abovementioned

scoring system is not appropriate for stratification since the grades are based on wether interventions or reoperation were necessary rather than on the extent of CAL. Apart from this lack of definition, designing a study for the optimal treatment of CAL remains demanding since individual surgeons do not encounter CAL very often. Although CAL is relatively common with a reported national incidence of 8,6% in the Netherlands in 2011 with an average of 150 colorectal resections per year per hospital this leads to approximately 13 cases of CAL per year per hospital. Assuming that three gastrointestinal surgeons equally divide the workload, it would result in an individual exposure of 4 cases of CAL per year per surgeon. However, with good multicenter logisitics, a trial in which next to mortality and morbidity, preservation of the anastomosis could be one of the endpoints should be possible.

Finally, CAL is one of the most serious complications of all surgical interventions. More research with regard to every aspect of it should still be undertaken. In this respect it is regrettable that national health care stimulation programs for research seem to neglect or underestimate the enormous impact of this complication alone on society. A traditonal taboo attitude from the surgeons themselves because of fear of finger pointing might certainly play a role in the underscored awareness of CAL in society. Developing a no blame-culture in the surgical departments and hospitals would be pivotal.

References

1. Komen N, van der Wal HC, Ditzel M, Kleinrensink GJ, Jeekel H, Lange JF. Colorectal anastomotic leakage: a new experimental model. J Surg Res 2009;155(1):7-12.
2. Wenger FA, Szucsik E, Hoinoiu BF, Ionac M, Walz MK, Schmid KW, et al. A new anastomotic leakage model in circular double stapled colorectal anastomosis after low anterior rectum resection in pigs. J Invest Surg 2013;26(6):364-72.
3. van Erning FN, van Steenbergen LN, van den Broek WT, Rutten HJ, Lemmens VE. No difference between lowest and highest volume hospitals in outcome after colorectal cancer surgery in the southern Netherlands. Eur J Surg Oncol 2013;39(11):1199-206.
4. Archampong D, Borowski DW, Dickinson HO. Impact of surgeon volume on outcomes of rectal cancer surgery: a systematic review and meta-analysis. Surgeon 2010;8(6):341-52.
5. Borowski DW, Bradburn DM, Mills SJ, Bharathan B, Wilson RG, Ratcliffe AA, et al. Volume-outcome analysis of colorectal cancer-related outcomes. Br J Surg 2010;97(9):1416-30.
6. Tan WS, Tang CL, Shi L, Eu KW. Meta-analysis of defunctioning stomas in low anterior resection for rectal cancer. Br J Surg 2009;96(5):462-72.
7. Snijders HS, van den Broek CB, Wouters MW, Meershoek-Klein Kranenbarg E, Wiggers T, Rutten H, et al. An increasing use of defunctioning stomas after low anterior resection for rectal cancer. Is this the way to go? Eur J Surg Oncol 2013;39(7):715-20.
8. Giannakopoulos GF, Veenhof AA, van der Peet DL, Sietses C, Meijerink WJ, Cuesta MA. Morbidity and complications of protective loop ileostomy. Colorectal Dis 2009;11(6):609-12.
9. Dekker JW, Liefers GJ, de Mol van Otterloo JC, Putter H, Tollenaar RA. Predicting the risk of anastomotic leakage in left-sided colorectal surgery using a colon leakage score. J Surg Res 2011;166(1):e27-34.
10. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. Intensive Care Med 2013;39(2):165-228.
11. Doeksen A, Tanis PJ, Wust AF, Vrouenraets BC, van Lanschot JJ, van Tets WF. Radiological evaluation of colorectal anastomoses. Int J Colorectal Dis 2008;23(9):863-8.
12. Komen N, Slieker J, Willemsen P, Mannaerts G, Pattyn P, Karsten T, et al. Acute phase proteins in drain fluid: a new screening tool for colorectal anastomotic leakage? The APPEAL study: analysis of parameters predictive for evident anastomotic leakage. Am J Surg. 2014, Jan 4 doi: 10.1016/j.amjsurg.2013.09.024. Epub
13. Vennix S, Abegg R, Bakker OJ, van den Boezem PB, Brokelman WJ, Sietses C, et al. Surgical re-interventions following colorectal surgery: open versus laparoscopic management of anastomotic leakage. J Laparoendosc Adv Surg Tech A 2013;23(9):739-44.
14. O'Riordan JM, Larkin JO, Mehigan BJ, McCormick PH. Re-laparoscopy in the diagnosis and treatment of postoperative complications following laparoscopic colorectal surgery. Surgeon 2013;11(4):183-6.
15. Nerup N, Johansen JL, Alkhefagie GA, Maina P, Jensen KH. Promising results after endoscopic vacuum treatment of anastomotic leakage following resection of rectal cancer with ileostomy. Dan Med J 2013;60(4):A4604.
16. Rahbari NN, Weitz J, Hohenberger W, Heald RJ, Moran B, Ulrich A, et al. Definition and grading of anastomotic leakage following anterior resection of the rectum: a proposal by the International Study Group of Rectal Cancer. Surgery 2010;147(3):339-51.

6.2 English summary

In 2011 6718 patients underwent restorative colorectal surgery in the Netherlands. In 463 of them (6,9%, 6,5% after colon resection, 9,2% after rectum resection), colorectal anastomotic leakage (CAL) occurred. CAL exposes the patient to increased mortality, morbidity, prolonged hospital stay, worse oncologic outcome and the risk of a permanent stoma. Better understanding of etiology, treatment and outcome is needed to reduce the occurrence and to ameliorate treatment and outcome. The aim of this thesis was to investigate aspects of anastomotic healing in the experimental setting, such as the influence of local ischemia, the optimal suture technique and effect of anastomotic sealing. Furthermore current available knowledge on the early detection of CAL and surgical treatment were investigated. The outcome of CAL, both expressed as surgical outcome and as effect on long term health-related quality of life and body image was studied.

In Part 2 surgical techniques for colorectal anastomosis were evaluated both in the experimental and clinical setting.
Chapter 2.1 describes the influence of local anastomotic ischemia induced by abundant suturing in a murine model. Compared to the control mice, no increased CAL was seen in the group with over thirty continuous stitches. It was concluded that optimal colonic edge apposition should be pursued even when extra sutures might cause local ischemia.
In Chapter 2.2 this experiment was repeated in a ratmodel. We concluded that although a higher number of stitches pro anastomosis caused more necrosis and local inflammation, this did not lead to impaired woundhealing.
In Chapter 2.3 a review over 3 meta-analyses, 26 randomized controlled trials, 11 non randomized comparative studies, 20 cohort studies and 57 experimental studies on different aspects of anastomotic surgical technique concluded that there was sufficient scientific support for a single-layer, inverting anastomosis with a slowly absorbable monofilament suture. However, for many aspects of the hand-sewn colorectal anastomosis, like suture format, continuous or interrupted sutures and configuration, available evidence was inconclusive.
Another review (Chapter 2.4) on the use of surgical glues for sealing of gastrointestinal anastomosis included 50 studies, mostly animal experiments. Most frequently used products were fibrin glue and cyanoacrylate glue. Using these glues seemed effective in protecting ileal anastomosis and was also beneficial in gastric/bariatric surgery studies. Results for sealing esophageal, pancreatico-digestive and colorectal anastomoses were equivocal. Standardization of experimental models and application

protocols should lead to better comparability in the future.
In Chapter 2.5 a clinical study is presented in which the appropriateness of emeregency stomas prior to definitive surgery for advanced or locally recurrent rectal cancer was assessed. 464 Patients were included, of whom 106 patients (22.8%) had a stoma prior to potentially curative surgery. Almost half of emergency stomas were considered inappropriate and had to be revised during definitive surgery. This exposed these patients to a higher risk of postoperative complications. An algorithm was proposed to facilitate emergency stoma placement.

In Part 3 early detection of CAL was investigated by one clinical study and one meta analysis on intraperitoneal microdialysis followed by a paper that reviewed all current predictive and diagnostic tools of CAL.
In Chapter 3.1 24 patients are described who underwent left sided hemicolectomy, sigmoid resection or low anterior resection and were included in a prospective study. Intraoperatively a intraperitoneal microdialysis catheter was placed next to the anastomosis to measure local levels of lactate, pyruvate, glucose and glycerol during the first 5 postoperative days. CAL was seen in 3 patients and in these patients CAL was preceded by a significantly higher area under the curve and mean value of lactate levels than the patients in whom no leakage occurred. It was concluded that intraperitoneal microdialysis was a promising tool for early detection of changes in local metabolism and that more research is needed to confirm this statement.
Chapter 3.2 consists of a systematic review of current literature on techniques for prediction and diagnosis of CAL. 69 Articles were included and divided in 5 subgroups (biochemical methods, intraoperative techniques, radiological investigations, clinical tools and peritoneal fluid analysis). Many lacked a no-test control group and reference; therefore the general level of evidence was relatively low. The air leak test is recommended for intraoperative assessment of CAL. When using a clinical diagnostic algorithm postoperatively, delay in diagnosis of CAL could be reduced. CRP measurement should be part of postoperative laboratory routine, since, due to a high negative predictive value, patients with an uncomplicated course could 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 a minimally invasive peritoneal “smart”-drain. When clinical signs are present, CT with rectal contrast is recommended. CT cannot only detect CAL but can also be used as a therapeutic instrument for percutaneous drainage of a pericolic/pelvic abscess.

In Part 4 aspects of incidence and treatment of CAL are discussed.
In Chapter 4.1 517 patients after curative surgery for locally advanced and/or recurrent rectal cancer were included in a study to assess incidence and treatment outcome of CAL and presacral abscesses. 219 Patients underwent low anterior resection and in 232 patients an (extralevator) abdominoperineal resection was performed. We found an overall incidence of 11.4% for CAL and 9.7% for presacral abscesses. The incidence of these complications was acceptable in our high-risk population with a relative high number of very low anastomosis and multivisceral resections. An interval between the last day of neo-adjuvant treatment and surgery <8 weeks was significantly associated with the development of presacral abscesses. CAL had a mortality of 12% and led to dismantling of the anastomosis and permanent colostomy in 7 out of 25 patients (28%) after low anterior resection.
In Chapter 4.2 the results of a national questionnaire amongst gastrointestinal surgeons on the treatment of CAL are provided. In this questionnaire clinical cases were formulated and surgeons were asked to describe their therapeutic response by multiple choice. After two anonymous rounds the response was 40%. Surgeons were more prone to preserve the anastomosis in younger patients than older patients or patients with a higher American Society for Anesthesiology classification. When the anastomosis was located below the promontoium, more respondents believed successful preservation of the anastomosis was plausible than for anastomosis above the level of the promontorium. The same was true for CAL in the presence of a local abscess compared to the presence of general peritonitis.

In Part 5 Health Related Quality of Life was investigated 10 years after colorectal surgery. Patients with CAL were matched with patient without CAL (1:2) for sex, type of surgery, indication, time after surgery and hospital. Surgical outcome was scored as well as HRQoL (SF 36, EORTC-QLQ-C30, EORTC-C29, EQ-5D-5L and Body Image Scale). Although there was no difference in all cause mortality after a follow up of almost 10 years after surgery (44.6% in group A; 38.3% in group B; p = 0.097), reoperations, complications other than CAL, permanent stomas and scars were more frequent in patients with CAL. Patients with CAL scored worse in the Physical Component Scale of the SF-36, the VAS-score of the EQ-5D-5L and the Body Image Score. Cancer patients subgroup after CAL scored worse compared to cancer patients without CAL in the Global Health Score (GHS) and the Functional Score (FS) of the EORTC questionnaires. These results showed detrimental effects on aspects of HRQoL for patients after colorectal anastomotic

leakage even after 10 years, compared to patients after uncomplicated colorectal surgery.

In Part 6 the main results of this thesis were commented and future perspectives were discussed.

6.3 Nederlandse samenvatting

In 2011 ondergingen 6.718 patienten een colorectale operatie met aanleggen van een anastomose in Nederland. Bij 463 van hen (6,9%, 6,5% na colonresectie, 9,2% na rectumresectie) trad colorectale naadlekkage (CAL) op. CAL leidt tot een verhoogde sterfte, morbiditeit, langdurig verblijf in het ziekenhuis, slechtere oncologische uitkomst en geeft een groter risico op een permanent stoma. Beter begrip van etiologie, behandeling en resultaat is nodig om het voorkomen ervan te reduceren en de uitkomst te verbeteren. Het doel van dit proefschrift is om aspecten van colorectale naadgenezing te onderzoeken, zoals de invloed van de lokale ischemie, de optimale hechttechniek en het effect van sealing van de naad. Verder worden de huidige beschikbare kennis over de vroege opsporing van CAL en chirurgische behandeling onderzocht. Tot slot zijn de lange termijn gevolgen van CAL, uitgedrukt als chirurgische uitkomst en als effect op de gezondheid gerelateerde kwaliteit van leven, bestudeerd.

In deel 2 worden chirurgische technieken voor de colorectale anastomose bestudeerd door middel van experimenteel en klinisch onderzoek.
Hoofdstuk 2.1 beschrijft de invloed van lokale ischemie ter plaatse van de anastomose, veroorzaakt door overvloedig hechten in een muismodel. In vergelijking met de controle dieren is geen toename van CAL te zien in de groep met meer dan dertig continue steken. De conclusie is dan ook dat een optimale appositie van de twee randen van het colon moet worden nagestreefd, zelfs als extra hechtingen lokale ischemie kunnen veroorzaken.
In hoofdstuk 2.2 is dit experiment herhaald in een rattenmodel. Hier concluderen we dat een verhoogd aantal hechtingen in colorectale anastomose weliswaar meer necrose en een verhoogde acute ontstekingsreactie veroorzaakt, maar dat dit geen negatieve invloed op de naadgenezing heeft. Hoofdstuk 2.3 bevat een review artikel waarin 3 meta-analyses, 26 gerandomiseerde gecontroleerde studies, 11 niet gerandomiseerde vergelijkende studies, 20 cohortstudies en 57 experimentele studies over verschillende chirurgisch technische aspecten van de colorectale anastomose zijn geïncludeerd. Er wordt geconcludeerd dat er voldoende wetenschappelijke ondersteuning bestaat voor een enkelrijïge, geïnverteerde anastomose met een langzaam absorbeerbare monofilament hechtdraad. Echter, voor veel aspecten van de handgelegde colorectale anastomose, zoals grootte van de hechtdraad, continu of onderbroken hechtingen en hechtconfiguratie, is het beschikbare bewijs niet conclusief.
Een ander onderzoek (hoofdstuk 2.4) over het gebruik van chirurgische sealants voor het afdichten van de gastrointestinale anastomose bevat 50 studies, voornamelijk

dierproeven. Meest frequent gebruikte producten zijn fibrine- en cyanoacrylaatlijm. Deze sealants lijken effectief bij het beschermen van de dunne darm anastomose en hebben ook goede resultaten in de studies waarbij hun toepassing bij maag- en bariatrische chirurgie wordt onderzocht. Resultaten voor het afdichten van de oesophageale, pancreatische en colorectale anastomose zijn niet overtuigend positief. Standaardisatie van experimentele modellen en de toepassing protocollen zou moeten leiden tot een betere vergelijkbaarheid van de verschillende studies in de toekomst.
In hoofdstuk 2.5 wordt een studie beschreven over aanleggen van een stoma voorafgaand aan voorbehandeling en definitieve chirurgie voor het gevorderde of lokaal terugkerende rectumcarcinoom. Van de 464 patiënten die worden geincludeerd, krijgen 106 patiënten (22,8%) een stoma voorafgaande aan, potentieel curatieve, chirurgie. Bijna de helft van deze "nood stoma's" dienen tijdens de definitieve operatie te worden herzien, daarbij de patiënten blootstellend aan een hoger risico van postoperatieve complicaties. Een algoritme wordt voorgesteld om de beslisvorming rond het plaatsen van een spoedstoma vergemakkelijken.

Het in een vroeg stadium ontdekken van CAL leidt tot snellere behandelinge en betere uitkomst voor de patiënt. In deel 3 wordt de vroege opsporing van CAL onderzocht in een klinisch onderzoek met de techniek van intraperitoneale microdialyse en in een review worden alle huidige methoden voor het voorspellen en diagnostiseren van CAL beoordeeld.
In hoofdstuk 3.1 worden 24 patiënten beschreven in een prospectieve studie die een linkszijdige hemicolectomie, sigmoïd resectie of laag-anterieure resectie ondergingen. Peroperatief wordt een intraperitoneale microdialyse catheter naast de anastomose geplaatst die gedurende de eerste 5 postoperatieve dagen de lactaat-, pyruvaat-, glucose- en glycerolspiegels meet. Bij de 3 patiënten die een lekkage zouden ontwikkelen, wordt CAL voorafgegaan door een significant hogere area under the curve en gemiddelde lactaatwaarde dan bij de patiënten bij wie geen lekkage zou optreden. Het lijkt er dus op dat intraperitoneale microdialyse een veelbelovend instrument is voor de vroegtijdige opsporing van veranderingen in de lokale stofwisseling en dat meer onderzoek nodig is om de toepassing ervan bij CAL te valideren.
Hoofdstuk 3.2 bestaat uit een systematic review van de huidige literatuur over technieken voor de voorspelling en diagnose van CAL. De 69 artikelen die werden opgenomen en zijn verdeeld in 5 subgroepen (biochemische methoden, intra-operatieve technieken, radiologische onderzoeken, klinische hulpmiddelen en peritoneale vloeistof analyse). Bij veel studies ontbreekt een "no-test" controlegroep

en gouden standaard; wat de oorzaak is van het betrekkelijk lage level-of-evidence van de geïncludeerde studies. Enkele conclusies kunnen aan de hand van de review worden getrokken: De fietsbandproef wordt aanbevolen voor intra-operatieve evaluatie van de anastomose. Bij gebruik van een klinisch diagnostisch algoritme postoperatief, kan vertraging van de diagnose CAL worden beperkt. Het bepalen van het C-reactive protein in het serum moet deel uitmaken van postoperatieve routine biochemische tests, omdat, door de hoge negatieve voorspellende waarde, patiënten met een ongecompliceerd beloop kunnen worden geïdentificeerd. Meting van cytokinespiegels in het peritoneale drainvocht is veelbelovend en het routinematig plaatsen van een drain bij de anastomose zou om die reden nuttig kunnen zijn. Peritoneale microdialyse zou na verdergaand onderzoek in de toekomst als een minimaal invasieve peritoneale "smart"-drain kunnen functioneren. Bij klinische symptomen, is CT met rectaal contrast aanbevolen. CT kan niet alleen CAL detecteren maar kan ook worden gebruikt als een therapeutisch instrument voor percutane drainage van het paracolische of presacrale bekken abces.

In deel 4 worden aspecten van de incidentie en de behandeling van CAL besproken. Hoofdstuk 4.1 bespreekt een onderzoek naar de incidentie en de behandeling van CAL en presacrale abcessen bij 517 patiënten na curatieve chirurgie voor lokaal gevorderd of recidief rectumcarcinoom. 219 Patiënten ondergingen een laag-anterieure resectie en bij 232 patiënten werd een (extralevatoire) abdominoperineale resectie uitgevoerd. We vinden een totale incidentie van 11,4% voor CAL en 9,7% voor presacrale abcessen. De incidentie van deze complicaties is acceptabel in onze hoog-risico populatie met een relatief hoog aantal zeer lage anastomoses en multiviscerale resecties. Een interval tussen de laatste dag van neo-adjuvante behandeling en chirurgie van minder dan acht weken is significant geassocieerd met de ontwikkeling van een presacraal abces. CAL heeft in onze studie een mortaliteit van 12% en leidde tot de ontmanteling van de anastomose en een permanent stoma in 7 van de 25 patiënten (28%) na laag-anterieure resectie.
In hoofdstuk 4.2 worden de resultaten van een nationale enquête onder de leden van de Nederlandse Vereniging van Gastrointestinale Chirurgie naar de behandeling van CAL besproken. In deze vragenlijst worden klinische casus geformuleerd en chirurgen worden gevraagd om hun therapeutische aanpak te beschrijven door middel van multiple choice. Na twee anonieme rondes is de respons 40%. Chirurgen zijn meer geneigd om te proberen de anastomose te behouden bij jongere patiënten dan bij oudere patiënten en bij patiënten met een hogere ASA-score.

Meer respondenten geloven dat de anastomose gespaard kan blijven wanneer de anastomose zich onder het promontorium bevindt dan wanneer deze zich boven het niveau van het promontorium bevindt. Hetzelfde geldt voor CAL in aanwezigheid van een lokaal abces in vergelijking met de aanwezigheid van algemene peritonitis.

In deel 5 wordt de gezondheidsgerelateerde kwaliteit van leven onderzocht 10 jaar na colorectale chirurgie. Patiënten met CAL zijn gematched met patiënten zonder CAL (1:2) voor sekse, type operatie, indicatie, de tijd na de operatie en het ziekenhuis. Chirurgische uitkomst werd ook gescoord als HRQoL (SF 36, EORTC-QLQ-C30, EORTC-C29, EQ-5D-5L en Body Image Scale). Hoewel er was geen verschil in mortaliteit na een follow-up van bijna 10 jaar na de operatie (44,6% in groep A, 38,3% in groep B, p = 0.097), heroperaties, anders dan CAL complicaties, permanente stoma's en littekens waren meer vaak voor bij patiënten met een CAL. Patiënten met CAL scoorden slechter in de Physical Component Scale van de SF-36, de VAS-score van de EQ-5D-5L en de Body Image Score. Kankerpatiënten subgroep na CAL scoorden slechter in vergelijking met patiënten met kanker zonder CAL in de Global Health Score (GHS) en de Functionele Score (FS) van de EORTC vragenlijst. Deze resultaten toonden nadelige effecten op aspecten van HRQoL bij patiënten na colorectale naadlekkage zelfs 10 jaar na het optreden van CAL, in vergelijking met patiënten na een ongecompliceerde colorectale chirurgie.

Deel 6 bestaat uit de discussie van de resultaten en de Engels- en Nederlandstalige samenvattingen.

6.4 Dankwoord

In de wetenschap niet volledig te zijn met bedanken, doe ik toch een poging. Allereerst veel dank aan de leden van de corona voor het opponeren. Daarnaast wilde ik nog enkelen persoonlijk noemen:

Beste Johan, dank voor het opnemen van mij in de REPAIR-groep. Een lidmaatschap dat me bij zal blijven door de goede sfeer binnen de groep, de grote dosis humor en de persisterende productiviteit op het gebied van darmnaadonderzoek. Dank ook voor de sturingen tijdens mijn periode in het ErasmusMC. Het was echt een eer voor mij om met je te werken.

Beste Tom, vooral bedankt voor al die whipples, slokdarmen, colons en rectums die we samen gedaan hebben. Daarnaast voor al die feesten, concerten en congressen die we bezocht hebben. Ben bang dat er nog vele gaan volgen. O ja, bedankt ook voor de wetenschappelijke input.

Beste Daniël, altijd een stapje verder dan ik, ben je altijd een groot voorbeeld voor me geweest. Zo loyaal naar vrienden, familie en patiënten tegelijk, dat zijn er echt maar heel weinig.

Beste Zhouqiao, veel dank voor je onvoorwaardelijke hulp. Veel succes bij je eigen promotie straks.

Beste Laurents, van jou kwamen de eerste ideeën. Mij in opleiding nemen was daar een van. Promoveren was t andere. Dank voor je geloof in de goede afloop.

Beste Maarten, je wordt bedankt, Stakie. Voor een onvergetelijke opleiding samen.

Beste Harm, veel dank voor je zwijgzame waardevolle lessen boven ogenschijnlijk ondoordringbare kleine bekkens. Ik zal je raad ter harte nemen.

Beste fiets-, schaats-, hardloopvrienden: tot snel!

Beste Johan, wat een feest om een vriend te hebben die er altijd is, nooit ergens een probleem ziet, om al je grappen moet lachen en alle passen hetzelfde zet.

Beste Maarten, je wordt bedankt, Lange. Voor een onvergetelijke opleiding samen.

Beste Huug, als ik dan toch iedereen bij de voornaam noem, dan maar consequent blijven. Veel dank voor de lessen fijnzinnigheid, dokterschap en welbespraaktheid.

Beste Bart-Jeroen, bedankt voor t lachen.

Beste Tessa, Joris, Max, Juliëtte, Konstantinos, Eva, Irene en alle anderen in het hok. Zonder daar ooit een stoel gehad te hebben, toch erg thuisgevoeld.

Beste Max, als ik nou ook maar iets van jouw analytisch vermogen en je vlijmscherpe tong had, was dat opponeren geen enkel probleem.

Beste Thomas, Ponten, Emiel, Jeroen en Ricardo ga zo door, stelletje blije eikels.

Beste Tobias, als er de keuze is om er nog eentje te doen, dan is dat met jou altijd een goed idee.

Beste Baba, goede ideeën wisselden slechte ideeën voor weer een onderbreking van de dagelijkse klinische zorg in hoog tempo af. Resultaat: iedereen altijd keihard lachen.

Beste Joris, heel mooi om je deze kant te zien opgaan. Je hebt enorm veel talent en ik ben je erg dankbaar dat je dat voor dit onderzoek hebt aangesproken.

Beste Geert, het werk in het VUMC is op zich al geweldig uitdagend. Dat dagelijks met jou uitvoeren, maakt het een wereldbaan.

Beste Kim, Dirk, Amy en Hamit: enorm bedankt voor jullie inzet.

Beste buben, niet terugbladeren: dit is het enige dat je hoeft te lezen. Al 16 jaar bedankt voor alles.

Beste Kees, elke keer als Nick en Simon op OK te horen zijn, kan ik nog steeds woordelijk meezingen, dus zeg niet dat ik niets geleerd heb in de DdHK.

Beste Kim, mooie chirurgische outpost bij de Pathologie. Geweldig bedankt voor je hulp.

Cari amici e parenti italiani. Grazie per tutte le volte che sono stato con voi e che avete mi ricevuto così dolce. A presto!

Lieve Nico, Juste, Bram, Tjarda, Luka, Silke, Cato, Hinke en Liesel. Tijdens het schrijven van dit boek heb ik al veel van jullie kunnen genieten, daar komt geen enkele verandering in.

Lieve Jasper en Anneke. Ik ben jullie dankbaar voor al het luisteren, het begrip, de humor, de liefde, de rust en adviezen.

Liefste Silvia. Het is elke dag weer feest om je te horen lachen in ons huis. Met jou alle dagen plezier maken, is wat ik t liefste doe. Zullen we dat dan maar gewoon nog heel lang gaan doen?

6.5 Curriculum Vitae

PhD Portfolio

PhD candidate:	Freek Daams
ErasmusMC Department:	Surgery
PhD period:	2008 – 2014
Research groups:	REPAIR-group, ErasmusMC, Rotterdam Catharina Ziekenhuis, Eindhoven
Supervisors:	Prof. Dr. J.F. Lange Dr. T.M. Karsten

PhD training (ECTS)	Year	Workload
General courses		
Animal Experiments (art. 9)	2009	3.0
Medical Writing	2012	1.0
Workshops		
Masterclass Liver Surgery	2012	0.5
TEMs Course	2012	1.0
Presentations		
National Conferences	2008/2009	1.0
International Conferences	2009	2.0
Grand rounds	2006/2008/ 2010	8.0
Teaching		
Education Bachelorprogramme	2011	1.0
Education Nurses	2011	1.0
Education Residents	2011	1.0
Skills examination	2010	0.2
Supervisor Masterthesis	2012-2013	5.0
Supervisor Medical Interns	2012-2014	5.0

Freek Daams werd geboren op 28 maart 1980 te Hilversum als jongste van drie broers. In 1998 rondde hij het gymnasium af aan het Comenius College te Hilversum. Hij studeerde Geneeskunde aan de Universiteit Maastricht, waar hij in 2005 afstudeerde Tijdens zijn studie verrichtte hij onderzoek op het gebied van bariatrische chirurgie bij afdeling Chirurgie van het Maastricht Universitair Medisch Centrum (Prof. Dr. J.W. Greve) en deed hij een stage in het Flinders Medical Centre te Adelaide. Na een korte periode als ANIOS Chirurgie in het Reinier de Graaf Gasthuis, volgde hij van 2006 tot en met 2012 de opleiding tot chirurg aan het ErasmusMC te Rotterdam (Prof. dr. J.N.M. IJzermans) en het Reinier de Graaf Gasthuis te Delft (Prof. dr. L.P.S. Stassen, Dr. M. van der Elst). Tijdens deze opleiding verrichtte hij bij de REPAIR onderzoeksgroep (Prof. dr. J.J. Jeekel, Prof. dr. G.J. Kleinrensink, Prof. dr. J.F. Lange) het onderzoek dat tot dit proefschrift heeft geleid. Van 2012 tot 2014 werkte hij als Chirurg in Vervolg Opleiding met aandachtsgebied gastro-intestinale chirurgie in het Catharina Ziekenhuis te Eindhoven (Prof. dr. H.J.T. Rutten). In augustus 2014 is hij toegetreden tot de staf van het VU Medisch Centrum te Amsterdam voor upperGI- en pancreaschirurgie. Hij woont in Amsterdam samen met Silvia Magnano di San Lio.


PLVTARCHVS