Improving Quality in Colorectal Surgery

Kwaliteitsverbetering van colorectale chirurgie

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Chapter 1

Introduction and outline of the thesis

Colorectal surgery is an important aspect of our current health system, due to the high incidence of colorectal cancer combined with an ageing population, improved long-term outcomes after colorectal surgery, and the perfectioning of the operative and postoperative aspects through laparoscopy and enhanced recovery programs.

However, postoperative complications painfully remain, despite efforts of amelioration of perioperative care. Research for molecular pathways and non-surgical treatment modalities of colorectal cancer and inflammatory bowel disease is rising in importance, however the improvement of quality and safety of colorectal surgery should remain and become ever more a key element for all colorectal surgeons. This thesis aims to add to this improvement.

COLORECTAL ANATOMY AND TYPE OF COLORECTAL RESECTION

Surgery of colon and rectum can be performed for both benign disease such as diverticular disease and inflammatory bowel disease, as for cancer of colon or rectum which is the third most common type of cancer worldwide.

Surgery for benign disease includes resection of the affected bowel segment, leaving healthy, well vascularized tissue when joining bowel ends together. For colon and rectum cancer complete resection, coupled with regional lymphadenectomy, is the standard of care. Lymph nodes of colon and rectum mostly follow the pattern of vascularization, therefore the major arterial vessels supplying the segment of the colon containing the malignancy should be excised at their origins. In **Chapter 2** the surgical anatomy of colon and rectum is described. According to the anatomy, the standard extent of resection for colorectal cancer is defined. However variability exists between surgeons, based on different interpretations on where the origin of the supplying arterial vessel is located [1-3]. The more radical the surgeon is in dealing with the lymphatic drainage, the more proximally the arterial vascularization will be ligated, and the greater the length of devascularized colon that will need to be resected.

For tumors of the rectum an anterior (with partial mesorectal excision for proximal rectal carcinoma) or low anterior resection (with total mesorectal excision: TME), or abdominoperineal resection is indicated. Both ligation of the inferior mesenteric artery (high tie) or the superior rectal artery (low tie) are possible. Which of the two is superior is matter for debate: a high tie is potentially better in quantity of harvested lymph nodes, while a low tie might result in better vascularization to the anastomosis. The results of a study addressing the difference in vascularization of the anastomosis between high and low tie are shown in **Chapter 3**.

COLORECTAL ANASTOMOSIS: TECHNIQUE AND HEALING

The gastrointestinal tract consists of four layers: mucosa, submucosa, muscularis propria, and serosa. Exceptions are esophagus and rectum, which have no serosal layer. The submucosal layer of the bowel is a tough fibrous membrane consisting mainly of collagen and elastin fibers and has the greatest tensile strength of the layers of the bowel wall[4]. It is the only layer strong enough to hold sutures or staples[5].

Healing of the gastrointestinal anastomosis begins with an inflammation phase. This facilitates the efflux of inflammatory cells into the wound. Shortly thereafter, macrophages can be observed in the intestinal wound, where they synthesize and release tissue growth factors. Collagenolysis will occur, being at its maximum in the first 24h and predominating over collagen synthesis for the first four postoperative days. This is caused by the upregulation of matrix metalloproteinases (MMPs), which are an important class of enzymes involved in collagen metabolism[6]. As a result, during the inflammation phase the wound edges are adhered only by fibrin and any sutures or staples. The holding strength of suture lines is dependent upon the collagen content of the submucosa. On the seventh day, collagen synthesis surpasses collagen degradation resulting in a net gain in collagen content. The density of macrophages and fibroblasts in the intestinal wound decreases, and newly formed collagen transforms into thick bundles and contractile units[4].

After resection of a segment of intestine, the creation of an anastomosis is necessary to re-establish intestinal continuity. Systematic studies on techniques of intestinal suturing really began in the early nineteenth century. In 1812, Travers studied the healing of handsewn anastomoses in rabbits, using an everting suture[7]. He emphasized the importance of the visceral peritoneum in the healing process, and uniform apposition of the intestinal surfaces. In 1826, Lembert stressed the importance of the serous coat in procuring early and permanent adhesions[8]. The vertical mattress suture, which bears his name, is an inverting suture apposing the serosal surfaces of the two ends of bowel. In 1881 Czerny advocated the addition of an inner layer of sutures, which apposes the mucosal surfaces. This layer served to prevent the escape of intestinal contents through the outer layer of Lembert sutures[9]. Until 1887, little concern about the technique of placing serosal stitches had been voiced. Halstead then revealed the importance of the submucosa in gastrointestinal anastomoses, stating that this layer is much stronger than the serosa and muscularis[5]. He preferred a single layer of stitches, and emphasized the importance of minimal surgical damage in successful intestinal suturing.

Surgeons first started to use intestinal staplers in the 1970s[10]. Initially, staplers were only used to divide tissue, but later they enabled stapling, transection and approximation of adjacent loops of intestine. The three main types of staplers are transverse staplers, linear stapling and cutting devices and circular staplers. Circular staplers are most frequently used for low colorectal anastomoses,

applying one anvil transanally. Linear staplers, applied intra-abdominally, create side-to-side anastomoses.

One of the main difficulties with regard to the technique of colorectal anastomosisis represented by the interpretation of the extensive research that has been published regarding the clinical results of this large variety of anastomotic techniques. Appreciating the conclusions from this large amount of literature is essential for the quality of colorectal surgery and for the resident being trained in colorectal surgery. **Chapter 4** provides a systematic review of all aspects of the technique of handsewn colorectal anastomosis, and of the comparison of handsewn to mechanical colorectal anastomosis.

The formation of adhesions is almost always present after abdominal surgery, as it is a physiologic response to surgical trauma or infection[11,12]. It is the most common cause of small bowel obstruction, female infertility, and often leads to major difficulties during subsequent operative procedures[13-15]. Several ways of adhesion prevention have been studied, the majority through intra-abdominally applied adhesion barriers based on prevention of adhesions by separating damaged peritoneal surfaces. However, if an adhesions barrier is capable to adequately diminish fibrin deposition and thus the formation of adhesions, it is essential to investigate whether wound healing and anastomotic healing, also relying on fibrin deposition followed by collagen formation, is not impaired. The study in **Chapter 5** tests the safety of a new adhesion barrier in a colon anastomosis rat model.

COLORECTAL ANASTOMOSIS: POSTOPERATIVE CARE

The main postoperative complications after colorectal surgery are wound infection, postoperative hemorrhage, ureter or bladder injuries, spleen injury, anorectal, bladder and sexual dysfunction (after low anterior resection), and anastomotic leakage. The latter is most feared: its incidence varies from 3 to 8% for colon surgery[16,17], and up to 20% for rectum surgery[18]. It accounts for the majority of complications of colorectal surgery, and prolongs stay in hospital and intensive care unit significantly[19]. When it occurs mortality is augmented to a range of 10-20%[20,21].

Postoperatively the anastomosis is obscured from inspection; direct monitoring of anastomotic healing is lacking. It is only when a patient becomes ill that anastomotic leakage is suspected. The mean time of detection is as late as at the 6-13th postoperative day[20,22]. Typical symptoms include fever, tachycardia, abdominal pain, and elevated laboratory findings. However, a large number of patients ultimately found to have anastomotic leakage develops a more atypical presentation, often with low-grade fever, prolonged ileus, failure to thrive, or symptoms simulating an acute cardiorespiratory event[21]. Abdominal signs are initially absent in case of an extraperitoneal rectal

anastomosis[20]. Radiologic imaging is usually required, and in the majority of cases re-operation is necessary, with creation of a stoma in 50% of patients[21,23,24]

Chapter 6 describes the results of the APPEAL study: a prospective study including 256 patients with colon and rectum anastomoses. The possibility of rapid detection of anastomotic leakage through PCR investigation on abdominal drain fluid after colorectal anastomosis is shown. **Chapter 7** addresses different treatment possibilities for diagnosed AL, through a questionnaire sent to Dutch surgeons asking what factors are taken into account when defining a therapeutic strategy for AL.

COLORECTAL ANASTOMOSIS: RISK FACTORS FOR LEAKAGE AND PREVENTION

Many articles have been published on risk factors for colorectal anastomotic leakage. The following risk factors have been identified in multivariate analyses, subdivided in patient- or intervention-related:

- Patient-related: male[25-28], smoking[29,30], alcohol abuse[29,31], obesity[32], denutrition[31,33], ASA>3[22,34].
- Intervention-related: low anastomosis (<7cm to anal margin)[25-28,35], tumor stage[25], emergency operation[32-34], blood loss and blood transfusion[19,26,30,31,33,36], and duration of surgery[22,31,37].

Initial retrospective studies showed that patients receiving preoperative radiotherapy in surgery for rectal carcinoma had a higher leakage rate[25,27]. However, recent prospective studies failed to show that the short scheme of preoperative radiotherapy increases the incidence of anastomotic leakage; however the use of a protective stoma was left to the discretion of the surgeon in these studies, which might have biased the data[38-40].

The increased risk for anastomotic leakage in low anastomoses has been most extensively proven; the five authors mentioned underneath have illustrated this risk well:

Vignali[35]	> 7cm 1% AL	< 7cm 7.7% AL		
Law[26]	PME 1.3% AL	TME 8.1% AL		
Rullier[28]	8.5-15cm 0% AL	5.5-8cm 7% AL	< 5cm 19% AL	
Matthiessen[27]	10-15cm 4% AL	6-10cm 13% AL	<6cm 24% AL	
Eriksen[25]	10cm 4.8%	7-9cm 7.6%	4-6cm 13.7%	<3cm 15.6%

One aspect is known to diminish the risk of clinical leakage: randomized controlled trials have shown that incidence and mortality of anastomotic leakage can be reduced in low rectum anastomosis by a defunctioning stoma. The study conducted by Matthiessen et al. randomized 234 anastomoses after low anterior resection between a defunctioning stoma or anastomosis alone. There was a 10.3% clinical leakage rate with a defunctioning stoma, compared to 28% leakage rate with an anastomosis alone[41]. Montedori et al. conducted a Cochrane review in 2010, combining six randomized controlled trials, showing significantly less anastomotic leakage, less urgent re-operations, and less mortality[42].

Identification of risk factors for AL is important: **Chapter 8** describes risk factors for AL identified in the prospective APPEAL study. In **Chapter** 9 a new risk factor for AL is identified through a retrospective database of patients having undergone colorectal resection and with a preoperative abdominal CT scan available.

Much debated is the role of glue applied around the colorectal anastomosis, acting as a sealant for prevention of AL. The evidence that is available today is based on studies with different types of sealants, different experimental models, and different outcome measures[43]. Therefore it is difficult to evaluate the safety and benefit of sealants in colorectal surgery, and its use in a clinical setting remains rare. **Chapter 10** describes results of six different sealants tested for safety and efficacy of preventing leakage in a validated mouse model for colorectal AL.

OPTIMIZING COLORECTAL LAPAROSCOPY

The introduction of laparoscopic procedures has led to an important progress in colorectal surgery. Not only does this technique achieve similar long-term results as the conventional open procedure in colorectal cancer surgery, short-term results have been shown to be superior[44-47]. These include less postoperative pain, earlier recovery of bowel function, less blood loss, and shorter hospital stay. Long-term results, defined as disease-free survival, do not differ between patients operated through laparotomy or laparoscopy[45,46]. However, it remains a technically challenging procedure, especially in rectal surgery, with general recognition of the relatively long and technically demanding learning curve[48]. Difficulties in laparoscopic performance are shown to exist during the early period of training; an average of approximately twenty seconds and two to three errors are required for one grasp[49]. Such results emphasize the need for training. A new possibility of training in colorectal laparoscopy is explained in **Chapter 11**, emphasizing the training of laparoscopic anatomical recognition.

Thorough mechanical cleansing of the bowel has long been considered essential prior to colorectal operations[50-52]. It was believed an empty bowel would diminish the risk of anastomotic leakage and septic complications. However, during the last decade several studies have been conducted investigating the use of mechanical bowel preparation (MBP). Most recent randomized controlled trials and meta-analyses uniformly conclude that there is no advantage of MBP prior to colorectal resection, finding equal or lower rates of anastomotic leakage and septic complications in patients without MBP compared to patients with pre-operative MBP[53-62]. However, these studies have not included patients operated by means of minimally invasive techniques, and therefore this conclusion cannot be extrapolated to laparoscopic surgery. Logically, one does not expect the effect of MBP on anastomotic leakage and other septic complications to be different between patients with a laparoscopic or open approach. However, the effect of bowel preparation on the volume of the bowel, and thus on exposure, could play an important role in the course of the laparoscopic intervention itself. In **Chapter 12** the members of the Dutch Society for Endoscopic Surgery specialized in gastro-intestinal surgery are asked if they use mechanical bowel preparation pre-operatively, and with what aim. **Chapter 13** describes the results of a pig study comparing the quantity of pneumoperitoneum between pigs having received mechanical bowel preparation and those having not.

REFERENCES

1. Nelson H, Petrelli N, Carlin A, et al. Guidelines 2000 for colon and rectal cancer surgery. J Natl Cancer Inst 2001;93:583-96.
2. Read TE, Mutch MG, Chang BW, et al. Locoregional recurrence and survival after curative resection of adenocarcinoma of the colon. J Am Coll Surg 2002;195:33-40.
3. Sternberg A. Carcinoma of the colon: margins of resection. J Surg Oncol 2008;98:603-6.
4. Thompson SK, Chang EY, Jobe BA. Clinical review: Healing in gastrointestinal anastomoses, part I. Microsurgery 2006;26:131-6.
5. Halstead W. Circular suture of the intestine: an experimental study. Am J Med Sci 1887;94:436-61.
6. Ho YH, Ashour MA. Techniques for colorectal anastomosis. World J Gastroenterol 2010;16:1610-21.
7. Travers B. An inquiry into the process of nature in repairing injuries of the intestines. London 1812:109-35.
8. Lembert A. Mémoire sur l'entéroraphie avec la description d'un procédé nouveau pour pratiquer cette opération chirurgicale. Répertoire général d'anatomie et de physiologie pathologique et des cliniques chirurgicales 1826;2:100-7.
9. Czerny V. Zur Darmresektion. Berl Klin Wschr 1880;17:637.
10. Ravitch MM, Lane R, Cornell WP, et al. Closure of duodenal, gastric and intestinal stumps with wire staples: experimental and clinical studies. Ann Surg 1966;163:573-9.
11. Postoperative adhesion development after operative laparoscopy: evaluation at early second-look procedures. Operative Laparoscopy Study Group. Fertil Steril 1991;55:700-4.
12. Becker JM, Dayton MT, Fazio VW, et al. Prevention of postoperative abdominal adhesions by a sodium hyaluronate-based bioresorbable membrane: a prospective, randomized, double-blind multicenter study. J Am Coll Surg 1996;183:297-306.
13. Menzies D, Ellis H. Intestinal obstruction from adhesions--how big is the problem? Ann R Coll Surg Engl 1990;72:60-3.
14. Milingos S, Kallipolitis G, Loutradis D, et al. Adhesions: laparoscopic surgery versus laparotomy. Ann N Y Acad Sci 2000;900:272-85.
15. Van Der Krabben AA, Dijkstra FR, Nieuwenhuijzen M, et al. Morbidity and mortality of inadvertent enterotomy during adhesiotomy. Br J Surg 2000;87:467-71.
16. Kavanagh DO, Gibson D, Moran DC, et al. Short-term outcomes following laparoscopic resection for colon cancer. Int J Colorectal Dis 2011;26:361-8.
17. Krarup PM, Jorgensen LN, Andreasen AH, et al. A nationwide study on anastomotic leakage after colonic cancer surgery. Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland 2012;14:e661-e7.
18. Hotta T, Yamaue H. Laparoscopic surgery for rectal cancer: review of published literature 2000-2009. Surg Today 2011;41:1583-91.
19. Alves A, Panis Y, Trancart D, et al. Factors associated with clinically significant anastomotic leakage after large bowel resection: multivariate analysis of 707 patients. World J Surg 2002;26:499-502.
20. Alberts JC, Parvaiz A, Moran BJ. Predicting risk and diminishing the consequences of anastomotic dehiscence following rectal resection. Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland 2003;5:478-82.
21. Hyman N, Manchester TL, Osler T, et al. Anastomotic leaks after intestinal anastomosis: it's later than you think. Ann Surg 2007;245:254-8.
22. Buchs NC, Gervaz P, Secic M, et al. Incidence, consequences, and risk factors for anastomotic dehiscence after colorectal surgery: a prospective monocentric study. Int J Colorectal Dis 2008;23:265-70.
23. Alves A, Panis Y, Pocard M, et al. Management of anastomotic leakage after nondiverted large bowel resection. J Am Coll Surg 1999;189:554-9.
24. Kanellos I, Vasiliadis K, Angelopoulos S, et al. Anastomotic leakage following anterior resection for rectal cancer. Tech Coloproctol 2004;8 Suppl 1:s79-81.

25. Eriksen MT, Wibe A, Norstein J, et al. 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;7:51-7.
26. Law WL, Chu KW. Anterior resection for rectal cancer with mesorectal excision: a prospective evaluation of 622 patients. Ann Surg 2004;240:260-8.
27. Matthiessen P, Hallbook O, Andersson M, et al. 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;6:462-9.
28. Rullier E, Laurent C, Garrelon JL, et al. Risk factors for anastomotic leakage after resection of rectal cancer. The British journal of surgery 1998;85:355-8.
29. Sorensen LT, Jorgensen T, Kirkeby LT, et al. Smoking and alcohol abuse are major risk factors for anastomotic leakage in colorectal surgery. The British journal of surgery 1999;86:927-31.
30. Bertelsen CA, Andreasen AH, Jorgensen T, et al. Anastomotic leakage after anterior resection for rectal cancer: risk factors. Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland 2010;12:37-43.
31. Makela JT, Kiviniemi H, Laitinen S. Risk factors for anastomotic leakage after left-sided colorectal resection with rectal anastomosis. Diseases of the colon and rectum 2003;46:653-60.
32. Komen N, Dijk JW, Lalmahomed Z, et al. After-hours colorectal surgery: a risk factor for anastomotic leakage. Int J Colorectal Dis 2009;24:789-95.
33. Golub R, Golub RW, Cantu R, Jr., et al. A multivariate analysis of factors contributing to leakage of intestinal anastomoses. J Am Coll Surg 1997;184:364-72.
34. Choi HK, Law WL, Ho JW. Leakage after resection and intraperitoneal anastomosis for colorectal malignancy: analysis of risk factors. Diseases of the colon and rectum 2006;49:1719-25.
35. Vignali A, Fazio VW, Lavery IC, et al. Factors associated with the occurrence of leaks in stapled rectal anastomoses: a review of 1,014 patients. J Am Coll Surg 1997;185:105-13.
36. Yeh CY, Changchien CR, Wang JY, 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;241:9-13.
37. Konishi T, Watanabe T, Kishimoto J, et al. Risk factors for anastomotic leakage after surgery for colorectal cancer: results of prospective surveillance. J Am Coll Surg 2006;202:439-44.
38. Peeters KC, Tollenaar RA, Marijnen CA, et al. Risk factors for anastomotic failure after total mesorectal excision of rectal cancer. The British journal of surgery 2005;92:211-6.
39. Sauer R, Becker H, Hohenberger W, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med 2004;351:1731-40.
40. Sebag-Montefiore D, Stephens RJ, Steele R, et al. Preoperative radiotherapy versus selective postoperative chemoradiotherapy in patients with rectal cancer (MRC CR07 and NCIC-CTG C016): a multicentre, randomised trial. Lancet 2009;373:811-20.
41. Matthiessen P, Hallbook O, Rutegard J, et al. Defunctioning stoma reduces symptomatic anastomotic leakage after low anterior resection of the rectum for cancer: a randomized multicenter trial. Ann Surg 2007;246:207-14.
42. Montedori A, Cirocchi R, Farinella E, et al. Covering ileo- or colostomy in anterior resection for rectal carcinoma. Cochrane Database Syst Rev 2010:CD006878.
43. Vakalopoulos KA, Daams F, Wu Z, et al. Tissue adhesives in gastrointestinal anastomosis: a systematic review. J Surg Res 2013;180:290-300.
44. Breukink S, Pierie J, Wiggers T. Laparoscopic versus open total mesorectal excision for rectal cancer. Cochrane Database Syst Rev 2006:CD005200.
45. Clinical Outcomes of Surgical Therapy Study G. A comparison of laparoscopically assisted and open colectomy for colon cancer. N Engl J Med 2004;350:2050-9.
46. Reza MM, Blasco JA, Andradas E, et al. Systematic review of laparoscopic versus open surgery for colorectal cancer. Br J Surg 2006;93:921-8.

47. Veldkamp R, Kuhry E, Hop WC, et al. Laparoscopic surgery versus open surgery for colon cancer: short-term outcomes of a randomised trial. Lancet Oncol 2005;6:477-84.
48. (NICE) NIfHaCE. Laparoscopic Surgery for Colorectal Cancer. Technology Appraisal Guidence 105 2006;August.
49. Hwang MR, Seo GJ, Yoo SB, et al. Learning curve of assistants in laparoscopic colorectal surgery: overcoming mirror imaging. Surg Endosc 2010.
50. Chung RS, Gurll NJ, Berglund EM. A controlled clinical trial of whole gut lavage as a method of bowel preparation for colonic operations. Am J Surg 1979;137:75-81.
51. Dunphy JE. Preoperative preparation of the colon and other factors affecting anastomotic healing. Cancer 1971;28:181-2.
52. Nichols RL, Condon RE. Preoperative preparation of the colon. Surg Gynecol Obstet 1971;132:323-37.
53. Bretagnol F, Alves A, Ricci A, et al. Rectal cancer surgery without mechanical bowel preparation. Br J Surg 2007;94:1266-71.
54. Bucher P, Gervaz P, Soravia C, et al. Randomized clinical trial of mechanical bowel preparation versus no preparation before elective left-sided colorectal surgery. Br J Surg 2005;92:409-14.
55. Contant CM, Hop WC, van't Sant HP, et al. Mechanical bowel preparation for elective colorectal surgery: a multicentre randomised trial. Lancet 2007;370:2112-7.
56. Fa-Si-Oen P, Roumen R, Buitenweg J, et al. Mechanical bowel preparation or not? Outcome of a multicenter, randomized trial in elective open colon surgery. Dis Colon Rectum 2005;48:1509-16.
57. Guenaga KK, Matos D, Wille-Jorgensen P. Mechanical bowel preparation for elective colorectal surgery. Cochrane Database Syst Rev 2009:CD001544.
58. Jung B, Pahlman L, Nystrom PO, et al. Multicentre randomized clinical trial of mechanical bowel preparation in elective colonic resection. Br J Surg 2007;94:689-95.
59. Pena-Soria MJ, Mayol JM, Anula R, et al. Single-blinded randomized trial of mechanical bowel preparation for colon surgery with primary intraperitoneal anastomosis. J Gastrointest Surg 2008;12:2103-8; discussion 8-9.
60. Ram E, Sherman Y, Weil R, et al. Is mechanical bowel preparation mandatory for elective colon surgery? A prospective randomized study. Arch Surg 2005;140:285-8.
61. Slim K, Vicaut E, Panis Y, et al. Meta-analysis of randomized clinical trials of colorectal surgery with or without mechanical bowel preparation. Br J Surg 2004;91:1125-30.
62. Zmora O, Mahajna A, Bar-Zakai B, et al. Is mechanical bowel preparation mandatory for left-sided colonic anastomosis? Results of a prospective randomized trial. Tech Coloproctol 2006;10:131-5.

Part I

Colorectal anatomy and type of colorectal resection

Chapter 2

Surgical anatomy of colon and rectum

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General characteristics colon

The colon can be recognized by the three taenia coli, the epiploic appendices, and the haustra coli. The taeniae start at the level of the caecum at the base of the appendix. The taeniae, appendices, and haustra disappear at the rectosigmoid junction.

Caecum

The caecum, with the appendix, is the first and the widest part of the colon. According to Laplace's low, this segment will be the first to perforate when an obstruction occurs distally. The caecum lies intraperitoneally in the right lower quadrant, but has no mesentery. Dorsally to the caecum one finds the iliac artery and vein, the right ureter, the gonadal artery and vein, and the psoas muscle with the femoral nerve subfascially; in case of malignities of the caecum all these structures can be involved.

Ascending colon

The ascending colon goes in cranial direction, over the perirenal fat and Gerota's fascia, up to the liver (segments V, VI). The hepatic flexure of the ascending colon is often adherant to the liver and gallblader. Not unoften the transverse colon or the greater omentum are attached with the ascending colon. During embryonic development the parietal peritoneum, covering the retroperitoneal structures at the right side (ureter, gonadal vessels), fuses with the right peritoneal fold of the embryonic mesentery of the ascending colon. This fusion-fascia is called Toldt's fascia, en is also present at the level of descending colon and sigmoid colon. Toldt's line, also situated both left and right, is the name of the natural adhesions between ascending or descending colon and the lateral bowel wall. During mobilization of the caecum and the ascending colon these adhesions, mostly avascular, must be transsected. During mobilisation the dissection plane is ventrally from Toldt's fascia and the duodenum. The right ureter and the gonadal vessels will this stay covered by this thin fascia. With excessive traction on the ascending colon during mobilization one risks tearing off the right branch of the middle colic vein, resulting in a bleeding at the level of the superior mesenteric vein. The lateral peritoneal folds at the level of the hepatic flexure contain veins, which must be cared for adequately during mobilization. During mobilization one risks dissecting too much in dorsal direction, into the perirenal fat. To prevent this one must stay close to the dorsal side of the ascending colon, both medially as laterally, without taking perirenal fat within the resection.

Figure 1. Toldt's fascia

Transverse colon

The transverse colon is situated intraperitoneally, and is attached to the greater curvature of the stomach through adherences of the taeniae coli through the gastrocolic ligament (cranial part of greater omentum). The transverse colon can be recognized immediately by lifting the greater omentum, to which it is attached.

The dorsal side of the tranverse colon is attached to the bowel wall through the mesentery (mesocolon), affixed at the level of the pancreas. Arriving at the splenic flexure, the colon is closely joined to the spleen, and obscured by adhesions with the greater omentum. Through the presence of ventral adhesions between the greater omentum and the splenic capsule, splenic injury can occur when applying traction on both the splenic flexure and the greater omentum. Some intervention necessitate seperation of greater omentum and transverse colon. In those situations it is easier to start at the left side, opening the lesser sac (omental bursa).

Descending colon

The retroperitoneal descending colon starts at the splenic flexure, becoming the sigmoid colon at the level of the superior anterior iliac spine. Cranially the descending colon lies above the perirenal fat and Gerota's fascia. However caudally it lies above Toldt's fusion-fascia, underneath wich are situated the left ureter and the gonadal artery and vein, just like at le right side. At the lateral sides of both ascending and descending colon one finds the paracolic gutter. Starting from here the colon can be mobilized in an avascular plane, after transsecting the natural adhesions with the lateral bowel wall (Toldt's line). Some surgeons prefer using the descending colon to the sigmoid colon as afferent loop for an anastomosis. This is in relation with the relative absence of diverticulosis and hypertrophy of the muscularis of the descending colon. When using the descending colon for a (colorectal) anastomosis, the splenic flexure will have to be mobilized. During mobilization of the splenic flexure three structures will have to be separated: 1) the greater omentum: by liberating the omentum from the colon or transsecting the omentum between stomach and splenic flexure (gastrocolic ligament), 2) the mesocolon: the mesocolon is transsected at the caudal limit of the pancreas thus sparing the vascular arcade, 3) Toldt's line.

Sigmoid colon

The sigmoid colon starts at the level of the anterior superior iliac spine, and continues up to approximately L3. Here it becomes the rectum. At this point epiploic appendices and taeniae coli disappear. The sigmoid colon first turns medially and cranially, and then turns caudally. This S-shaped structure is attached through a mesentery (sigmoid mesocolon) to the dorsal bowel wall. The mesentery attach follows the shape of a V, with the point of the V at the level of the aortic bifurcation. The sigmoid arteries and the superior rectal artery lie in this sigmoid mesocolon, together with nerves and lymphatics. Natural adhesions exist between the sigmoid and the lateral parietal peritoneum of the bowel wall: the caudal part of Toldt's line. In female patients the left ovary and fallopian tube can be adherent to the sigmoid. The sigmoid can be of such size that it can sometimes easily reach up to the caecum (dolichosigmoid). The sigmoid colon often is in contact with the bladder, explaining the frequent involvement of this organ in malignancies or diverticulitis of the sigmoid.

Vascularisation colon

The vascularization of the colon is partly coming from the **superior mesenteric artery** (SMA: caecum, ascending and transverse colon), and partly from the **inferior mesenterc artery** (IMA: descending and sigmoid colon, rectum). Out of these two arteries originate the main branches wich will end in an arcade localized along the entire colon: Drummond's marginal artery. It is preferential not to use the

name of Riolan's arcade anymore when speaking of the anastomosis between the SMA and IMA . First of all the French anatomis Riolan never published on this specific subject, and secondly in literature it is interpreted in many different ways. It is sufficient to understand that the connection between the SMA (left branch middle colic artery) and the IMA (ascending branch of the left colic artery) is localized in the arcade at the level of the splenic flexure. In 10% of cases the arcade is incomplete at this level (Griffith's point), meaning one of both mesenteric arteries cannot compensate for the other. In case of occlusion (atherosclerosis, iatrogenous) necrosis of the bowel will be the consequence.

Superior mesenteric artery

The **superior mesenteric artery** (SMA) appears beneath the caudal limit of the pancreas, and crosses over the third (horizontal) part of the duodenum. The branches of the SMA to the right side are (cranially to caudally) the inferior pancreaticoduodenal artery, the middle colic artery, the right colic artery, and the ileocolic artery.

The **middle colic artery** is the first of the three branches going the the colon at the right side. It bifurcates from the SMA at the level of the inferior limit of the pancreas and crosses over the duodenum. The middle colic artery lies in the mesocolon of the transverse colon and bifurcates in a left and right branch at the level of the centre of the transverse colon. The right branch anastomoses through the marginal artery with the right colic artery, while the left branch anastomoses with the ascending branch of the left colic artery. The blood flow towards the splenic flexure seems variable: in 89% of cases it comes from the left colic artery, and in 11% of cases from the middle colic artery. The middle colic artery can be indentified easily by opening the covering gastrocolic ligament. It is this artery that warrants the vascularisation of the left side of the colon after ligation of the IMA during rectal resection (high tie).

The **right colic artery** is the second of the three branches, originating at the right side of the SMA. Of the colic arteries it is the one with the highest incidence of anatomical variation; it often originates from the ileocolic artery instead of directly from the SMA.

Between the ileocolic artery and vein and the right branch of the middle colic artery is a large empty mesenterial surface without vessels; here the duodenum shows through the parietal peritoneum when holding the transverse colon cranially. During a right hemicolectomy one can create safely a window at this level to control the ileocolic artery and vein.

The last branch of the SMA, the **ileocolic artery**, has the least anatomic variation. This artery originates from the SMA 5cm after the origin of middle colic arter (approximately the lower limit of the third part of the duodenum). The ileocolic artery continues in the direction of the ileocaecal corner. It can be identified by pulling the ileocaecal corner caudally and to the right.

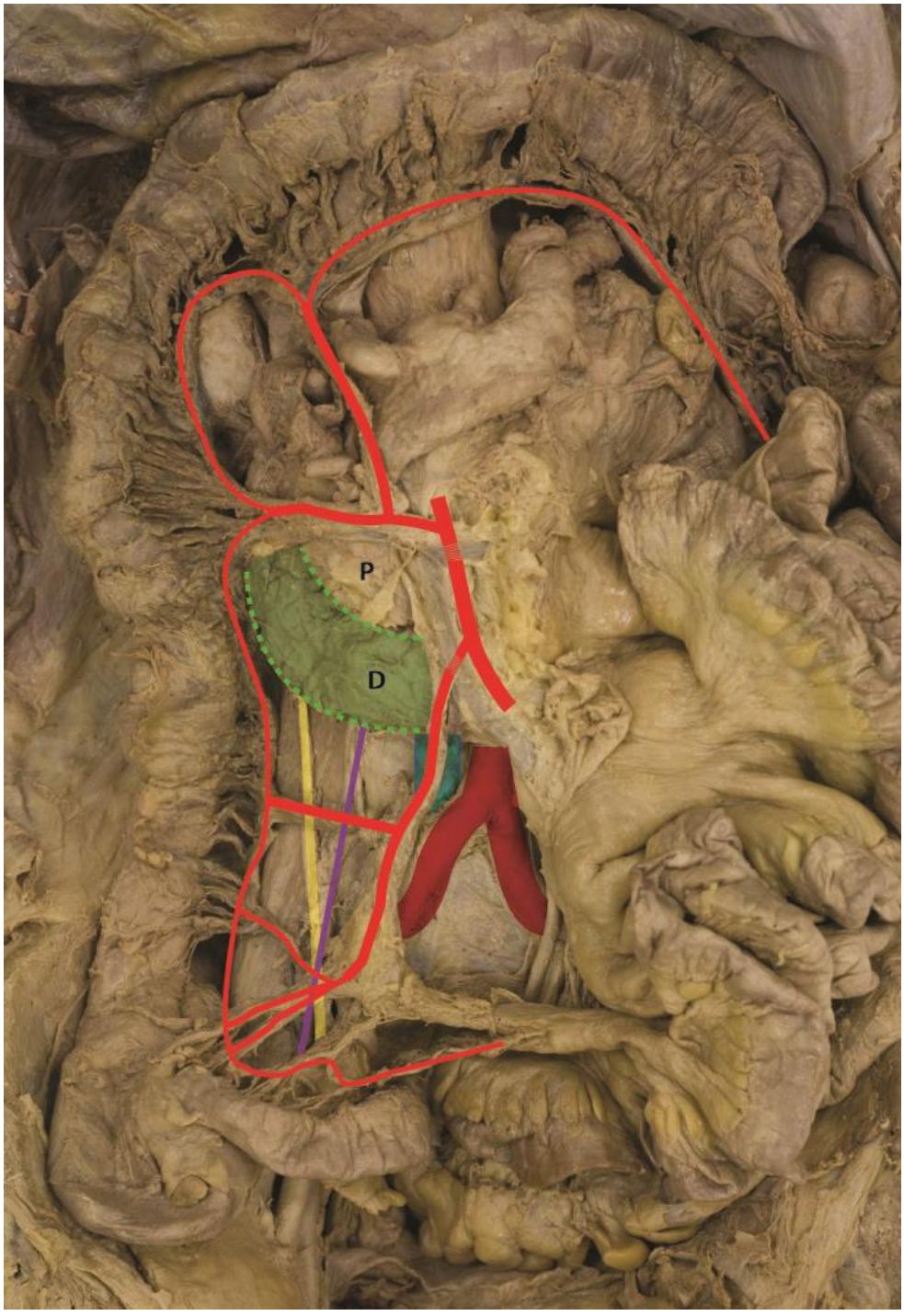

Figure 2. Superior mesenteric artery. Dark red: aorta and iliac arteries. Red: superior mesenteric artery with its branches, finishing in the marginal artery. Blue: vena cava. Yellow: ureter. Purple: testicular-ovarian a/v. Green (D): duodenum. P: pancreas.

Inferior mesenteric artery

The origin of the **inferior mesenteric artery** (IMA) is at the ventral part of the abdominal aorta, approximately 4 cm upwards from the aortic bifurcation. The branches of the IMA are the left colic artery, the sigmoid arteries, and the superior rectal artery.

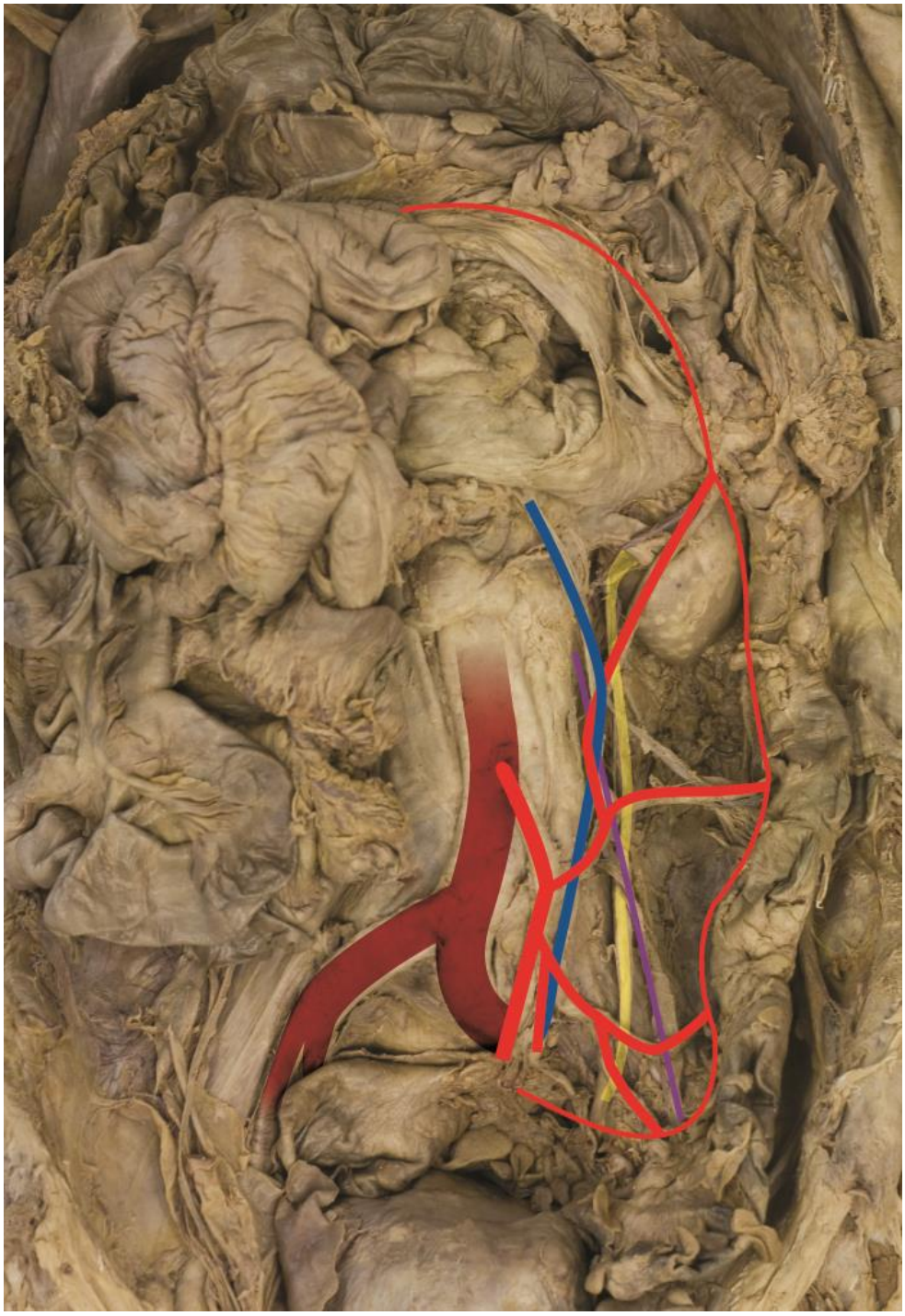

Figure 3. Inferior mesenteric artery.
Dark red: aorta and iliac arteries. Red: inferior mesenteric artery with its branches, finishing in the marginal artery. Blue: inferior mesenteric vein. Yellow: ureter. Purple: testicular-overian a/v.

The **left colic artery** is the first branch of the IMA. It originates 4cm after the beginning of the IMA, often just cranially to the aortic bifurcation, en follows a slightly upwards direction in the retroperitoneum during 5cm after which it bifurcates into an ascending and descending branch.

The ascending branch of the left colic artery follows the upward direction of the inferior mesenteric vein a few centimeters lateral to the aorta. It then enters the mesocolon and will go cranially to the splenic flexure, vascularizing the upper part of the descending colon and the distal part of the transverse colon. The ascending branch anastomoses with branches of the middle colic artery and is important for the vascularisation of the descending colon after a sigmoid resection. The descending branch of the left colic artery goes caudally, and vascularizes the lower part of the descending colon, and anastomoses through the marginal artery with the first sigmoid artery.

There are two to four **sigmoid arteries**, descending to the left in the mesosigmoid. One or more arteries can originate from the left colic artery; often one comes directly from the IMA ; others can originate from the superior rectal artery. Often sigmoid arteries originate from the angle between the superior rectal artery and the left colic artery.

The **veins** of the colon largery follow the position arteries. All veins will finally drain into the portal vein. The vein showing the largest anatomical variation is the inferior mesenteric vein (IMV), that can end in the splenic vein, the proximal part of the superior mesenteric vein, or in the confluens of these both arteries. More caudally the IMV lies at the left side of the aorta and the first jejunal loop, dorsally of the mesocolon, together with the ascending branch of the left colic artery. The IMV is often used as landmark in laparoscopic surgery to mobilize the splenic flexure: at its left side the peritoneum of the mesocolon can safely be incised, and the caudal limit of the pancreas indentified, to thus mobilize the entire dorsal side of the flexure (disconnecting the mesocolon). The right branch of the middle colic vein deserves special attention, as it can be easily teared off its main branch during mobilization of the ascending colon, for example during a right hemicolectomy.

The **lymphatics** of the colon largery follow the vascularization. The size of resection will be mostly determined by the extent of lymphadenectomy.

Four types of lymph nodes exist in colonic anatomy: epicolic, paracolic, intermediate, and central lymph nodes. Epicolic lymph nodes are situated on the colon, the paracolic lymph nodes a localized along the marginal artery, the intermediate lymph nodes are situated along the branches of the SMA and IMA, and the central lymph nodes are localized on the SMA and IMA.

The lymph nodes of the caecum, ascending colon, and right part of the transverse colon drain thourgh the intermediate lymph nodes along the branches of the SMA to the lymph nodes of the SMA. The lymph nodes of the left side of the tranverse colon, the descending colon, and the sigmoid drain through the intermediate lymph nodes along the branches of the IMA to the lymph nodes of the IMA. Malignities of the hepatic flexure metastasize in 64% of cases in the territory of the right

colic artery, and in 36% of cases in the territory of the middle colic artery. When performing a curative resection of a malignancy of the right colon it is useful to extend the right hemicolectomy to to the lymphatic nodes along the right branch of the middle colic artery. In the same manner for a malignancy of the left colon the left hemicolectomy should be extended to the left branch of the middle colic artery. In case of malignancy of the sigmoid, lymphadenectomy should be performed up to the IMA.

Innervation

The parasympathetic innervation is provided by the branches of the vagal nerve, lying along the sacral plexus; the dorsal root of the vagal nerve provides for the caecum, ascending colon, and transverse colon. The pelvic splanchnic nerves, originating from S2-S4, provide for the descending colon, sigmoid, and rectum. The parasympathetic efferent branches stimulate peristalsis en secretion; the afferent branches transmit pain stimuli.

The sympathetic innervation is provided by branches coming from the inferior and superior mesenteric ganglia. The sympathetic efferent branches inhibit peristalsis and secretion, the afferent branches transmit pain stimuli.

Rectum

The rectosigmoidal junction lies intraperitoneally, at the level of S3 where epiploic appendices and taeniae coli become absent. The rectum prolonges caudally, with a total length of approximately 15cm, into to anal canal (4cm). The cranial third of the rectum is situated intraperitoneally, the middle and caudal third of the rectum are extraperitoneal. The extraperitoneal part of the rectum (10cm) is in direct ventral connection with the bladder, seminal vesicles and prostate in men, and cervix and posterior part of the vagina in women.

After mobilisation from the sacral space the rectum seems to gain length. This explains the difference between endoscopically measured distances of anus to tumour, and the real intra-operatively measured distance. In general the endoscopically measured distance will be greater to the distance intra-operatively. At the point where the peritoneum does no longer cover the rectum it goes ventrally from the rectum towards cranial over the uterus in women and over the bladder in men. This forms the rectovesical pouch in men and the recto-uterine pouch in women (cavum Douglasi).

At the junction with the anus the anal canal makes an angle of 90-115º. This angle is caused by the puborectal sling, being part of the levator ani muscle. The extraperitoneal rectum is surrounded by **mesorectum**, in which are present vessels, fatty tissue, and lymph nodes. The dorsal mesorectum is much more voluminous than the ventral part, and presents two fatty ‘lobes’, around both branches of the superior rectal artery: the buttocks of Heald. The mesorectum gives the rectum its freedom of movement during defecation, however it is no real mesentery.

The mesorectum in surrounded by the **visceral endopelvic fascia**, also known as the 'fascia propria' of the rectum. The **parietal endopelvic fascia** covers the sides and 'floor' of the pelvis. This fascia covers the internal obturator muscle, the piriformis muscle, the levator ani muscle, and the coccygeus muscle, and continues as fascia transversalis. Dorsally, between visceral and parietal endopelvic fascia, is a thin layer of fatty tissue with loose tissue, called the **'holy plane' of Heald.** The rectosacral fascia (formally called Waldeyer's fascia), seperates the holy plane of Heald in a cranial and caudal part. **Denonvilliers' fascia** lies caudodorsally of the seminal vesicles, en seperates the prostate and the seminal vesicles of the rectum.

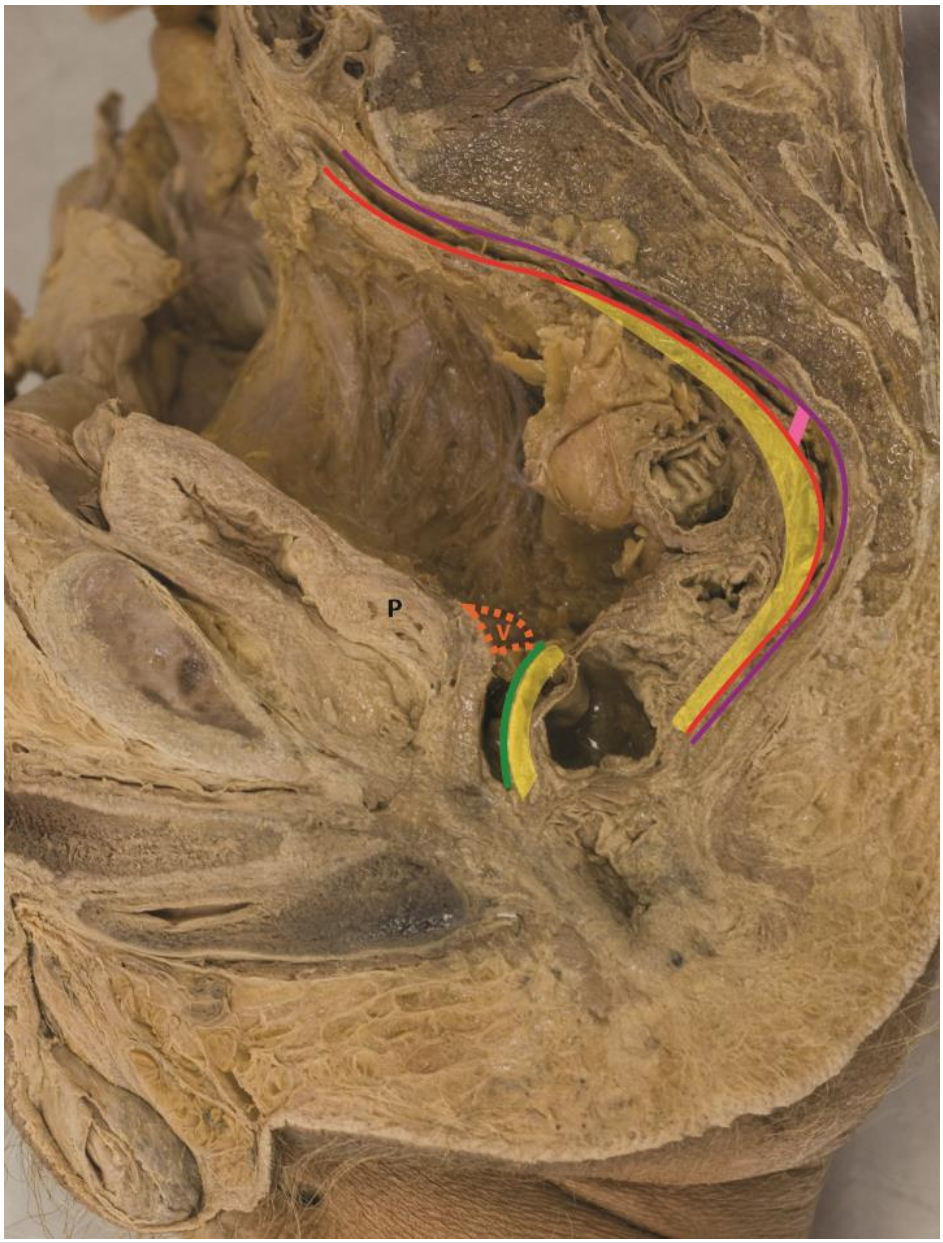

Figure 4. Sagital cross-section rectum
Purple: parietal endopelvic fascia. Red: visceral endopelvic fascia. Between purple-red: holy plane of Heald. Pink: rectosacral fascia (Waldeyer's fascia). Green: Denonvilliers' fascia. Yellow: mesorectum. Orange (V): seminal vesicles. P: prostate.

In women Denonvilliers's fascia is much thinner and localized between vagina and rectum (rectovaginal septum, which prevents rectocele). The fascia is connected much closer to the rectum than to the urogenital structures, and ends in the caudal part of the urogenital diaphragm. The **lateral ligaments** are situated ventro-laterally between visceral and parietal fascia, just medially to the inferior hypogastric plexus. They hardly exist of any connective tissue, and contain the very variably present middle rectal artery and vein. To prevent injury to the plexus, one should transsect the lateral ligaments close to the rectum. The left ureter lies dorsally of the sigmoid mesentery and the fusion-fascia of Toldt at the level of the bifurcation of the common iliac artery, and is therefore at risk of injury in rectal resection and vascular ligation.

Vascularisation rectum

The **superior rectal artery** is the caudal prolongation of the IMA. This artery descends into the pelvis in the mesosigmoid and bifurcates at the level of S3. The two branches descend at the dorsal side of the rectum, giving smaller branches to the rectal bowel wall. These small branches continue up to the internal anal sphincter and anastomose with the branches of the middle rectal artery and the inferior rectal artery. This last artery does hardly vascularize the distal rectum but is much more important for the anal canal. When the superior and middle rectal artery are sacrificed the entire rectum must be resected up to the anal canal.

The **middle rectal artery** originates from the internal iliac artery (hypogastric artery). The anatomical position of the middle rectal artery is poorly defined, just as its contribution to the vascularization of the rectum. The middle rectal artery goes to the caudal part of the rectum, arriving at the anterior side at the level of the seminal vesicles in men, just caudally to the lowest point of the rectovesical pouch through the lateral ligaments.

The **inferior rectal artery** originates from the internal pudendal artery. This artery exists of two or more branches coming through the wall of the anal canal at the level of the external sphincter. These branches communicate with the branches of of the infectior rectal artery at the controlateral side, but also create intramural anastomoses with the superior and middle rectal artery. During the perineal phase of an abdominal perineal resection (APR) the inferior rectal artery will be encountered in the 'roof' of the ischio-rectal fossa.

The **veins** of the rectum follow the anatomical position of the arteries.

The **lymphatic drainage** of the rectum follows the vascularization of the rectum. The extramural lymphatics of the rectum go tow the pararectal lymph nodes, localized in the mesorectum. From there lymph flows to the intermediate lymph nodes along the superior rectal artery and IMA. Only very caudally localted rectum malignancies can drain to inguinal lymph nodes.

Concensus on the level of arterial ligation in rectal resection is missing. Many surgeons apply a **'high tie'**, ligating the IMA up to its origin including the IMA lymph nodes with the resection.

Figure 5. High tie vs low tie
High tie: ligation inferior mesenteric artery. Low tie: ligation superior rectal artery. Pink: lymph nodes high tie.

In this situation the vascularization to the residual descending colon is depending upon on the middle colic artery and the marginal artery. In case of a **'low tie'** the superior rectal artery is ligated, meaning the vascularization of the residual descending colon and sigmoid is provided for by the left colic artery.

In case of a curative resection of rectum carcinoma all pararectal lymph nodes must be resected by including the circular mesorectum with the visceral mesorectal fascia up to the pelvic floor in the resection (total mesorectal excision TME). Only in case of carcinomas of the upper third of the rectum a partial resection of the (proximal) mesorectal can be sufficient (partial mesorectal excision PME). These extended resections of the mesorectum can be performed without damaging the surrounding extended autonomous neural network.

Innervation rectum

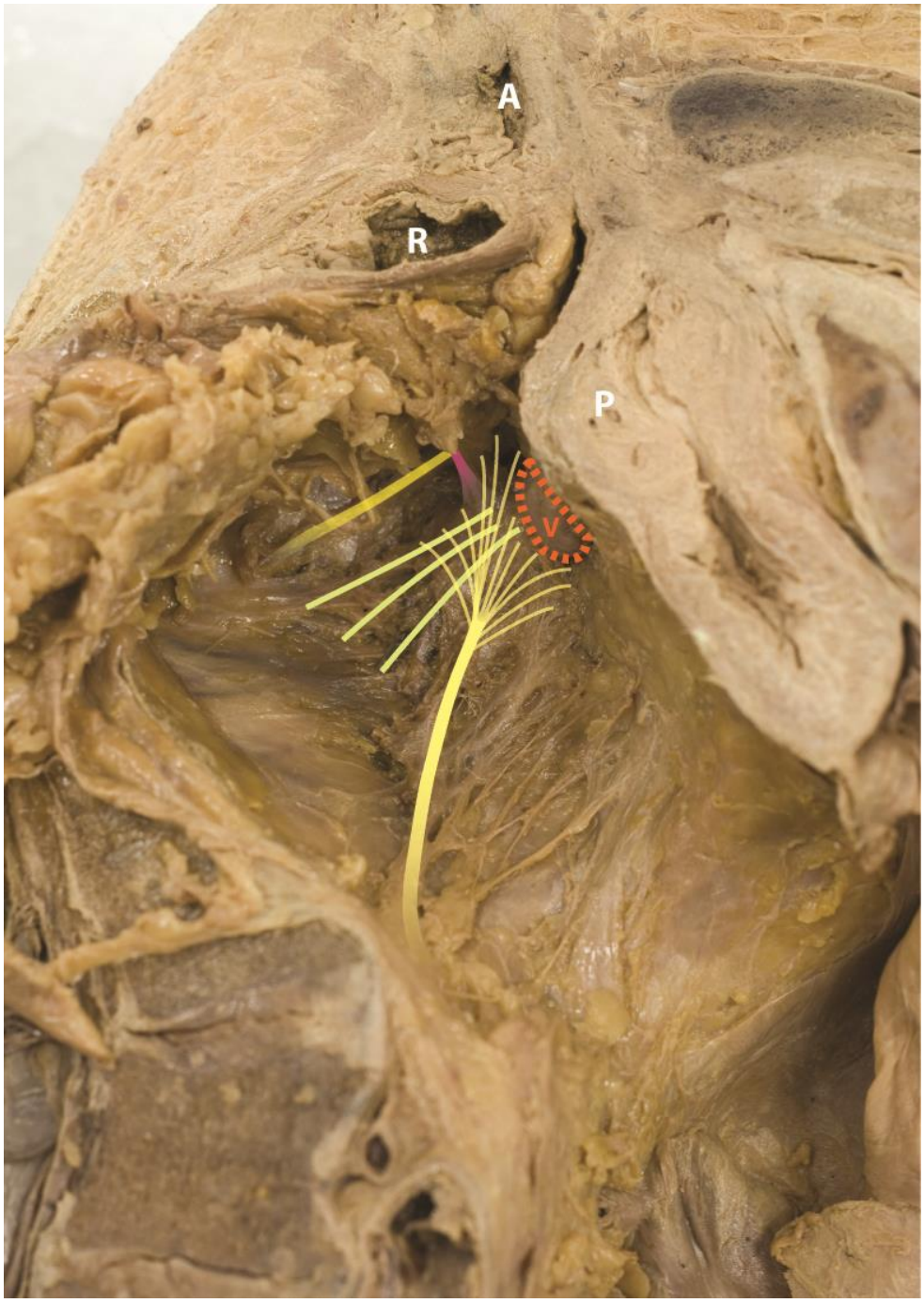

Figure 6. Hypogastric nerve and plexus.
Yellow: hypogastric nerve with hypogastric plexus, and pelvic splanchnic nerves (nervi erigentes) coming from the sacrial roots and joining the plexus. Dark yellow: levator ani nerve. Pink: lateral ligament. Orange (V): seminal vesicle. P: prostate. R: rectum. A: anus.

The sympathetic innervation of the rectum is coming from the superior hypogastric plexus, situated at the lever of the aortic bifurcation (L4-S1). From here originate both hypogastric nerves to the left and right (wisbone), going dorsally of the parietal pelvic fascia, 1-2cm caudally to the ureters, to the inferior hypogastric plexus situated dorsally to the holy plane of Heald. When mobilizing the mesorectum the risk exists of taking these nerves into the resection when dissecting the loose tissue of the holy plane of Heald too dorsally. The hypogastric nerves are responsable for the sympathetic innervation of the rectum and urogenital organs: ejaculation (contraction of the seminal vesicles and closure of the sphincter of the bladder, lubrification of the vagina). These nerves are particularly at risk at the origin of the IMA (high tie) and at the crossing of the mesosigmoid at the level of the aortic bifurcation. The parasympathetic innervation of the rectum is provided for by the pelvic splanchnic nerves (nervi erigentes), originating from the sacral roots of S2, S3, and S4. These cross through the parietal pelvic fascia and add to the inferior hypogastric plexus. Then they descend to the rectum and the urogenital organs. The the pelvic splanchnic nerves are at risk of injury when the middle rectal artery is ligated too laterally during TME. They innervate the rectum and urogenital organs. In case of injury bladder disfunction, impotence, and constipation will occur.

We wish to thank Göran van Rooyen en Fleur van Midwoud for their help in making the anatomical figures.

Chapter 3

High tie versus low tie in rectal surgery: comparison of anastomotic perfusion

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ABSTRACT

Introduction: Both “high tie” (HT) and “low tie” (LT) are well-known strategies in rectal surgery. The aim of this study was to compare colonic perfusion after HT to colonic perfusion after LT.

Methods: Patients undergoing rectal resection for malignancy were included. Colonic perfusion was measured with laser Doppler flowmetry, immediately after laparotomy on the antimesenterial side of the colon segment that was to become the afferent loop (measurement A). This measurement was repeated after rectal resection (measurement B). The blood flow ratios (B/A) were compared between the HT group and the LT group.

Results: Blood flow was measured in 33 patients, 16 undergoing HT and 17 undergoing LT. Colonic blood flow slightly decreased in the HT group whereas the flow increased in the LT group. The blood flow ratio was significantly higher in the LT group (1.48 vs. 0.91; p=0.04), independent of the blood pressure.

Conclusion: This study shows the blood flow ratio to be higher in the LT group. This suggests that anastomoses may benefit from better perfusion when LT is performed.

INTRODUCTION

To date, 100 years after the introduction of the low tie and high tie techniques for colorectal surgery by Miles and Moynihan, respectively[1, 2], the discussion on which is the best technique continues, as illustrated by two recently published reviews[3, 4]. Titu et al. have summarized literature comparing low tie and high tie techniques for curative colorectal surgery[3]. They concluded that no undisputable evidence favouring one technique exists. Nevertheless, they propagate the high tie technique since it allows better lymph node retrieval and therefore a more accurate tumour staging. In another review comparing the low tie with the high tie technique, Lange et al. distinguished three aspects in the discussion: oncological, anatomical and technical[4]. They concluded that for each aspect the evidence is insufficient to favour one technique. Nevertheless, they favour the low tie technique since it is less invasive, also with regard to colonic innervation and motility, and it would be beneficial for anastomotic perfusion compared to the high tie technique. Adequate anastomotic perfusion is considered essential for anastomotic healing. Performing a high tie (HT) technique allows anastomotic perfusion only through the marginal artery, which may lead to a decrease in anastomotic perfusion[5, 6]. When a low tie (LT) technique is performed, anastomotic perfusion is allowed not only through the marginal artery, but through the left colic artery and its ascending branch as well. This anatomical reality suggests that anastomotic perfusion is higher after low tie; however, no evidence exists supporting this hypothesis. The aim of this study is to compare the high tie technique to the low tie technique with regard to anastomotic perfusion.

METHODS

Patients planned for elective rectal resection for malignancy in four participating hospitals, with nine participating surgeons, were eligible for this non-randomized, prospective study. The procedure was represented by a Total Mesorectal Excision with or without anastomosis.

Blood flow was measured with the O2C system. The O2C system (“oxygen to see”, Lea Medizin Technik, Giessen, Germany) is a laser Doppler flowmetry system that has often been used to measure intestinal blood flow for research purposes[7, 8]. Blood flow, expressed in arbitrary units, is determined by analysing the Doppler frequency shifts in laser light (820 nm) reflected from moving red blood cells. The laser light is emitted into the tissue, and the backscattered light is detected with a flat probe with a measurement depth of 4–6 mm (Lea Medizin Technik, Giessen, Germany). The O2C measurement frequency is 30 Hz. Measurements were performed at two moments during the operation, being (a) right after median laparotomy and (b) just before construction of the anastomosis or colostomy, in case of abdominoperineal resection. The measurements were performed on the antimesenterial, serosal side of the colon segment that was to become, or was after resection (at moment b), the proximal loop. For all measurements, after placement of the flat

probe, the flow measurement was allowed to stabilize until a constant flow was measured. Afterwards, the flow was recorded for 30s, obtaining 15 values. The mean of these 15 measurements was used to calculate the blood flow ratio (BFR), B/A. During the measurements, the blood pressure was measured as well, and the mean arterial pressure (MAP) was calculated.

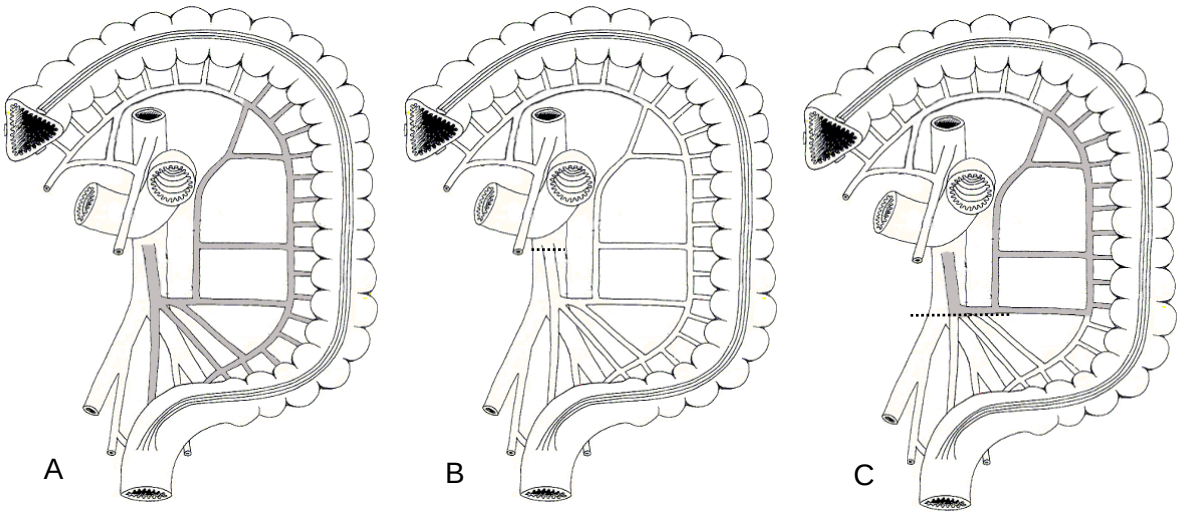

Figure 1*. The vasculature of the colon.*
A) Grey indicates the flow area of IMA, B) The dashed line indicates the level of ligature in HT, leaving no flow in the inferior mesenteric artery and its branches C) The dashed line indicates the level of ligature in LT, grey indicates the flow area of IMA after LT

The high tie technique was defined as ligation of the inferior mesenteric artery (IMA) at its origin. The low tie technique was defined as ligation of the superior rectal artery (SRA), just below the branching of the left colic artery (Fig. 1). The surgeon decided which technique was used. The BFR distribution was normalised by a logarithmic transformation and compared between the HT and LT groups by means of an unpaired t test. MAP was compared between moments A and B with a paired sample t test. Statistical analysis was performed with SPSS 15.0.

RESULTS

During 1 year, 33 patients were included in four different medical centers. A HT was performed in 16 patients (48%) of whom 12 (75%) received a primary anastomosis. A LT was performed in 17 patients (52%) of whom also 12 (71%) received a primary anastomosis. In all patients receiving a primary anastomosis, the splenic flexure was mobilised. Nine patients (75%) in the high tie group and ten patients (83%) in the low tie group received a defunctioning stoma. The mean number of lymph nodes harvested in the high tie group was 11 (range, 6–23); in the low tie group, 12 (range, 6–33)

(p=0.35). The mean number of positive lymph nodes harvested in the high tie group was 3 (1–5); in the low tie group, 4 (1–9) (p=0.32).

Baseline characteristics	High Tie	Low Tie	p-value
Gender (M/F)	11/5	12/5	1,000
Age	55 ± 17	61 ± 13	0,363
BMI	25 ± 3	27 ± 7	0,473
Operation			1,000
APR	4	5	
LAR	12	12	
Neoadjuvant therapy			0,024
RT	14	8	
No RT	2	9	
ASA-score			0,170
I	7	5	
II	8	6	
III	1	6	
Cardiovascular comorbidity	2 (13 %)	4 (24 %)	0,656
Operating time (minutes)	160 (100–340)	145 (45–225)	0.450
Tumour stage			0,250
0	1	0	
I	4	4	
IIa	2	4	
IIb	1	0	
IIIa	2	3	
IIIb	1	3	
IIIc	0	1	
IV	4	0	

Table 1. *Patient characteristics of included patients.*
M/F = Male / Female; BMI = Body Mass Index (kg/m^2); APR = Abdomino-Perineal Resection; LAR = Low Anterior Resection; RT = Radiotherapy; ASA-score = American Society of Anaesthesiologists score.

Two patients developed anastomotic leakage, one in the HT group and one in the LT group. In the HT group, significantly more patients received neoadjuvant radiotherapy. No significant differences were found in the remaining baseline characteristics (Table 1). The mean BFR was significantly higher in the LT group as depicted in Table 2, whereas the blood pressure during measurements was not significantly different as depicted in Table 3.

Ratio	HT / LT	Mean Ratio	Std. Error Mean	p-value
B/A	HT	0,91	0,24	0,04
	LT	1,48	0,32	

Table 2. *Comparison of blood flow ratios between the high tie (HT) and the low tie (LT) technique.*

Group	MAP A/B	Mean	Std. Error Mean	p-value
HT	A	67,1	2,2	0,473
	B	64,2	3,2	
LT	A	69,8	4,4	0,075
	B	75,7	2,0	

Table 3. *Mean Arterial Pressures (MAP) measured during the blood flow measurements at time points A and B, respectively.*

DISCUSSION

To date, the discussion on the matter of high tie versus low tie continues. This study focuses on the colorectal vasculature and the flow change after HT or LT. Seike et al. found the colonic blood flow to vastly decrease after ligation of IMA or SRA[5], with the subsequent conclusion that this could be an unavoidable factor in the pathophysiology of colorectal anastomotic leakage. However, this study shows otherwise. After a HT procedure, only a slightly decreased blood flow was observed at the end of the operation (BFR 0, 91), whereas an increased blood flow was measured after LT (BFR 1, 48). The blood flow changes occurred independently from the systemic blood pressure (Table 3). These different findings may be explained by the time interval between arterial ligation and measurement. Seike et al. performed their measurements immediately after clamping of the artery. In this study the first measurement was performed immediately after laparotomy, and the second measurement, just before construction of the anastomosis or colostomy, i.e. at the end of the operation. Therefore, the interval between ligation and measurement is much longer in this study compared to the aforementioned study. This suggests that over time, a recruitment of colonic arteries occurs, allowing recovery of blood flow. In order to study whether these blood flow changes are permanent or not, blood flow measurements in the postoperative period would be interesting. In addition, since anastomotic leakage is generally detected around the eighth postoperative day[9], it could provide important information on the pathophysiological processes concerning blood flow leading to AL. The BFR was significantly higher after LT which means LT allows better perfusion of the proximal anastomotic loop at the end of the operation. Most likely, this is due to the preservation of the left colic artery and its ascending branch. In addition to the marginal artery, these arteries allow a second pathway for blood supply and faster and/or a more extensive recruitment of colonic arteries. Therefore, since good perfusion is essential for proper anastomotic healing, LT would be the preferred technique for this aspect of the high tie–low tie comparison. The average BFR after LT shows an increase in blood flow compared to the initial value at the end of the operation. This has been described before by Karlicek et al.[10] and could be due to reactive hyperaemia as a result of colon manipulation. However, it could also be due to a variety of ischaemia reperfusion injuries (IRI). These injuries have been well described in animal models in which an IRI leads to visible hyperaemia and decreased anastomotic strength[11]. This response is probably also present after HT; however, it is

more outspoken after LT most likely due to preservation of the left colic artery. Whether these findings have an impact on the incidence of anastomotic leakage should be evaluated by analysing the blood flow during the postoperative period or in a similar but larger study. The O2C allows non-invasive measurement of blood flow; however, the measurements are sensitive to several variables. First, it depends on placement of the probe. The probe has to be placed on the exact same spot for perfect comparability. Since it is virtually impossible to mark a spot on the colon without influencing the local blood flow or without hindering the progress of the operation, placement of the probe will be slightly variable. Second, the measurements are sensitive to different pressures applied on the probe when holding it in the right position. Higher pressures are likely to lead to more compressed arteries and a lower blood flow. In order to limit the influence of these variables on the outcome, measurements were performed by the same surgeon, allowing reproducibility of the measurement. In addition, the blood flow ratio was calculated for which the first measurement served as a control. The use of a ratio also allowed standardizing intrinsic, patient-related differences like microangiopathy due to atherosclerosis and diabetes mellitus. Table 1 shows baseline characteristics to be comparable between HT and LT except for radiotherapy. Significantly more people in the HT group received neoadjuvant radiotherapy. This is, however, unlikely to have an effect on the blood flow in the proximal anastomotic loop since this loop is located outside the radiation field. In addition, the high tie group contained a higher number of patients with metastasized disease (stage 4 present in 25% in the HT group vs. 0% in the low tie group). This difference most likely illustrates the participating surgeons having preferred to perform a high tie technique in patients with metastasized disease.

CONCLUSION

When comparing high tie ligation to low tie ligation, this study shows the perfusion of the proximal loop of the anastomosis to be better after low tie ligation. Considering neither of both techniques is favourable on the oncological or technical aspect, low tie ligation may be the technique of choice in patients undergoing rectum resection.

REFERENCES

1. Miles WE (1971) A method of performing abdomino-perineal excision for carcinoma of the rectum and of the terminal portion of the pelvic colon (1908). CA Cancer J Clin 21(6):361–364
2. Moynihan B (1908) The surgical treatment of cancer of the sigmoid flexure and rectum. Surg Gynecol Obstet 6:463–466
3. Titu LV, Tweedle E, Rooney PS (2008) High tie of the inferior mesenteric artery in curative surgery for left colonic and rectal cancers: a systematic review. Dig Surg 25(2):148–157
4. Lange MM et al (2008) Level of arterial ligation in rectal cancer surgery: low tie preferred over high tie. A review. Dis Colon Rectum 51(7):1139–1145
5. Seike K et al (2007) Laser Doppler assessment of the influence of division at the root of the inferior mesenteric artery on anastomotic blood flow in rectosigmoid cancer surgery. Int J Colorectal Dis 22(6):689–697
6. Dworkin MJ, Allen-Mersh TG (1996) Effect of inferior mesenteric artery ligation on blood flow in the marginal artery-dependent sigmoid colon. J Am Coll Surg 183(4):357–360
7. De Bruin AF et al (2009) The impact of chronic smoking on rectal mucosal blood flow. Tech Coloproctol 13(4):269–272
8. Albuszies G et al (2005) Effect of increased cardiac output on hepatic and intestinal microcirculatory blood flow, oxygenation, and metabolism in hyperdynamic murine septic shock. Crit Care Med 33(10):2332–2338
9. Komen N et al (2009) After-hours colorectal surgery: a risk factor for anastomotic leakage. Int J Colorectal Dis 24(7):789–795
10. Karliczek A et al (2010) Intraoperative assessment of microperfusion with visible light spectroscopy for prediction of anastomotic leakage in colorectal anastomoses. Colorectal Dis 12:1018–1025
11. Posma LA et al (2007) Transient profound mesenteric ischemia strongly affects the strength of intestinal anastomoses in the rat. Dis Colon Rectum 50(7):1070–1079

Part IIa

Colorectal anastomosis: technique and healing

Chapter 4

Systematic review of the technique of colorectal anastomosis

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ABSTRACT

Background: Many different techniques of colorectal anastomosis have been described in search for the technique with the lowest incidence of anastomotic leak. A systematic review of leakage rates of techniques of handsewn colorectal anastomosis was conducted, to provide a guideline for residents and promote standardization of its technique.

Methods: Clinical and experimental articles on colorectal anastomotic techniques and ananstomotic healing published in the past 4 decades were searched. We included evidence on suture material, suture format, single- vs double-layer sutures, interrupted vs continuous sutures, handsewn vs stapled and compression colorectal anastomosis, and anastomotic configuration.

Results: In total, 3 meta-analyses, 26 randomized trials, 11 nonrandomized comparative studies, 20 cohort studies, and 57 experimental studies were found.

Discussion: Results show that, for many aspects of the technique of a hand-sewn colorectal anastomosis, evidence is lacking. A single-layer continuous technique using inverting sutures with slowly absorbable monofilament material seems preferable. However, in contrast to stapled and compression colorectal anastomoses, the technique for hand-sewn colorectal anastomoses is non-standardized with regard to intersuture distance, suture distance to the anastomotic edge, and tension on the suture. We believe detailed documentation of the anastomotic technique of all colorectal operations is needed to determine the role of the hand-sewn colorectal anastomosis .

INTRODUCTION

Construction of a colorectal anastomosis is a hallmark of surgical training. However, although surgical residents can refer to key publications with evidence based conclusions for many topics, mere imitation of an experienced surgeon traditionally is considered the basic source for the technique of hand-sewn colorectal anastomosis. The large variety of anastomotic techniques is one of the main difficulties in the interpretation of the literature. Anastomotic leakage (AL) following colorectal resection is a major problem of surgical care, with an incidence between 3-19%[1-4]. Although accurate prediction of risk is impossible, certain factors are known to contribute to AL, including surgeon-related factors (e.g. increased incidence of AL in a colorectal anastomosis constructed after hours[5], and the positive role of specialization on complications in colorectal surgery[6]) and patient-related risk factors (e.g., the inverse relationship between the height of colorectal anastomosis from the anal verge and the leak rate[7-12]). Decades of research have resulted in many studies investigating different techniques for constructing colorectal anastomosis in search for the safest method. Appreciating the conclusions from this extensive research is essential for the quality of colorectal surgery and for the resident being trained in colorectal surgery. Our aims were to perform a systematic review of all aspects of the technique of hand-sewn colorectal anastomosis, and compare hand-sewn with mechanical colorectal anastomosis to provide a guideline for residents and to promote standardization of the technique.

METHODS

Search strategy

A literature was searched using Medline, Embase, and Cochrane databases for studies between Janueary 1, 1970 and February 1, 2011, using the key words presented in Figure 1. The search was restricted to articles published in English, Dutch and French. References in the selected publications were searched for additional studies.

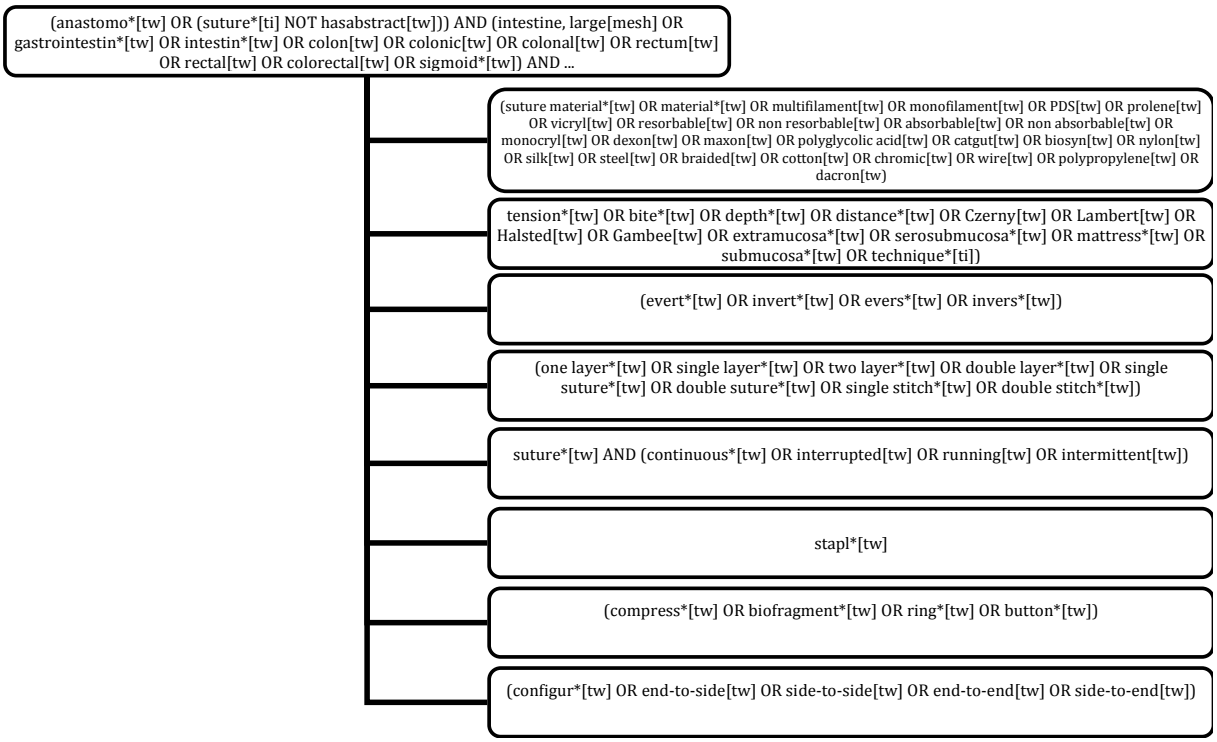


Figure 1. *Literature search (keywords for Medline-search; a comparable search was performed in Embase / Cochrane*)

Study selection

Clinical as well as experimental studies were selected to address several aspects of the technique of hand-sewn colorectal anastomosis. These included:

1. Suture material

2. Suture format (size of suture bites, in-between distance of bites, suture tension, configuration of the bite, and inverting versus everting sutures)

3. Single- vs double-layer colorectal anastomosis

4. Interrupted vs continuous sutures

5. Hand-sewn vs stapled colorectal anastomosis

6. Hand-sewn vs compression colorectal anastomosis

7. Configuration of colorectal anastomosis (end-to-end (ETE), end-to-side (ETS), side-to-end (STE), side-to-side (STS), length of the side-limb, length of the enterotomy)

Inclusion criteria for clinical studies

Only clinical articles comparing 2 or more colorectal anastomotic techniques with regard to clinical AL were considered relevant. When only 1 comparative study was available on a particular subject,

clinical cohort studies were added to the selection. Results were analysed only if the study groups and results were clearly described with proper statistical analysis.

Inclusion criteria for experimental studies

Experimental articles were selected when comparing 2 or more colorectal anastomotic techniques together with objective measurements for anastomotic healing: AL, anastomotic bursting pressure (ABP), anastomotic breaking strength, histologic results, or collagen concentration. When 2 studies were reported by the same institution, either the better quality study or the most recent publication was included. As with clinical studies, results were analysed only if the study groups and results were clearly described with proper statistical analysis. However, the lack of statistical analysis of histological findings in experimental studies was accepted.

Exclusion criteria:

Because the healing of small-bowel anastomoses is different and the incidence of AL lower compared with large-bowel anastomoses, studies including both procedures without differentiating the results and statistical analysis were excluded. Ileocolic anastomoses after right hemicolectomy or ileocecal resection represent healing of the colon, and were therefore included. Studies reporting radiological AL without distinction of clinical AL were excluded, as were studies reporting only on emergency operations, children, and colo-anal anastomosis or pouches. Results of experimental studies measured directly after the construction of colorectal anastomosis were not taken into account because these do not reflect anastomotic healing.

Data extraction for clinical studies

Two physicians (J.C.S. and F.D.) entered data in a database following standard protocols. Seven factors were considered for clinical studies. These included:

- First author and year of publication
- Level of evidence (following the Centre of Evidence Based Medicine, University of Oxford)
- Study design
- Number of patients
- Location of anastomosis in gastrointestinal tract
- Definition of outcome by the authors (AL, clinical AL, radiological AL)
- Results and statistical analysis

Data extraction for experimental studies

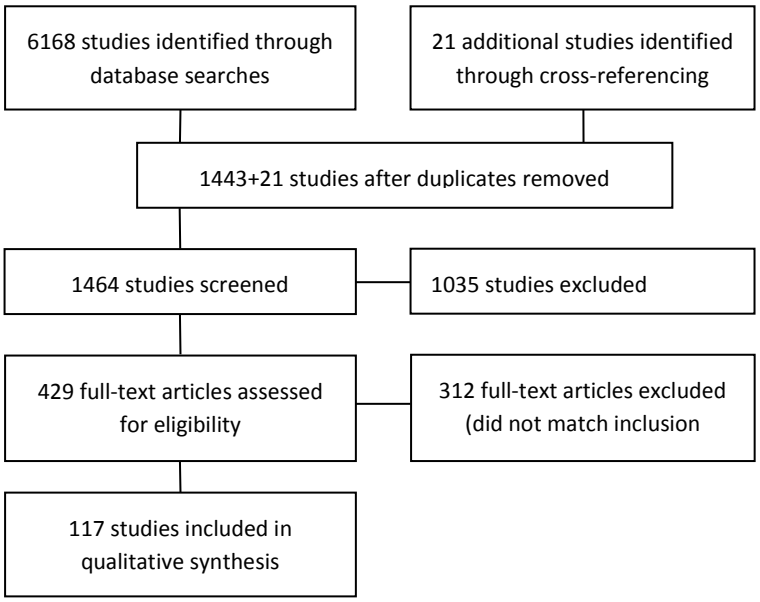
Six factors were considered for experimental studies. These included:

- First author and year of publication
- Study design
- Number of animals per group
- Species
- Outcome factors for anastomotic healing (AL, ABP, breaking strength, histology, or collagen-concentration)
- Results

RESULTS

The literature search identified 6168 articles. 1443 articles remained after duplicates were removed. The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyeses) flowchart in figure 2 shows the selection of studies: 117 studies were included in the systematic review. Included studies and their characteristics are listed in table 1, together with all results of outcome measures. The results per research question are summarized herein.

***Figure 2**. The PRISMA flow-chart: selection of relevant studies*



1. Suture material

Decades ago, several materials such as silk, linen, catgut, polyglactin 910, and nylon were commonly used for colorectal anastomosis. Today most gastrointestinal anastomoses, including colorectal anastomosis, are constructed with polydioxanone sutures. Ten experimental studies were included[13-22]. Results show that absorbable sutures compared with non-absorbable or slowly-absorbable sutures cause more tissue reaction[16, 17, 20], one study showing absorbable sutures dissolve too rapidly, influencing anastomotic strength[16]. Multifilament compared to monofilament sutures cause more tissue damage and easier adherence of material within the interstices of multifilament sutures[14, 15, 18, 19], providing a basis for infection[23]. Surprisingly, experimental studies on healing of colorectal anastomosis constructed with polydioxanone sutures are scarce; only two studies were included, finding equal ABP and histology between polydioxanone and polyglycolic acid[13, 15]. Non-comparative experimental studies that did not match the inclusion criteria for the present review have shown that polydioxanone sutures possesses all aspects considered important: monofilament, little histological reaction, slowly-absorbable with long preservation of strength, and low adherence of bacteria to the material[23-26].

New possibilities of sutures coated with mesenchymal stem cells and doxycycline were explored in 2 experimental studies with promising, but not yet convincing results[21, 22].

Two included randomized clinical trials (RCTs) on suture material fail to achieve a unanimous conclusion, because of the small number of patients included and the different suture materials tested that are rarely used today[27, 28].

In conclusion, on the basis of experimental studies, non-absorbable or slowly absorbable monofilament sutures seem to be the suture of choice for colorectal anastomosis. However there is no level 1 evidence to confirm this hypothesis.

2. Suture format

a. Size of suture bites

Since Lembert[29] described the construction of intestinal anastomoses in dogs using suture bites with 5mm distance to the cut edge nearly 2 centuries ago, this aspect seems to have become less clear in surgical literature. One experimental study was found for this systematic review that investigated the difference in anastomotic strength in rats with sutures placed between 3mm and 1.5mm from the cut edges. Results showed lower breaking strength for small bites, measured at day 2[30]. One RCT by Greenall et al. reporting on the distance of the suture to the wound edge matched the inclusion criteria. They randomly allocated patients to have bowel sutures placed either 5 or 10mm from the cut edges, with no significant differences in AL[31]. Because it is not possible to extrapolate the

distances used in a rat model to the clinical situation, we can only conclude from one level 1b RCT that distances of 5 and 10mm from the cut edge will probably give adequate results.

b. In-between distance of bites

Lembert described in 1826 an in-between distance of approximately 1cm between sutures[29]. One experimental study conducted by Waninger et al. investigating the distance between sutures in rats was included in our review. It concluded that a small distance between sutures (1.5mm) improves apposition compared with a large distance (2.5mm)[32]. Neither clinical comparative studies nor cohort studies were found. Again, distances in a rat model are difficult to extrapolate to the patient. Because clinical studies on this topic are lacking, no precise maxim can be distilled from the literature.

c. Suture tension

In routine clinical practice, 2 undefined schools of thought seem to exist: the first believes that sutures should be tightened to prevent dehiscence of the anastomosis, and the second considers that sutures should be applied more loosely, allowing maximal perfusion of the cut edges. Again only one rat study[32] investigated this, with moderate tension giving the best histological and microangiographic results. Whether tension on knots could influence the incidence of AL in a clinical setting has not been investigated for interrupted or continuous suturing. On the basis of the literature evaluated in the present review, nothing can be concluded on the proper tension on the thread or on the knot.

d. Configuration of the bite

Historically, all opinion leaders proposed their own configuration of gastrointestinal sutures. Anatomical apposition of all layers promoting primary healing was thought to be important. These days, most surgeons will use a simple through-all-layers technique. From ex vivo studies it is known that sutures through the mucosal layer do not contribute to anastomotic strength[33, 34].

The present review included 2 experimental studies on rat colon, comparing histological results of full-thickness sutures to serosubmucosal sutures. Houdart et al. found no histological differences[35], but Krasniqi et al. found better histological results for full-thickness sutures with equal anastomotic strength[36]. No comparative clinical studies were found on the configuration of the bite. Because of this lack of evidence, we have included cohort studies, reporting low rates of AL for both serosubmucosal and full-thickness suture formats (AL 0% - 4.4%) [37-41].

We can only conclude, using scarce level 2b evidence from the cohort studies evaluated, that both serosubmucosal as full-thickness suture seem to provide low rates of AL. It is clear that the configuration of the suture bite is considered of little interest in studies regarding AL.

e. Inverting vs everting sutures

Since the publication of Lembert[29], surgeons generally have advocated an inverting technique of gastrointestinal anastomosis because it is believed that protruding mucosa will lead to AL. However, in the 1960s, 2 clinical studies showed good healing of everting anastomoses with a low incidence of AL[42, 43]. Between 1960 and 1970, these 2 non-comparative studies were followed by many experimental publications comparing everting with inverting techniques. They failed to achieve a unanimous conclusion on anastomotic healing; however they were consistent in showing that everting anastomoses cause more adhesions but less stenosis[44-51]. All 3 experimental studies published after 1970 included in this present review seem to show improved anastomotic healing for inverted anastomoses[44, 47, 51]. The only clinical study matching the inclusion criteria was a RCT[52] showing a 5-fold increased incidence of AL in patients receiving an everting colorectal anastomosis compared to those receiving an inverting colorectal anastomosis. No cohort studies matching our inclusion criteria were found. Therefore, on the basis of available experimental and level 1b clinical studies, there seems to be an advantage of inverting over everting colorectal anastomosis; nonetheless level 1a evidence is lacking.

3. Single- vs double-layer colorectal anastomosis

The technique developed by Lembert[29] and later modified by Czerny[53] is based on a double-layer inverting anastomotic technique. In the 19th and the greater part of the 20th centuries, this was the criterion standard for gastrointestinal anastomosis; in the second half of the 20th century, however, the single-layer anastomosis regained attention through the favorable results obtained by Halstead, Gambee, and Gambee et al.[54-56]. The 13 included experimental studies come to the same conclusion: double-layer anastomoses are inferior to single-layer anastomoses because of increased inflammation and diminished circulation[47, 57-68]. One RCT matched the inclusion criteria, showing no significant differences in AL between single- and double-layer colorectal anastomosis in 92 patients[69]. This RCT conducted a subgroup analysis of 25 low colorectal anastomosis, finding a significantly higher incidence of AL in colorectal anastomosis created with the double-layer technique. None of the 3 non-randomized comparative studies included in this review found a significant difference in AL between the 2 techniques[65, 70, 71]. In conclusion, these results, added to the knowledge that single-layer anastomoses take significantly less time to construct and are less costly[72], are in favor of single anastomoses, on the basis of level 1b evidence.

4. Interrupted vs continuous sutures

The question whether to use interrupted or continuous sutures arose when single layer anastomoses became common practice. Six experimental studies were included, showing equivocal results: better serosal apposition[73] and blood flow in continuous sutures[74], with equal results on ABP and histologic examination[35, 75-77]. Randomized controlled trials investigating interrupted and continuous sutures for colorectal anastomosis are lacking; therefore, only 1 small, nonrandomized, comparative clinical study finding no significant differences was included[78], and noncomparative cohort studies were selected on continuous and interrupted suturing finding equally low leakage rates[38, 79-92]. Clinical and experimental studies have not concluded that one technique is superior to the other, and a high level of evidence is lacking (limited here to level 2b); however from a technical and time-consuming point of view a continuous suture is preferable over interrupted sutures for creating colorectal anastomosis.

5. Hand-sewn vs stapled colorectal anastomosis

After the introduction of stapled colorectal anastomosis in the 1980s, both techniques have become prevalent, without defined indications but for the lower rectal anastomoses. Most surgeons apply both techniques, although often with a personal preference.

Thirteen RCTs[93-105] and 3 meta-analyses were included[106-108]. Lustosa et al. published a Cochrane meta-analysis of 9 RCTs conducted between 1981 and 1991. In this group of 1233 patients, there was no difference in mortality, AL, strictures or reoperation between stapled and handsewn colorectal anastomosis[107]. An earlier meta-analysis, conducted in 1998 combined 13 RCTs concerning patients with colorectal anastomosis, and found similar results: no significant differences in AL or mortality[108]. The Cochrane review conducted by Choy et al. included studies on colorectal anastomosis after right hemicolectomy. This review showed significant less overall AL in the stapled group; however when clinical AL was used as the only outcome measure, this difference did not reach statistical significance[106]. An interesting subgroup analysis made by Friend et al.[101] found more AL in handsewn colorectal anastomosis when the anastomoses made by residents were separately analyzed. Their conclusion was that stapling seems to have an advantage in less experienced hands. Of 7 included nonrandomized cohort studies included in this review, 5 found no superiority of one technique[109-113]. Two studies found significantly more AL in stapled compared with hand-sewn anastomoses[114, 115]. However, one of these had significantly more patients with corticosteroids in the stapled group[115], while the other included 505 hand-sewn compared with 28 stapled colorectal anastomoses[114]. Thirteen experimental studies included herein found results approximately similar to in the clinical setting: no significant differences in AL, with equal or higher ABP in stapled colorectal anastomosis [59, 63, 68, 116-125].

In conclusion, the field of hand-sewn vs stapled colorectal anastomosis has been well studied. On the basis of level 1a evidence, no superiority of stapled over hand-sewn colorectal anastomosis exists.

6. Hand-sewn vs compression colorectal anastomosis

Denans described the first technique to create intestinal anastomoses by compression in 1827[126], followed by other devices, such as the Murphy button in 1892[127]. Today the biofragmentable anastomotic ring, made of absorbable polyglycolic acid, is used most often. Four included experimental studies show that compression colorectal anastomosis leads to acceptable healing and strength[128-131]; 6 included RCTs provide equivalent conclusions, finding no significant differences between hand-sewn and compression colorectal anastomosis [132-137]. Also, noncomparative clinical cohort studies including up to 1360 patients have reported incidences of AL between 0,7% and 5%[138-141]. Although few gastrointestinal surgeons routinely use compression colorectal anastomosis, it seems a safe method. On the basis of 6 level 1b studies, no superiority of compression over hand-sewn colorectal anastomosis exists when comparing leak rates.

7. Configuration of colorectal anastomosis

Studies regarding the configuration of the afferent and efferent ileal, colonic or rectal loops are heterogeneous in patient selection and configuration, and often concentrate on stapled pouches for very low anastomoses with outcome variables other than AL. Only 2 experimental studies matched the inclusion criteria; one study found no difference in blood flow between ETE or side-to-side anastomosis after rectal resection in pigs[142], and the other found better blood flow in ETE compared with side-to-end anastomosis after rectal resection in dogs[143]. The included RCTs are also scarce: one on ETE versus end-to-side finding more AL in ETE[144], and the other on the optimum side limb for side-to-end colorectal anastomosis found no difference between 3cm- and 6cm sized limbs[145]. No studies investigating the ideal length of the enterotomy were identified.

It is difficult to draw a conclusion out of this small amount of studies; there is one level 1b study showing a lower incidence of AL with end-to-side colorectal anastomosis and one level 1b study indicating that a 3-cm or a 6-cm side limb does not affect the incidence of AL.

CONCLUSION

In the clinical setting, healing of colorectal anastomosis is obscured from direct postoperative inspection. When AL occurs, diagnosis can be made only after the patient has become ill, making it a feared complication with high morbidity and mortality[1, 4, 146-148]. This systematic review of all aspects of hand-sewn colorectal anastomosis and the comparison of handsewn to mechanical anastomosis provides an overview on the existing colorectal anastomotic techniques combined with the available

scientific evidence on anastomotic healing. Evaluation of studies on colorectal anastomosis with clinical AL as outcome measure and proper statistics produced very little level 1 evidence for all aspects of handsewn colorectal anastomosis. Nevertheless, we can formulate a conclusion using experimental results combined with clinical results for many aspects: the single-layer continuous suture technique by an inverting technique with slowly absorbable monofilament material seems preferable on the basis of level 1b evidence. However, for the other aspects of the technique, such as how far to place the suture from the anastomotic edge, the intersuture distance in relationship to the distance to the edge, which layers to include in the bite, how high the tension on the suture should be, and through what configuration the anastomosis should be made, surgeons probably rely on their teachers and instinct rather than on scientific evidence.

Large cohort studies that are available, describing low rates of AL for the used anastomotic technique, might indicate that dedicated, high-volume colorectal surgery has a role in lowering the incidence of AL because of a surgeon's familiarity with a certain technique.

Considering mechanical colorectal anastomosis, level 1a evidence indicates that stapling and hand-sewn anastomoses give equal results with regard to clinical AL, and level 1b evidence determines that compression and hand-sewn colorectal anastomosis have similar AL rates. In contrast to all possible variations that exist when sewing an anastomosis by hand, the technique of a stapled anastomosis is much more uniform in the hands of surgeons. This could lead to standardizing colorectal anastomosis, and prevent the nonscientific practice of the preferences of individual surgeons from being handed down from teacher to student without documentation of their exact properties and incidence of AL.

We can conclude from this review that, until now, hand-sewn colorectal anastomosis is constructed following a largely non-defined technique. The circumstances of RCTs do not reflect daily practice; therefore routine detailed documentation of anastomotic technique of all colorectal operations will be instrumental in formulating a definite conclusion on the role of the unstandardized hand-sewn colorectal anastomosis.

Table 1. *Included studies and their characteristics (AL= anastomotic leakage, histol= histology, ABP= anastomotic bursting pressure, bstrenght= breaking strength, coll= collagen, blflow= blood flow). NIR= not included in this review (in case a supplemental subgroup was also studied, outside the topic of this review, NS: not significant.*

1. **Suture material**

Source	Level	No. of cases	Outcome	Results
Clinical				
Gillatt '87[28]	1b (RCT)	57pt, colorectal	Clinical AL	AL: PDS 0% (n=30); silk 3,7% (n=27). NS
Clark '77[27]	1b (RCT)	194pt, colon	Clinical and radiological AL	24% AL catgut(n=99) vs 8.4% AL polyglycolic acid(n=95). Significant
Experimental				
Andersen '89[13]		196 rats	Histology	Polyglactin 910 vs PDS. Equal histolologic results at days 7 and 56.
Foresman '89[15]		160 rats	ABP	Polyglyconate vs PDS. No significant difference in ABP at days 0-7-14-21-42.
Lord '78[18]		30 rats	Histology of the submucosa	Rough surface vs smooth surface. Rough surface (catgut, braided silk, polyglycolic acid) most damage to submucosa. Polyethylene terephthalate coated with polytetrafluoroethylene better, polypropylene best histologic results.
Orringer '77[20]		84 dogs	Histology	Silk vs polypropylene vs wire: silk most inflammation, polypropylene less inflammation, wire least inflammation at days 4-7-10-14.
Munday '76[19]		44 rats	ABP, histology	Catgut vs polyglycolic acid. Equal ABP and histology at day 7.
Deveney '77[14]		60 dogs	Breaking strength, histology	Catgut vs chromic catgut vs polyglycolic acid vs polyglactin 910: equal strength and equal histologic results at day 4-7-14.
Hastings '75[16]		127 dogs	Breaking strength, histology, collagen	Absorbable vs nonabsorbable sutures : Absorbable: less breaking strength at day 14-28, equal collagen at day 120, worse histolologic results at day 120.
Letwin '75[17]		28 dogs	Histology, ABP	Double layer anastomoses 'chromic catgut-silk' vs 'polyglycolic acid – polyglycolic acid': catgut-silk significantly more suture reaction and lower ABP at day 7.
Pasternak '07[22]		85 rats	Breaking strength	Doxycycline (MMP-i) coated sutures vs control carrier-coated sutures: higher breaking strength in doxycycline sutures at day 0-3.
Pascual '08[21]		40 rats	AL, ABP	Polyglactin 910 with mesenchymal cells vs polyglactin 910: no difference in AL, no difference in ABP, fewer adhesions in polyglactin 910 with mesenchymal cells at day 4-7-14-21.

2. Suture format

Source	Level	No. of cases	Outcome	Results
Size of suture bites - clinical				
Greenall '79[31]	1b (RCT)	100pt, colon	Clinical AL	Suture bite 5mm AL 4% (n=50) vs 10mm 6% AL(n=50), NS
Size of suture bites - experimental				
Hogstrom '85[30]		80 rats	Breaking strength	1.5mm vs 3.0mm distance from wound edges: less breaking strength 1.5mm at day 2.
In-between distance of bites - experimental				
Waninger '92[32]		432 rats	Histology	2.5mm vs 1.5mm suture distance: 1.5mm better histology.
Suture tension - experimental				
Waninger '92[32]		432 rats	ABP, histology	No tension vs moderate tension vs high tension on knot: moderate tension better histology, and higher ABP at day 4. No tension: higher ABP at day 7.
Configuration of the bite - clinical				
Leslie '03[37]	2b (cohort)	484pt, colon	Clinical AL	Interrupted serosubmucosal stitches: 0.2% AL.
Pye '96[38]	2b (cohort)	214pt, colorectal	Clinical AL	Interrupted serosubmucosal stitches: 0.5% AL.
Carty '91[39]	2b (cohort)	421pt, colorectal	Clinical AL	Interrupted extramucosal stitches: 2.1% AL.
Lafreniere '85[40]	2b (cohort)	134pt, colorectal	Clinical AL	Interrupted full thickness (modified Gambee): 0% AL.
Motson '84[41]	2b (cohort)	92pt, colon	Clinical AL	Interrupted full thickness (mattress suture): 4.4% AL.
Configuration of the bite experimental				
Krasniqi '09[36]		73 rats	Histology	Serosubmucosal (Halsted) vs full tickness (Gambee) vs posterior Gambee/anterior Halsted stitch: better macroscopic and microscopic histology with full thickness.
Houdart '83[35]		210 rats	Histology	Extramucosal vs full thickness stitch: equal histology.
Inverting versus everting - clinical				
Goligher '70[52]	1b (RCT)	70pt, colon	Clinical AL	AL: 2.9% inverting(n=35) vs 28.6% everting(n=35), significant.
Inverting versus everting – experimental				
Ortiz '75[44]		88 rats	AL, histology	Inverting vs everting: no AL, slower healing and equal adhesions with everting.
Irvin '73[47]		93 rabbits	AL, ABP, histology	Inverting 1layer vs inverting 2layer vs everting: more AL, lower ABP, and delayed mucosal union with everting.
leDouarec '72[51]		65 rabbits	Histology	Direct (everting) vs intraluminal (inverting) sutures: direct more severe inflammation, intraluminal better histological repair.

3. <u>Single vs double layer colorectal anastomosis</u>

Source	Level	No. of cases	Outcome	Results
Clinical				
Everett '75[69]	1b (RCT)	92pt, colorectal	Clinical AL	AL: 5% 1layer(n=40); 4.8% 2layer(n=52), NS
Ceraldi '93[70]	2b (nonrandomized)	84pt, colon	Clinical AL	AL: 6.8% 1layer(n=44); 9.5% 2layer(n=21), NS
Fielding '80[71]	2b (nonrandomized)	1466pt, colon	Clinical AL	AL: 12% 1layer(n=458); 13.5% 2layer(n=968), NS
Reichel '75[65]	2b (nonrandomized)	408pt, colorectal	Clinical and radiological AL	AL: 10.3% 1layer(n=320); 10.3% 2layer(n=88), NS
Experimental				
Athar '96[66]		18 dogs	Breaking strength	1layer more strength, 2layer less adhesions and smaller diameter anastomosis.
Langer '96[64]		26 rabbits	AL, ABP	Steroid model, 1layer vs 2layer (vs stapled, NIR): equal AL, 2layer higher ABP.
Templeton '85[60]		40 dogs	AL, ABP, histology, collagen	1layer vs 2layer (vs 2xstapled, NIR): 0 vs 30% AL, histology worse for 2layer, equal ABP and collagen.
Yesilkaya '85[61]		20 dogs	Collagen	1layer vs 2layer: lower collagen in 2layer.
Graffner '84[59]		18 pigs	AL, breaking strength, histologoy, blood flow	1layer vs 2layer (vs stapled, NIR): No AL, equal breaking strength, more inflammation and less blood flow 2layer.
Wheeless '83[68]		81 dogs	Blood flow	1 layer (Gambee) vs 2 layer (vs stapler, NIR): 1 layer higher blood flow.
Schillaci '79[62]		30 dogs	ABP, collagen	1layer vs 2layer (vs sleeve, NIR): equal ABP and collagen.
Chung '87[63]		30 dogs	Blood flow	Different handsewn vs stapled anastomoses: 2layer more reduction of blood flow.
Langer '75[57]		80 dogs and rats	Histology, blood flow	1layer vs 2 layer: 2layer delayed recovery, more ulceration and stenosing, delayed revascularisation.
Reichel '75[65]		360 dogs	AL, ABP, histology	1layer vs 2layer: no AL, equal ABP, histology worse in 2layer.
Irvin '73[47]		93 rabbits	ABP, histology, collagen	1layer vs 2layer (vs everting, NIR): equal ABP, collagen, and histology.
Herzog '73[67]		200 rats	Breaking strength, blood flow	1layer better vascularisation and higher bursting strength.
McAdams '70[58]		116 dogs	Histology	1layer (Gambee) vs 2layer (Czerny-Lembert). More inflammation 2layer.

4. Interrupted vs continuous sutures

Source	Level	No. of cases	Outcome	Result
Clinical				
Deen '95[78]	2b (nonranomized)	53pt, colon	Clinical AL	AL: 3.8% continuous(n=26) ; 3.8% interrupted (n=27), NS
Volk '11[92]	2b (cohort)	463pt, ileocolonic	Clinical AL	AL:3.1% AL continuous
Law '99[86]	2b (cohort)	500pt, colorectal	Clinical AL	AL:1.4% AL continuous
AhChong '96[79]	2b (cohort)	93pt, colorectal	Clinical AL	AL:2.2% AL continuous
Flyger '95[81]	2b (cohort)	105pt, colon	Clinical AL	AL:1.0% AL continuous
Max '91[88]	2b (cohort)	1000pt, colorectal	Clinical AL	AL:1.0% AL continuous
Sarin '89[90]	2b (cohort)	65pt, colon	Clinical AL	AL:6.2% AL continuous
Harder '88[82]	2b (cohort)	143pt, colon	Clinical AL	AL:0.0% AL continuous
Bailey '84[80]	2b (cohort)	100pt, colorectal	Clinical AL	AL:0.0% AL continuous
Thomson[91]	2b (cohort)	200pt, colorectal	Clinical AL	AL:2.0% AL continuous
Pramateftakis '10[89]	2b (cohort)	276pt, colorectal	Clinical AL	AL:2.5% AL interrupted
Pye '96[38]	2b (cohort)	213pt, colorectal	Clinical AL	AL:0.5% AL interrupted
Huguier '82[83]	2b (cohort)	105pt, colorectal	Clinical AL	AL:3.8% AL interrupted
Khubchandani '82[85]	2b (cohort)	112pt, colorectal	Clinical AL	AL:4.5% AL interrupted
Matheson '81[87]	2b (cohort)	168pt, colorectal	Clinical AL	AL:4.2% AL interrupted
Jonsell '78[84]	2b (cohort)	165pt, colorectal	Clinical AL	AL:8.5% AL interrupted
Experimental				
Shandall '85[74]		40 rabbits	Blood flow	Continuous vs interrupted: continuous sign lower blood flow.
Houdart '83[35]		210 rats	Histology	Extramucosal continuous vs extramucosal interrupted vs continuous. Equal histology at day2-180.
Jiborn '78[77]		64 rats	Collagen	Continuous vs interrupted vs control : continuous lower collagen metabolism until day4.
Jiborn '78[76]		71 rats	ABP	Continuous vs interrupted vs control : equal ABP at day4 and 7.
Jiborn '78[75]		71 rats	Breaking strength	Continuous vs interrupted vs control. Equal breaking strength at day4 and 10.
Delaitre '77[73]		83 rabbits	Histology	Continuous vs interrupted: continuous more mucous evagination, and better apposition (from 1 day to 3months).

5. **Handsewn versus stapled colorectal anastomosis** *indicates a RCT also included in the meta-analysis of Lustosa, # indicates a RCT also included in the meta-analysis of Choy, ^ indicates a RCT also included in the meta-analysis of MacRae.

Source	Level	No. of cases	Outcome	Result
Clinical				
Choy '07[106]**#**	1a (meta-analysis)	955pt, ileocolic	Clinical AL	AL: 1.1% stapled(n=357); 3.8% sutured(n=598), NS
Lustosa'01[107]*****	1a (meta-analysis)	1233pt, colorectal	Clinical AL	AL: 6.3% stapled(n=622); 7.1% handsewn(n=611), NS
MacRae '98[108]**^**	1a- (meta-analysis)	2256pt, colorectal	Clinical AL	AL: odds ratio stapled vs handsewn 0.89 (CI 0.58-1.29), NS
Fingerhut '95[100]*^	1b (RCT)	159pt, colorectal supraperitoneal	Clinical AL	AL: 0% stapled(n=85); 0% handsewn(n=74), NS
Docherty '95[96]^#	1b (RCT)	625pt, colorectal	Clinical AL	AL: 4.5% stapled(n=330); 4.4% handsewn(n=321), NS
Fingerhut '94[99]*^	1b (RCT)	113pt, left colon	Clinical AL	AL: 3.7% stapled(n=54); 8.5% handsewn(n=59), NS
Sarker '94[105]*^	1b (RCT)	60pt, rectum	Clinical AL	AL: 0% stapled(n=30); 6.7% handsewn(n=30), NS
Kracht '93[102]*^#	1b (RCT)	268pt, colorectal	Clinical AL	AL: 8.8% stapled(n=137); 12.2% handsewn(n=131), NS
Friend '90[101]^	1b (RCT)	239pt, left colon	Clinical AL	AL: 3.5% stapled(n=114); 8.8% handsewn(n=125), NS
Cajozzo '90[95]^	1b (RCT)	48pt, colorectal	Clinical AL	AL: 8.3% stapled(n=24); 4.2% handsewn(n=24), NS
Elhadad '90[97]*	1b (RCT)	272pt, colorectal	Clinical fistula	AL: 8.3% stapled(n=139); 11.5% handsewn(n=133), NS
Gonzalez '87[104]*^	1b (RCT)	113pt, rectum	Clinical AL	AL: 10.9% stapled(n=55); 10.3% handsewn(n=58), NS
Everett '86[98]	1b (RCT)	94pt, left colon	Clinical AL	AL: 0% stapled(n=44); 4% handsewn(n=50), NS
McGinn '85[103]*^	1b (RCT)	118pt, low colorectal	Clinical AL	AL: 12.1% stapled(n=58); 3.3% handsewn(n=60), significant
Brennan '82[94]^	1b (RCT)	100pt, colorectal	Clinical AL	AL:10% stapled(n=50); 6% handsewn(n=50), NS
Beart '81[93]*^	1b (RCT)	70pt, colorectal	Clinical AL	AL: 2.9% stapled(n=35); 2.9% handsewn(n=35), NS
Resegotti '05[115]	2b (nonrandomized)	122pt, ileocolic crohn	Clinical AL	AL: 2.0% stapled(n=51); 14.1% handsewn(n=71), significant
Anwar '04[110]	2b (nonrandomized)	100pt, ileocolic malign	Clinical AL	AL: 0% stapled(n=41); 0% handsewn(n=59), NS
Smedh '02[113]	2b (nonrandomized)	42pt, crohn	Clinical AL	AL: 0% STS stapled(n=20); 0% ETE handsewn(n=22), NS
Sielezneff '01[112]	2b (nonrandomized)	116pt, sigmoid diverticular disease	Clinical AL	AL: 0% stapled(n=49); 0% handsewn(n=67), NS
Montesani '92[114]	2b (nonrandomized)	533pt, colorectal	Clinical AL	AL: 28.5% stapled(n=28); 3.1% handsewn(n=505), significant

Scher '82[111]	2b (nonrandomized)	242pt, colon	Clinical AL	AL: 2.3% stapled(n=87); 2.6% handsewn(n=155), NS
Adloff '80[109]	2b (nonrandomized)	51pt, rectum	Clinical AL	AL: 7.7% stapled(n=26); 8% handsewn(n=25), NS
Experimental				
Singer '04[119]		20 pigs	ABP, histology, collagen	Steroid-model. Equal ABP and collagen, inflammation worse for hand-sewn at day4.
Senagore '92[118]		42 pigs	ABP, histology, blood flow, collagen	Equal ABP, histology, blood flow, and hydroxyproline.
Kent '92[125]		20 dogs	ABP, histology	Handsewn: higher ABP, equal histology at day3 and 5.
Jansson '91[116]		30 pigs	AL, breaking strenght, blood flow, collagen	Handsewn vs stapled (vs glued, NIR): no AL, equal breaking strength, blood flow and collagen.
Dziki '91[124]		24 dogs	ABP, histology, collagen	Handsewn: higher ABP at day4, better histology, equal collagen.
Julian '89[123]		56 dogs	Blood flow	Equal vascularisation at day3 to 13.
Kozol '88[120]		8 dogs	Histology (edema)	No significant differences in edema at t=28h.
Chung '87[63]		30 dogs	Blood flow	Tight stapling: less blood flow; adjusted stapling: better blood flow than hand-sewn.
Graffner '84[59]		18 pigs	AL, breaking strength, histology, blood flow	1layer vs 2layer vs stapled: no AL, more necrosis stapled, equal blood flow and breaking strength.
Moss '84[121]		10 dogs	ABP	Stapled higher ABP at day4.
Buchmann '83[122]		8 dogs	Histology	Equal histology at day4. Stapled more fibrosis at 2,3,6 months.
Wheeless '83[68]		81 dogs	Blood flow	1layer (Gambee) vs 2layer vs stapled: stapled higher blood flow than 1 and 2layer.
Polglase '81[117]		24 dogs	AL, histology	Equal AL, handsewn more narrowing, stapled more ulcerative gap.

6. Handsewn versus compression colorectal anastomosis

Source	Level	No. of cases	Outcome	Results
Clinical				
Pahlman '97[137]	1b (RCT)	100pt, colon	Clinical AL	AL: 4% BAR(n=50); 2% handsewn(n=50), NS
Gullichsen '92[135]	1b (RCT)	150pt, colon	Clinical AL	AL: 2.5% BAR(n=79); 4.2% handsewn 2layer(n=71), NS
Bubrick '91[134]	1b (RCT)	782pt, colorectal	Clinical AL	AL: 3% BAR(n=395); 3% handsewn(n=283); 4% stapled(n=104), NS
Dyess '90[136]	1b (RCT)	59pt, colon	Clinical AL	AL: 0% BAR(n=27); 0% handsewn(n=16); 0% stapled(n=16), NS
Cahill '89[132]	1b (RCT)	202pt, colorectal	Clinical AL	AL:2% BAR(n=101); 8.2% handsewn(n=85); 6.3% stapled(n=16), NS
Corman '89[133]	1b (RCT)	438pt, colon	Clinical AL	AL: 2.7% BAR(n=222); 2.5% handsewn(n=162); 1.9% stapled(n=54), NS
Experimental				
Bundy '93[129]		36 dogs	ABP	BAR vs handsewn vs stapled: handsewn higher ABP at day3, equal ABP at day7.
Gullichsen '93[131]		42 dogs	Histology	BAR vs handsewn vs stapled: more edema and inflammation BAR at day1 and7.
Smith '88[128]		40 dogs	AL	Radiotherapy model. 2 sizes BAR vs handsewn vs stapled: BAR 1.5mm more AL, other groups equal.
Maney '88[130]		178 dogs	AL, ABP, histology	BAR vs EEA vs handsewn: no AL, equal ABP, equal histology.

7. Configuration

Source	Level	No. of cases	Outcome	Result
Clinical				
Brisinda '09[144]	1b (RCT)	77pt, rectum	Clinical AL	AL: 29.2% ETE(n=37); 5.0% ETS(n=40), significant
Tsunoda '09[145]	1b (RCT)	40pt, rectum	Clin AL + stump leakage	AL: 5% short limb(n=20); 10% long limb(n=20), NS
Experimental				
Willis '06[143]		18 dogs	Perfusion	Stapled ETE vs stapled STE (vs Jpouch, NIR): ETE better blood flow compared with STE.
Sailer '00[142]		32 pigs	Blood flow	ETE vs STS (vs small pouch vs large pouch, NIR): equal blood flow.

REFERENCES

1. Hyman N, Manchester TL, Osler T, et al. Anastomotic leaks after intestinal anastomosis: it's later than you think. Ann Surg 2007; 245(2):254-8.
2. Matthiessen P, Hallbook O, Rutegard J, et al. Defunctioning stoma reduces symptomatic anastomotic leakage after low anterior resection of the rectum for cancer: a randomized multicenter trial. Ann Surg 2007; 246(2):207-14.
3. Alves A, Panis Y, Trancart D, et al. Factors associated with clinically significant anastomotic leakage after large bowel resection: multivariate analysis of 707 patients. World J Surg 2002; 26(4):499-502.
4. Peeters KC, Tollenaar RA, Marijnen CA, et al. Risk factors for anastomotic failure after total mesorectal excision of rectal cancer. Br J Surg 2005; 92(2):211-6.
5. Komen N, Dijk JW, Lalmahomed Z, et al. After-hours colorectal surgery: a risk factor for anastomotic leakage. Int J Colorectal Dis 2009; 24(7):789-95.
6. Zorcolo L, Covotta L, Carlomagno N, Bartolo DC. Toward lowering morbidity, mortality, and stoma formation in emergency colorectal surgery: the role of specialization. Dis Colon Rectum 2003; 46(11):1461-7; discussion 1467-8.
7. Yeh CY, Changchien CR, Wang JY, 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.
8. Matthiessen P, Hallbook O, Andersson M, et al. Risk factors for anastomotic leakage after anterior resection of the rectum. Colorectal Dis 2004; 6(6):462-9.
9. Rullier E, Laurent C, Garrelon JL, et al. Risk factors for anastomotic leakage after resection of rectal cancer. Br J Surg 1998; 85(3):355-8.
10. Vignali A, Fazio VW, Lavery IC, et al. Factors associated with the occurrence of leaks in stapled rectal anastomoses: a review of 1,014 patients. J Am Coll Surg 1997; 185(2):105-13.
11. Mann B, Kleinschmidt S, Stremmel W. Prospective study of hand-sutured anastomosis after colorectal resection. Br J Surg 1996; 83(1):29-31.
12. Detry RJ, Kartheuser A, Delriviere L, et al. Use of the circular stapler in 1000 consecutive colorectal anastomoses: experience of one surgical team. Surgery 1995; 117(2):140-5.
13. Andersen E, Sondenaa K, Holter J. A comparative study of polydioxanone (PDS) and polyglactin 910 (Vicryl) in colonic anastomoses in rats. Int J Colorectal Dis 1989; 4(4):251-4.
14. Deveney KE, Way LW. Effect of different absorbable sutures on healing of gastrointestinal anastomoses. Am J Surg 1977; 133(1):86-94.
15. Foresman PA, Edlich RF, Rodeheaver GT. The effect of new monofilament absorbable sutures on the healing of musculoaponeurotic incisions, gastrotomies, and colonic anastomoses. Arch Surg 1989; 124(6):708-10.
16. Hastings JC, Winkle WV, Barker E, et al. Effect of suture materials on healing wounds of the stomach and colon. Surg Gynecol Obstet 1975; 140(5):701-7.
17. Letwin ER. Evaluation of polyglycolic aicd sutures in colon anastomoses. Can J Surg 1975; 18(1):30-2.
18. Lord MG, Broughton AC, Williams HT. A morphologic study on the effect of suturing the submucosa of the large intestine. Surg Gynecol Obstet 1978; 146(2):211-6.
19. Munday C, McGinn FP. A comparison of polyglycolic acid and catgut sutures in rat colonic anastomoses. Br J Surg 1976; 63(11):870-2.
20. Orringer MB, Appleman HD, Argenta L, et al. Polypropylene suture in esophageal and gastrointestinal operations. Surg Gynecol Obstet 1977; 144(1):67-70.
21. Pascual I, de Miguel GF, Gomez-Pinedo UA, et al. Adipose-derived mesenchymal stem cells in biosutures do not improve healing of experimental colonic anastomoses. Br J Surg 2008; 95(9):1180-4.
22. Pasternak B, Rehn M, Andersen L, et al. Doxycycline-coated sutures improve mechanical strength of intestinal anastomoses. Int J Colorectal Dis 2008; 23(3):271-6.

23. Durdey P, Bucknall TE. Assessment of sutures for use in colonic surgery: an experimental study. J R Soc Med 1984; 77(6):472-7.
24. Houdart R, Lavergne A, Valleur P, Hautefeuille P. Polydioxanone in digestive surgery. An experimental study. Am J Surg 1986; 152(3):268-71.
25. Lerwick E. Studies on the efficacy and safety of polydioxanone monofilament absorbable suture. Surg Gynecol Obstet 1983; 156(1):51-5.
26. Ray JA, Doddi N, Regula D, et al. Polydioxanone (PDS), a novel monofilament synthetic absorbable suture. Surg Gynecol Obstet 1981; 153(4):497-507.
27. Clark CG, Wyllie JH, Haggie SJ, Renton P. Comparison of catgut and polyglycolic acid sutures in colonic anastomoses. World J Surg 1977; 1(4):501-5.
28. Gillatt DA, Corfield AP, May RE, et al. Polydioxanone suture in the gastrointestinal tract. Ann R Coll Surg Engl 1987; 69(2):54-6.
29. Lembert A. Mémoire sur l'entéroraphie avec la description d'un procédé nouveau pour pratiquer cette opération chirurgicale. Répertoire général d'anatomie et de physiologie pathologique et des cliniques chirurgicales 1826; 2:100-7.
30. Hogstrom H, Haglund U, Zederfeldt B. Suture technique and early breaking strength of intestinal anastomoses and laparotomy wounds. Acta Chir Scand 1985; 151(5):441-3.
31. Greenall MJ, Evans M, Pollock AV. Influence of depth of suture bite on integrity of single-layer large-bowel anastomoses: controlled trial. J R Soc Med 1979; 72(5):351-6.
32. Waninger J, Kauffmann GW, Shah IA, Farthmann EH. Influence of the distance between interrupted sutures and the tension of sutures on the healing of experimental colonic anastomoses. Am J Surg 1992; 163(3):319-23.
33. Egorov VI, Schastlivtsev V, Turusov RA, Baranov AO. Participation of the intestinal layers in supplying of the mechanical strength of the intact and sutured gut. Eur Surg Res 2002; 34(6):425-31.
34. Tera H, Aberg C. Tissue holding power to a single suture in different parts of the alimentary tract. Acta Chir Scand 1976; 142(5):343-8.
35. Houdart R, Lavergne A, Galian A, Hautefeuille P. [Anatomo-pathological evolution of single-layer end-to-end digestive anastomoses. A study of 210 colonic anastomoses in rats from the 2d to the 180th day]. Evolution anatomo-pathologique des anastomoses digestives bord a bord en un plan. Etude de 210 anastomoses coliques chez le rat du 2e au 180e jour. Gastroenterol Clin Biol 1983; 7(5):465-73.
36. Krasniqi A, Gashi-Luci L, Krasniqi S, et al. A comparison of three single layer anastomotic techniques in the colon of the rat. Int J Surg 2009; 7(1):31-5.
37. Leslie A, Steele RJ. The interrupted serosubmucosal anastomosis - still the gold standard. Colorectal Dis 2003; 5(4):362-6.
38. Pye G, Steele RJ. Anastomoses involving the colon and rectum: an 8-year experience. J R Coll Surg Edinb 1996; 41(2):95-6.
39. Carty NJ, Keating J, Campbell J, et al. Prospective audit of an extramucosal technique for intestinal anastomosis. Br J Surg 1991; 78(12):1439-41.
40. Lafreniere R, Ketcham AS. A single layer open anastomosis for all intestinal structures. Am J Surg 1985; 149(6):797-8.
41. Motson RW, Bolwell JS, Heath AL, et al. One-layer colonic anastomosis with polyglycolic acid (Dexon) suture: a 3-year prospective audit. Ann R Coll Surg Engl 1984; 66(1):19-21.
42. Buyers RA, Meier LA. Everting suture of the bowel: experimental and clinical experience in duodenal closure and colorectal anastomosis. Surgery 1968; 63(3):475-80.
43. Getzen LC. Clinical use of everted intestinal anastomoses. Surg Gynecol Obstet 1966; 123(5):1027-36.
44. Ortiz H, Azpeitia D, Casalots J, Sitges A. [Comparative experimental study of inverting and everting sutures in the colon]. J Chir (Paris) 1975; 109(5-6):691-6.
45. Ballantyne GH. The experimental basis of intestinal suturing. Effect of surgical technique, inflammation, and infection on enteric wound healing. Dis Colon Rectum 1984; 27(1):61-71.

46. Thornton FJ, Barbul A. Healing in the gastrointestinal tract. Surg Clin North Am 1997; 77(3):549-73.
47. Irvin TT, Edwards JP. Comparison of single-layer inverting, two-layer inverting, and everting anastomoses in the rabbit colon. Br J Surg 1973; 60(6):453-7.
48. Yale CE, Van Gemert JV. Healing of inverted and everted intestinal anastomoses in germfree rats. Surgery 1971; 69(3):382-8.
49. Getzen LC, Roe RD, Holloway CK. Comparative study of intestinal anastomotic healing in inverted and everted closures. Surg Gynecol Obstet 1966; 123(6):1219-27.
50. Garner A, Hargreaves AW, Keddie NC. Colonic anastomosis: a histopathological study in the rabbit. Br J Surg 1969; 56(9):673-6.
51. Le Douarec P, Jouanneau P. [Colic anastomosis. Experimental study of sutures in one plane of the rabbit colon; comparison of direct and intraluminal sutures] Anastomose colique. Etude experimentale du monoplan sur le colon du lapin; comparaison des points dits (directs) aux points dirs (intra-luminaux. J Chir (Paris) 1972; 104(5):451-64.
52. Goligher JC, Morris C, McAdam WA, et al. A controlled trial of inverting versus everting intestinal suture in clinical large-bowel surgery. Br J Surg 1970; 57(11):817-22.
53. Czerny V. Zur Darmresektion. Berl Klin Wschr 1880; 17:637.
54. Halstead W. Circular suture of the intestine: an experimental study. Am J Med Sci 1887; 94:436-61.
55. Gambee LP. A single-layer open intestinal anastomosis applicable to the small as well as the large intestine. West J Surg Obstet Gynecol 1951; 59(1):1-5.
56. Gambee LP, Garnjobst W, Hardwick CE. Ten years' experience with a single layer anastomosis in colon surgery. Am J Surg 1956; 92(2):222-7.
57. Langer S. Complex investigation of the efficiency of large bowel anastomosis techniques (Clinical and experimental studies). Chirurgia Gastroenterologica 1975; 9(1):69-80.
58. McAdams AJ, Meikle AG, Taylor JO. One layer or two layer colonic anastomoses? Am J Surg 1970; 120(4):546-50.
59. Graffner H, Andersson L, Lowenhielm P, Walther B. The healing process of anastomoses of the colon. A comparative study using single, double-layer or stapled anastomosis. Dis Colon Rectum 1984; 27(12):767-71.
60. Templeton JL, McKelvey ST. Low colorectal anastomoses. An experimental assessment of two sutured and two stapled techniques. Dis Colon Rectum 1985; 28(1):38-41.
61. Yesilkaya Y, Soyhan N, Bengisu N, et al. The effects of different suture techniques on collagen metabolism in experimental distal colonic anastomoses. Br J Surg 1985; 72(12):987-9.
62. Schillaci A, Cavallaro A, Stipa S. Comparative results of three different techniques for colonic anastomosis in the dog. Surg Gynecol Obstet 1979; 149(2):238-40.
63. Chung RS. Blood flow in colonic anastomoses. Effect of stapling and suturing. Ann Surg 1987; 206(3):335-9.
64. Langer JC, Srinathan SK, Pelletier GJ. Effect of surgical technique on intestinal anastomotic healing in steroid-treated rabbits. Digestive Surgery 1996; 13(3):205-208.
65. Reichel K, Rauner P, Guthy E. Clinical and experimental evaluation of single and double layer entero anastomosis. Chirurgia Gastroenterologica 1975; 9(4):461-467.
66. Athar M, Chaudhry NI, Shakoor A, Khan MA. Studies on end-to-end colonic anastomosis in the dog: a comparison of techniques. Acta Vet Hung 1996; 44(3):349-56.
67. Herzog B. The one-layer and two-layer intestinal anastomosis in animal experiments. Prog Pediatr Surg 1973; 5:37-59.
68. Wheeless CR, Jr., Smith JJ. A comparison of the flow of iodine 125 through three different intestinal anastomoses: standard, Gambee, and stapler. Obstet Gynecol 1983; 62(4):513-8.
69. Everett WG. A comparison of one layer and two layer techniques for colorectal anastomosis. Br J Surg 1975; 62(2):135-40.

70. Ceraldi CM, Rypins EB, Monahan M, et al. Comparison of continuous single layer polypropylene anastomosis with double layer and stapled anastomoses in elective colon resections. Am Surg 1993; 59(3):168-71.
71. Fielding LP, Stewart-Brown S, Blesovsky L, Kearney G. Anastomotic integrity after operations for large-bowel cancer: a multicentre study. Br Med J 1980; 281(6237):411-4.
72. Burch JM, Franciose RJ, Moore EE, et al. Single-layer continuous versus two-layer interrupted intestinal anastomosis: a prospective randomized trial. Ann Surg 2000; 231(6):832-7.
73. Delaitre B, Champault G, Chapuis Y, et al. [Continuous and interrupted intestinal sutures. Experimental and clinical study (author's transl)] Sutures intestinales par surjets et points separes. Etude experimentale et clinique. J Chir (Paris) 1977; 113(1):43-57.
74. Shandall A, Lowndes R, Young HL. Colonic anastomotic healing and oxygen tension. Br J Surg 1985; 72(8):606-9.
75. Jiborn H, Ahonen J, Zederfeldt B. Healing of experimental colonic anastomoses. II. Breaking strength of the colon after left colon resection and anastomosis. Am J Surg 1978; 136(5):595-9.
76. Jiborn H, Ahonen J, Zederfeldt B. Healing of experimental colonic anastomoses. I. Bursting strength of the colon after left colon resection and anastomosis. Am J Surg 1978; 136(5):587-94.
77. Jiborn H, Ahonen J, Zederfeldt B. Healing of experimental colonic anastomoses. The effect of suture technic on collagen concentration in the colonic wall. Am J Surg 1978; 135(3):333-40.
78. Deen KI, Smart PJ. Prospective evaluation of sutured, continuous, and interrupted single layer colonic anastomoses. Eur J Surg 1995; 161(10):751-3.
79. AhChong AK, Chiu KM, Law IC, et al. Single-layer continuous anastomosis in gastrointestinal surgery: a prospective audit. Aust N Z J Surg 1996; 66(1):34-6.
80. Bailey HR, LaVoo JW, Max E, et al. Single-layer polypropylene colorectal anastomosis. Experience with 100 cases. Dis Colon Rectum 1984; 27(1):19-23.
81. Flyger HL, Hakansson TU, Jensen LP. Single layer colonic anastomosis with a continuous absorbable monofilament polyglyconate suture. Eur J Surg 1995; 161(12):911-3.
82. Harder F, Vogelbach P. Single-layer end-on continuous suture of colonic anastomoses. Am J Surg 1988; 155(4):611-4.
83. Huguier M, Houry S. [Manual colorectal anastomosis. Immediate results (author's transl)] Anastomoses colo-rectales manuelles. Resultats immediats. Nouv Presse Med 1982; 11(29):2211-3.
84. Jonsell G, Edelmann G. Single-layer anastomosis of the colon. A review of 165 cases. Am J Surg 1978; 135(5):630-2.
85. Khubchandani M, Upson JF. Single-layer anastomosis of the colon and rectum. Dis Colon Rectum 1982; 25(2):113-7.
86. Law WL, Bailey HR, Max E, et al. Single-layer continuous colon and rectal anastomosis using monofilament absorbable suture (Maxon): study of 500 cases. Dis Colon Rectum 1999; 42(6):736-40.
87. Matheson NA, Valerio D, Farquharson A, Thomson H. Single-layer anastomosis in the large bowel: ten years' experience. J R Soc Med 1981; 74(1):44-8.
88. Max E, Sweeney WB, Bailey HR, et al. Results of 1,000 single-layer continuous polypropylene intestinal anastomoses. Am J Surg 1991; 162(5):461-7.
89. Pramateftakis MG, Vrakas G, Hatzigianni P, et al. The handsewn anastomosis after colon resection due to colonic cancer. Tech Coloproctol 2010; 14 Suppl 1:S57-9.
90. Sarin S, Lightwood RG. Continuous single-layer gastrointestinal anastomosis: a prospective audit. Br J Surg 1989; 76(5):493-5.
91. Thomson WH, Robinson MH. One-layer continuously sutured colonic anastomosis. Br J Surg 1993; 80(11):1450-1.
92. Volk A, Kersting S, Held HC, Saeger HD. Risk factors for morbidity and mortality after single-layer continuous suture for ileocolonic anastomosis. Int J Colorectal Dis 2011; 26(3):321-7.

93. Beart RW, Jr., Kelly KA. Randomized prospective evaluation of the EEA stapler for colorectal anastomoses. Am J Surg 1981; 141(1):143-7.
94. Brennan SS, Pickford IR, Evans M, Pollock AV. Staples or sutures for colonic anastomoses--a controlled clinical trial. Br J Surg 1982; 69(12):722-4.
95. Cajozzo M, Compagno G, DiTora P, et al. Advantages and disadvantages of mechanical vs. manual anastomosis in colorectal surgery. A prospective study. Acta Chir Scand 1990; 156(2):167-9.
96. Docherty JG, McGregor JR, Akyol AM, et al. Comparison of manually constructed and stapled anastomoses in colorectal surgery. West of Scotland and Highland Anastomosis Study Group. Ann Surg 1995; 221(2):176-84.
97. Elhadad A. [Colorectal anastomosis: manual or mechanical? A controlled multicenter study] Anastomoses colo-rectales: a la main ou a la machine? Essai controle multicentrique par tirage au sort. Chirurgie 1990; 116(4-5):425-8.
98. Everett WG, Friend PJ, Forty J. Comparison of stapling and hand-suture for left-sided large bowel anastomosis. Br J Surg 1986; 73(5):345-8.
99. Fingerhut A, Elhadad A, Hay JM, et al. Infraperitoneal colorectal anastomosis: hand-sewn versus circular staples. A controlled clinical trial. French Associations for Surgical Research. Surgery 1994; 116(3):484-90.
100. Fingerhut A, Hay JM, Elhadad A, et al. Supraperitoneal colorectal anastomosis: hand-sewn versus circular staples--a controlled clinical trial. French Associations for Surgical Research. Surgery 1995; 118(3):479-85.
101. Friend PJ, Scott R, Everett WG, Scott IH. Stapling or suturing for anastomoses of the left side of the large intestine. Surg Gynecol Obstet 1990; 171(5):373-6.
102. Kracht M, Hay JM, Fagniez PL, Fingerhut A. Ileocolonic anastomosis after right hemicolectomy for carcinoma: stapled or hand-sewn? A prospective, multicenter, randomized trial. Int J Colorectal Dis 1993; 8(1):29-33.
103. McGinn FP, Gartell PC, Clifford PC, Brunton FJ. Staples or sutures for low colorectal anastomoses: a prospective randomized trial. Br J Surg 1985; 72(8):603-5.
104. Moreno Gonzalez E, Rico Selas P, Mansilla Molina D, et al. Results of surgery for cancer of the rectum with sphincter conservation. A randomized study on instrumental versus manual anastomosis. Acta Oncol 1989; 28(2):241-4.
105. Sarker SK, Chaudhry R, Sinha VK. A comparison of stapled vs handsewn anastomosis in anterior resection for carcinoma rectum. Indian J Cancer 1994; 31(2):133-7.
106. Choy PY, Bissett IP, Docherty JG, et al. Stapled versus handsewn methods for ileocolic anastomoses. Cochrane Database Syst Rev 2007(3):CD004320.
107. Lustosa SA, Matos D, Atallah AN, Castro AA. Stapled versus handsewn methods for colorectal anastomosis surgery. Cochrane Database Syst Rev 2001(3):CD003144.
108. MacRae HM, McLeod RS. Handsewn vs. stapled anastomoses in colon and rectal surgery: a meta-analysis. Dis Colon Rectum 1998; 41(2):180-9.
109. Adloff M, Arnaud JP, Beehary S. Stapled vs sutured colorectal anastomosis. Arch Surg 1980; 115(12):1436-8.
110. Anwar S, Hughes S, Eadie AJ, Scott NA. Anastomotic technique and survival after right hemicolectomy for colorectal cancer. Surgeon 2004; 2(5):277-80.
111. Scher KS, Scott-Conner C, Jones CW, Leach M. A comparison of stapled and sutured anastomoses in colonic operations. Surg Gynecol Obstet 1982; 155(4):489-93.
112. Sielezneff I, Malouf AJ, Pirro N, et al. Short-term functional outcome following elective surgery for complicated sigmoid diverticular disease: sutured or stapled end-to-end anastomosis to the proximal rectum? Colorectal Dis 2001; 3(1):23-7.
113. Smedh K, Andersson M, Johansson H, Hagberg T. Preoperative management is more important than choice of sutured or stapled anastomosis in Crohn's disease. Eur J Surg 2002; 168(3):154-7.
114. Montesani C, De Milito R, Chiappalone S, et al. Critical evaluation of the anastomoses in large bowel surgery: experience gained in 533 cases. Hepatogastroenterology 1992; 39(4):304-8.

115. Resegotti A, Astegiano M, Farina EC, et al. Side-to-side stapled anastomosis strongly reduces anastomotic leak rates in Crohn's disease surgery. Dis Colon Rectum 2005; 48(3):464-8.
116. Jansson OK, Zilling TL, Walther BS. Healing of colonic anastomoses: comparative experimental study of glued, manually sutured, and stapled anastomoses. Dis Colon Rectum 1991; 34(7):557-62.
117. Polglase AL, Hughes ES, McDermott FT, et al. A comparison of end-to-end staple and suture colorectal anastomosis in the dog. Surg Gynecol Obstet 1981; 152(6):792-6.
118. Senagore A, Milsom JW, Walshaw RK, et al. Direct comparison between Czerny-Lembert and circular-stapled anastomotic techniques in colorectal anastomosis: a similar pattern of healing for both. Dis Colon Rectum 1992; 35(9):862-9.
119. Singer MA, Cintron JR, Benedetti E, et al. Hand-sewn versus stapled intestinal anastomoses in a chronically steroid-treated porcine model. Am Surg 2004; 70(2):151-6; discussion 156.
120. Kozol RA, Mulligan M, Downes RJ, et al. Early colonic anastomotic edema. Evaluation of stapled vs. hand-sewn anastomoses. Dis Colon Rectum 1988; 31(7):503-6.
121. Moss G. Colorectal anastomotic strength: Staples versus conventional sutures. Journal of Abdominal Surgery 1984; 26(7-8):73-77.
122. Buchmann P, Schneider K, Gebbers JO. Fibrosis of experimental colonic anastomosis in dogs after EEA stapling or suturing. Dis Colon Rectum 1983; 26(4):217-20.
123. Julian TB, Kolachalam RB. Microangiographic study of healing wounds in canine intestinal anastomoses. Vascular Surgery 1989; 23(4):296-303.
124. Dziki AJ, Duncan MD, Harmon JW, et al. Advantages of handsewn over stapled bowel anastomosis. Dis Colon Rectum 1991; 34(6):442-8.
125. Kent C, Warner K, Miller J, Schreiber H. Ileocolonic anastomosis: a comparison of the patency of stapled versus hand-sewn techniques. Am Surg 1992; 58(10):638-40.
126. Denans F. Nouveau procédé pour la guerison des plaies des intestins. Receuil de la société Royale de Medecine de Marseille 1827; Marseille: Imprimerie d'Archard(Tome I):4.
127. Murphy JB. Cholecysto-intestinal, gastro-intestinal, entero-intestinal anastomosis, and approximation without sutures. Medical Record 1892; 42:665-676.
128. Smith AD, Bubrick MP, Mestitz ST, et al. Evaluation of the biofragmentable anastomotic ring following preoperative irradiation to the rectosigmoid in dogs. Dis Colon Rectum 1988; 31(1):5-9.
129. Bundy CA, Jacobs DM, Zera RT, Bubrick MP. Comparison of bursting pressure of sutured, stapled and BAR anastomoses. Int J Colorectal Dis 1993; 8(1):1-3.
130. Maney JW, Katz AR, Li LK, et al. Biofragmentable bowel anastomosis ring: comparative efficacy studies in dogs. Surgery 1988; 103(1):56-62.
131. Gullichsen R. The biofragmentable ring in intestinal surgery. Eur J Surg Suppl 1993(569):1-31.
132. Cahill CJ, Betzler M, Gruwez JA, et al. Sutureless large bowel anastomosis: European experience with the biofragmentable anastomosis ring. Br J Surg 1989; 76(4):344-7.
133. Corman ML, Prager ED, Hardy TG, Jr., Bubrick MP. Comparison of the Valtrac biofragmentable anastomosis ring with conventional suture and stapled anastomosis in colon surgery. Results of a prospective, randomized clinical trial. Dis Colon Rectum 1989; 32(3):183-7.
134. Bubrick MP, Corman ML, Cahill CJ, et al. Prospective, randomized trial of the biofragmentable anastomosis ring. The BAR Investigational Group. Am J Surg 1991; 161(1):136-42; discussion 142-3.
135. Gullichsen R, Havia T, Ovaska J, Rantala A. Colonic anastomosis using the biofragmentable anastomotic ring and manual suture: a prospective, randomized study. Br J Surg 1992; 79(6):578-80.
136. Dyess DL, Curreri PW, Ferrara JJ. A new technique for sutureless intestinal anastomosis. A prospective, randomized, clinical trial. Am Surg 1990; 56(2):71-5.
137. Pahlman L, Ejerblad S, Graf W, et al. Randomized trial of a biofragmentable bowel anastomosis ring in high-risk colonic resection. Br J Surg 1997; 84(9):1291-4.
138. Wullstein C, Gross E. Compression anastomosis (AKA-2) in colorectal surgery: results in 442 consecutive patients. Br J Surg 2000; 87(8):1071-5.

139. Kim SH, Choi HJ, Park KJ, et al. Sutureless intestinal anastomosis with the biofragmentable anastomosis ring: experience of 632 anastomoses in a single institute. Dis Colon Rectum 2005; 48(11):2127-32.
140. Di Castro A, Biancari F, Brocato R, et al. Intestinal anastomosis with the biofragmentable anastomosis ring. Am J Surg 1998; 176(5):472-4.
141. Thiede A, Geiger D, Dietz UA, et al. Overview on compression anastomoses: biofragmentable anastomosis ring multicenter prospective trial of 1666 anastomoses. World J Surg 1998; 22(1):78-86; discussion 87.
142. Sailer M, Debus ES, Fuchs KH, et al. Comparison of anastomotic microcirculation in coloanal J-pouches versus straight and side-to-end coloanal reconstruction: an experimental study in the pig. Int J Colorectal Dis 2000; 15(2):114-7.
143. Willis S, Holzl F, Krones CJ, et al. Evaluation of anastomotic microcirculation after low anterior rectal resection: an experimental study with different reconstruction forms in dogs. Tech Coloproctol 2006; 10(3):222-6.
144. Brisinda G, Vanella S, Cadeddu F, et al. End-to-end versus end-to-side stapled anastomoses after anterior resection for rectal cancer. J Surg Oncol 2009; 99(1):75-9.
145. Tsunoda A, Kamiyama G, Narita K, et al. Prospective randomized trial for determination of optimum size of side limb in low anterior resection with side-to-end anastomosis for rectal carcinoma. Dis Colon Rectum 2009; 52(9):1572-7.
146. Alberts JC, Parvaiz A, Moran BJ. Predicting risk and diminishing the consequences of anastomotic dehiscence following rectal resection. Colorectal Dis 2003; 5(5):478-82.
147. Branagan G, Finnis D, Wessex Colorectal Cancer Audit Working G. Prognosis after anastomotic leakage in colorectal surgery. Dis Colon Rectum 2005; 48(5):1021-6.
148. Fielding LP, Phillips RK, Hittinger R. Factors influencing mortality after curative resection for large bowel cancer in elderly patients. Lancet 1989; 1(8638):595-7.

Chapter 5

Effects of a new anti-adhesion polyvinyl alcohol gel on healing of colon anastomoses in rats

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ABSTRACT

Background: Adhesions following abdominal surgery occur with an incidence up to 95%, resulting in invalidating complications such as bowel obstruction, female infertility, and chronic pain. Studies have been performed in search for a safe and effective adhesion barrier, however in the past adhesion barriers have been shown to impair anastomotic wound healing. The aim of this study was to investigate the effect of a new adhesion barrier, polyvinyl-alcohol gel, on healing of colonic anastomoses using a rat model, and secondly evaluate its effect on intra-abdominal adhesions.

Methods: Thirty-two Wistar rats were divided in two groups. In all animals an anastomosis was constructed in the ascending colon. The first group received no adhesion barrier, in the second group 2 ml of polyvinyl alcohol gel (A-Part Gel®; Aesculap AG, Tuttlingen, Germany) was applied circularly around the anastomosis. All animals were sacrificed on the seventh postoperative day and the abdomen was inspected for signs of anastomotic leakage. The anastomotic bursting pressure, the adhesions around the anastomosis, and the collagen content of the excised anastomosis were measured.

Results: No significant differences were observed between the two groups considering the incidence of anastomotic leakage, the anastomotic bursting pressure (p-value 0.08), and the collagen concentration (p-value 0.91). No significant reduction in amount of adhesions was observed in the rats having received polyvinyl alcohol gel.

Conclusion: This experimental study shows no significant differences in anastomotic leakage, anastomotic bursting pressure, or collagen content of the anastomosis when using the adhesion barrier polyvinyl alcohol around colonic anastomoses. The barrier did not prevent adhesion formation.

INTRODUCTION

The formation of fibrous adhesions is almost always present after abdominal surgery[1,2], and has been shown to be a significant cause of morbidity[3-5]. Though adhesions are a physiologic response to surgical trauma or infection, they are also the most common cause of small bowel obstruction, female infertility, and may lead to major difficulties during subsequent operative procedures[6-10]. The underlying mechanism is based on local tissue ischemia and mesothelial injury produced by surgical intervention, which disrupts the balance between coagulation and fibrinolysis causing fibrous bands that result in adhesions[11]. Furthermore, inflammation intensifies this formation by attracting and activating fibroblasts and disrupting the mechanism of fibrinolysis[12,13].

Numerous products have been used trying to minimize the formation of adhesions, based on barriers that aim to separate the injured surfaces long enough to allow repair without adhesions. A new adhesion barrier consisting of polyvinyl-alcohol (PVA) and carboxymethylcellulose (CMC) gel (A-Part gel®; Aesculap AG, B. Braun, Tuttlingen, Germany) has shown promising results in in vitro as well as in vivo studies[14-16]. However, in the past years several anti-adhesive agents have not gained wide-spread clinical use due to concerns on anastomotic wound healing[17,18]. Therefore the primary aim of this study was to investigate the effect of the adhesion barrier polyvinyl-alcohol (PVA) on healing of colonic anastomoses using a rat model, and secondly evaluate its effect on intra-abdominal adhesions.

METHODS

Animals

Thirty-two male Wistar rats (Harlan Laboratory, Horst, the Netherlands), weighing approximately 400 grams were randomly divided into two equal groups of 16: the control group and the study group that received PVA gel. The study was approved by the local ethical committee on animal welfare in accordance with animal protection laws. Animals were kept under standard laboratory conditions with individually ventilated cages, fed with chow and water ad libitum throughout the study.

PVA gel

Polyvinyl-alcohol gel (A-Part gel®; Aesculap AG, B. Braun, Tuttlingen, Germany) consists of PVA and CMC. PVA is the anti-adhesion component while CMC prevents the gel of slipping away from the wound side. The gel acts as a barrier and is applied at the end of the operation. Polyvinyl-alcohol gel is completely absorbed in three to four weeks and its main route of excretion is via urine[19].

Study Design

Animals were anaesthetized by inhalation of an isoflurane-oxygen mixture. The abdomen was shaved and cleaned with alcohol 70%. The abdominal cavity was opened through a midline incision of 4 cm. The mesentery was cleaved one centimetre aborally to the cecum, without damaging the vessels,

after which the colon was transected. An end-to-end anastomosis was formed with 12 interrupted monofilament non-absorbable polyamide sutures (Dafilon 8-0, B. Braun). In the study group 2.0 ml of PVA gel was applied around the anastomosis; the control group did not receive any treatment. The colon was repositioned and the abdominal wall was closed in two layers with synthetic braided absorbable sutures of polyglacolic acid (Safil 5-0, B. Braun). Postoperatively rats were observed and weighed daily during one week.

Outcome measurements after 7 days

On the 7th postoperative day rats were re-operated through a laparotomy. The abdomen was inspected for signs of anastomotic leakage (peritonitis with visible anastomotic dehiscence, or peri-anastomotic abscesses).

Anastomotic Bursting Pressure

Anastomotic bursting pressure (ABP) was performed in vivo with intact adhesions. A catheter was introduced into the colon 2 cm proximally to the anastomosis, with the tip lying intraluminally at the site of the anastomosis. Subsequently the colon was ligated proximal of the probe and distal of the anastomosis in order to create a closed cavity. The pressure in the cavity was increased by pumping air through the probe at a constant rate of 100ml/hr. One limb of the probe was connected to a pressure transducer, continuously measuring pressure during infusion. Bursting of the colon followed by a sudden drop in pressure was considered to be the ABP. After measuring ABP animals were sacrificed.

Adhesions

Adhesions around the anastomosis were evaluated in two steps. First the amount of adhesions was measured by determining the percentage of the anastomosis covered with adhesions. Then, the extent and characteristics of adhesions was scored according to the system of van der Ham et al.[20] presented in table 1.

Table 1. *Scoring system following van der Ham et al.*[20]

Score	Extent and characteristics of adhesions
0	No adhesions
1 +	Minimal adhesions, mainly between anastomosis and omentum
2 +	Moderate adhesions, i.e. between omentum and the anastomotic site and between the anastomosis and a loop of small bowel
3 +	Severe and extensive adhesions, including abscess formation

Histopathological examination

One centimetre colon with the anastomosis in the middle was excised and histopathologically evaluated. Hydroxyproline was determined as a reflection of the amount of collagen, since it is a collagen-specific amino acid. Processing of the tissue was done according to the method of Creemers et al[21]. A colorimetric hydroxyproline assay was performed to determine the amount of collagen in the anastomotic tissue samples. Samples were first treated with 6N acid hydrolysis, followed by chloramine-T to oxidize hydroxyproline into pyrrol. Pyrrol was converted into a chromophore (red) by dimethylaminobenzaldehyde. Using a wavelength of 570nm the amount of red colour reflects the amount of hydroxyproline, assuming 300 hydroxyproline residues per collagen triple helix.

Statistics

Normality of the data was determined by means of Shapiro-Wilk test and visual assessment.

Categorical data (adhesions scores) are presented as numbers with percentages, numerical data are presented as means with standard errors of the mean (normally distributed), or medians with interquartile ranges (not normally distributed). Differences between groups were assessed using a chi-square test in case of categorical data (adhesion scores), or an unpaired t-test (normally distributed) or Mann-Whitney U test (not normally distributed) in case of numerical data.

RESULTS

In the control group there were no sick or dead animals before day 7. There was one death in the study group on day 3, due to dehiscence of the laparotomy. Necropsy showed no intra-abdominal pathology. As can be seen in figure 1 there was no significant difference in weight loss between both groups.

At the time of reoperation on day 7 no animals were found to have signs of anastomotic leakage, neither in the control group nor in the study group. There were no visual remnants of PVA gel intra-abdominally. Mean result of ABP measurements can be seen in figure 2: 155 ± 6.7 mmHg in the PVA group and 173 ± 7.5 mmHg in the control group. This difference was not statistically significant (p-value 0.08). All sites of bursting were at the anastomosis. The median circumference of the anastomosis covered with adhesions was 90% (70-100%) in the PVA group, and 80% (70-83.8%) in the control group (figure 3). This difference was not statistically significant (p-value 0.30). The results of the extent and characteristics of the adhesions covering the anastomosis can be found in table 2. Adhesion scores between the PVA and the control group were not statistically different from each other (p-value 0.39). The median quantity of μg collagen per mg dry weight was 7.9 (6.8 – 12.9) in the PVA group and 8.9 (6.7 – 9.4) μg/mg dry weight in the control group (figure 4). This difference was not statistically significant (p-value 0.91).

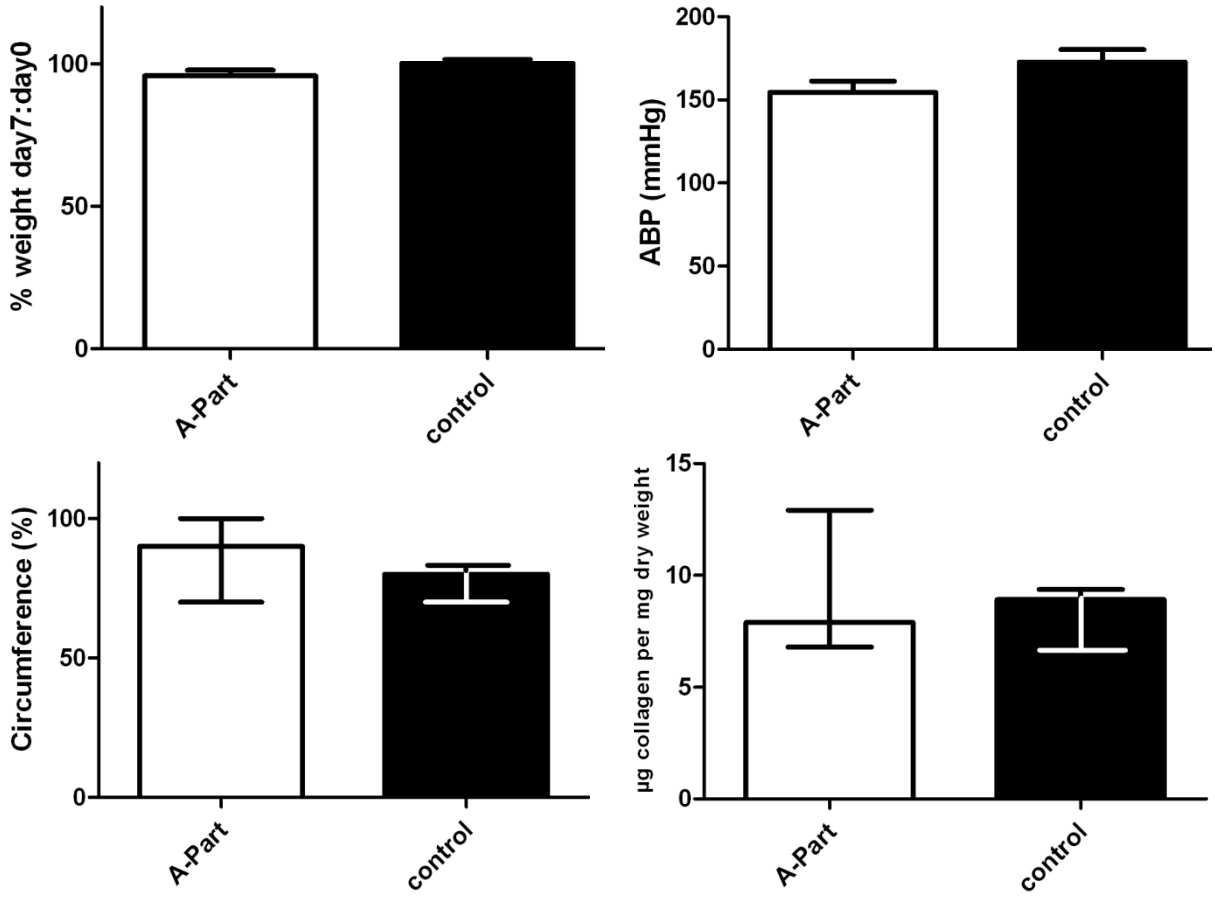

Figure 1-4:

1. Percentage of weight on day 7 compared to day 0 (mean with SEM).

2. Anastomotic Bursting Pressure (mmHg) (mean with SEM). A-Part: 155 ± 6.7 mmHg; control: 173 ± 7.5 mmHg; p-value 0.08.

3. Circumference of the anastomosis covered with adhesions (%) (median with interquartile range). A-Part: 90% (70-100); control: 80% (70-83.8); p-value 0.30.

4. Collagen (µg collagen per mg dry weight) (median with interquartile range). A-Part: 7.9 µg/mg (6.8-12.9); control: 8.9 µg/mg (6.7-9.4); p-value 0.91.

Table 2. *Results of adhesions score.*

Adhesions score	A-Part (n=15)	Control (n=16)	p-value
0	0	0	
1	3 (20%)	1 (6.3%)	
2	9 (60%)	13 (81.3%)	
3	3 (20%)	2 (12.5%)	0.39

DISCUSSION

Adhesions are fibrous bands between two damaged peritoneal surfaces that are normally separated. In 1973 Raftery has shown that injury of the serosal layer of the peritoneum leads to an inflammatory exudate followed by fibrin deposition, which is the beginning of adhesion formation[22].

The precise underlying mechanism is complex: the clotting pathway, extracellular matrix proteins, and various cytokines and growth factors are involved[23-25], with eventually the production of a fibrin matrix with fibroblasts and collagen resulting in adhesion formation. Fibrinolytic activity resolves this fibrin matrix[26,27] and is necessary for a balance between the formation and breaking down of fibrous depositions. However fybrinolysis is reduced by inflammation and infection and thus the balance is disturbed after surgery, particularly when surgery is followed by an infectious complication.

Adhesions are a frequent problem after abdominal surgery with an incidence up to 95%, resulting in important and invalidating complications such as bowel obstruction, female infertility, and chronic pain[1,2,6-8,10]. In addition to their undesirable clinical impact, adhesions are associated with substantial increases in health costs as has been shown by large trials on adhesion-related readmissions conducted by Ellis et al. and Parker et al.[3,4]. Therefore, adhesion prevention would be a highly valuable extension of surgical interventions, as surgical trauma is one of the most important triggers in the formation of adhesions.

Several ways of adhesion prevention have been studied, the majority through intra-abdominally applied adhesion barriers based on prevention of adhesions by separating damaged peritoneal surfaces. The adhesion barrier used in this study, polyvinyl alcohol (PVA), is used in many other medical fields [28-30], and has a solubility, biocompatibility and inactivation in body fluids that makes it a suitable adhesion barrier [31]. PVA has shown to effectively diminish adhesions in vitro, after spinal surgery, and after tendon surgery [31-33]. To improve quality of adherence of the barrier to the viscera CMC was added to PVA-gel (A-Part gel®). Jaenigen et al.[14] have shown in a rabbit sidewall model this PVA-CMC gel effectively diminishes adhesions compared to untreated controls and 4% icodextrin. Lang et al.[15] found similar results in their rabbit sidewall model; significantly less adhesions in rabbits treated with PVA-CMC gel compared to 4% icodextrin and controls, as well as in their relaparotomy model[16].

However, if an adhesions barrier is capable to adequately diminish fibrin deposition and thus the formation of adhesions, it is essential to investigate whether wound healing, also relying on fibrin deposition followed by collagen formation, is not impaired. The consequence of impaired wound healing of a gastro-intestinal anastomosis is anastomotic leakage, leading to abscesses or peritonitis with mortality between 10-20%. This life-threatening complication makes the balance between diminishing adhesions without impairing wound healing crucial in gastro-intestinal surgery. Previous studies have emphasized this fragile balance through results showing more anastomotic leakage in patients receiving a hyaluronic acid and carboxymethylcellulose (HA-CMC) anti-adhesive film. Initial results with this film were promising, with an impressive reduction in 50% in adhesions to the midline incision. Following these results a randomized safety study was performed by Beck et al.[17] with 1791 patients undergoing abdominopelvic surgery. This study showed there were significantly more

abscesses, anastomotic leakage, and peritonitis in the patients with the HA-CMC film. Subgroup analysis of all patients with anastomoses showed the placement of HA-CMC film directly on the anastomosis increased the risk of anastomotic leakage compared to controls, in contrary to patients having the HA-CMC film not at the anastomosis. An experimental study with the same anti-adhesive HA-CMC film showed wrapping the film around an irradiated bowel anastomosis in rats resulted in significantly more peri-anastomotic abscesses compared to non-treated controls[18]. Such results stress the importance of testing adhesion barriers in situations were the impairment of wound healing has severe and potentially life-threatening consequences.

The aim of this study was to investigate the effect of PVA-CMC gel (A-Part gel®) on healing and strength of colonic anastomoses using a rat model. The model used, 12-suture anastomosis in the colon, represents normal healing of an anastomosis without leakage. No difference in weight loss was observed in rats with and without PVA gel, nor were there any signs of anastomotic leakage in both groups. No significant differences in ABP were observed between PVA and control rats. One dead animal was found during the study at day 3. The death probably was not related to the A-Part® Gel since there was a dehiscence of the laparotomy and the stitch was bitten through. Measurements of collagen showed no significant differences in amounts between PVA rats and controls after seven days, indicating this adhesion barrier does not interact with collagen synthesis during wound healing. The seventh postoperative day was chosen for collagen measurement and ABP since collagen synthesis is highest between the fifth and the seventh postoperative day, and wound strength depends mainly on newly formed collagen [34].

This study has several weaknesses. Pre-study power analysis showed 16 animals per group to be sufficient; however a power analysis always implies some theoretical supposition. With a p-value of 0.08 a trend towards more anastomotic leakage in the study group cannot be excluded completely. Therefore more experimental research with A-Part gel® and intestinal anastomoses is necessary. Also, the effect of the coverage of the anastomoses with adhesions is not certain. In our rodent model, we practically always see a large coverage of the anastomosis by adhesions on day 7, mainly coming from omentum attached to suture material and anastomotic edges, without anastomotic leakage. Adhesions formation in this setting may be due to a foreign body reaction to suture material, which differs from the response seen to bacterial soiling or blood clot. Other studies, from Lauder et al.[35] and Silva et al[36], have observed similar results: persistence of adhesions to anastomosis in both control group and adhesion barrier-group. In this study, we saw coverage of the anastomosis with adhesions in both groups, therefore whether there is an influence of these adhesions on anastomotic leakage is not known from these results. In our model no reduction of adhesions was found. However, the effect of PVA gel on adhesions has been described in several studies using the sidewall model, with excellent results concerning adhesion reduction.

In conclusion, this randomized study in rats shows no significant differences in anastomotic leakage, anastomotic bursting pressure, nor collagen content of the anastomosis when using the adhesion barrier PVA gel around colonic anastomoses.

REFERENCES

1. Postoperative adhesion development after operative laparoscopy: evaluation at early second-look procedures. Operative Laparoscopy Study Group. Fertil Steril 1991;55:700-4.
2. Becker JM, Dayton MT, Fazio VW, et al. Prevention of postoperative abdominal adhesions by a sodium hyaluronate-based bioresorbable membrane: a prospective, randomized, double-blind multicenter study. J Am Coll Surg 1996;183:297-306.
3. Ellis H, Moran BJ, Thompson JN, et al. Adhesion-related hospital readmissions after abdominal and pelvic surgery: a retrospective cohort study. Lancet 1999;353:1476-80.
4. Parker MC, Ellis H, Moran BJ, et al. Postoperative adhesions: ten-year follow-up of 12,584 patients undergoing lower abdominal surgery. Dis Colon Rectum 2001;44:822-29; discussion 9-30.
5. Wilson MS, Ellis H, Menzies D, et al. A review of the management of small bowel obstruction. Members of the Surgical and Clinical Adhesions Research Study (SCAR). Ann R Coll Surg Engl 1999;81:320-8.
6. McEntee G, Pender D, Mulvin D, et al. Current spectrum of intestinal obstruction. Br J Surg 1987;74:976-80.
7. Menzies D, Ellis H. Intestinal obstruction from adhesions--how big is the problem? Ann R Coll Surg Engl 1990;72:60-3.
8. Milingos S, Kallipolitis G, Loutradis D, et al. Adhesions: laparoscopic surgery versus laparotomy. Ann N Y Acad Sci 2000;900:272-85.
9. Stewart RM, Page CP, Brender J, et al. The incidence and risk of early postoperative small bowel obstruction. A cohort study. Am J Surg 1987;154:643-7.
10. Van Der Krabben AA, Dijkstra FR, Nieuwenhuijzen M, et al. Morbidity and mortality of inadvertent enterotomy during adhesiotomy. Br J Surg 2000;87:467-71.
11. Reijnen MM, Bleichrodt RP, van Goor H. Pathophysiology of intra-abdominal adhesion and abscess formation, and the effect of hyaluronan. Br J Surg 2003;90:533-41.
12. Cahill RA, Wang JH, Soohkai S, et al. Mast cells facilitate local VEGF release as an early event in the pathogenesis of postoperative peritoneal adhesions. Surgery 2006;140:108-12.
13. Liebman SM, Langer JC, Marshall JS, et al. Role of mast cells in peritoneal adhesion formation. Am J Surg 1993;165:127-30.
14. Jaenigen BM, Weis C, Odermatt EK, et al. The new adhesion prophylaxis membrane A-part--from in vitro testing to first in vivo results. J Biomed Mater Res B Appl Biomater 2009;89B:293-9.
15. Lang RA, Gruntzig PM, Weisgerber C, et al. Polyvinyl alcohol gel prevents abdominal adhesion formation in a rabbit model. Fertil Steril 2007;88:1180-6.
16. Lang RA, Weisgerber C, Gruntzig PM, et al. Polyvinyl alcohol gel prevents adhesion re-formation after adhesiolysis in a rabbit model. J Surg Res 2009;153:12-6.
17. Beck DE, Cohen Z, Fleshman JW, et al. A prospective, randomized, multicenter, controlled study of the safety of Seprafilm adhesion barrier in abdominopelvic surgery of the intestine. Dis Colon Rectum 2003;46:1310-9.
18. Bowers D, Raybon RB, Wheeless CR, Jr. Hyaluronic acid-carboxymethylcellulose film and perianastomotic adhesions in previously irradiated rats. Am J Obstet Gynecol 1999;181:1335-7; discussion 137-8.
19. Besheer A, Mader K, Kaiser S, et al. Tracking the urinary excretion of high molar mass poly(vinyl alcohol). J Biomed Mater Res B Appl Biomater 2007;82:383-9.
20. van der Ham AC, Kort WJ, Weijma IM, et al. Effect of fibrin sealant on the healing colonic anastomosis in the rat. Br J Surg 1991;78:49-53.
21. Creemers LB, Jansen DC, van Veen-Reurings A, et al. Microassay for the assessment of low levels of hydroxyproline. Biotechniques 1997;22:656-8.
22. Raftery AT. Regeneration of parietal and visceral peritoneum: an electron microscopical study. J Anat 1973;115:375-92.

23. McBride WH, Mason K, Withers HR, et al. Effect of interleukin 1, inflammation, and surgery on the incidence of adhesion formation and death after abdominal irradiation in mice. Cancer Res 1989;49:169-73.
24. Milligan DW, Raftery AT. Observations on the pathogenesis of peritoneal adhesions: a light and electron microscopical study. Br J Surg 1974;61:274-80.
25. Ryan GB, Grobety J, Majno G. Mesothelial injury and recovery. Am J Pathol 1973;71:93-112.
26. Raftery AT. Regeneration of peritoneum: a fibrinolytic study. J Anat 1979;129:659-64.
27. Thompson JN, Whawell SA. Pathogenesis and prevention of adhesion formation. Br J Surg 1995;82:3-5.
28. Li F, Su Y, Wang J, et al. Influence of dynamic load on friction behavior of human articular cartilage, stainless steel and polyvinyl alcohol hydrogel as artificial cartilage. J Mater Sci Mater Med 2010;21:147-54.
29. Mohammadi H, Boughner D, Millon LE, et al. Design and simulation of a poly(vinyl alcohol)-bacterial cellulose nanocomposite mechanical aortic heart valve prosthesis. Proc Inst Mech Eng H 2009;223:697-711.
30. Abramowitz SD, Israel GM, McCarthy SM, et al. Comparison of four embolic materials at uterine artery embolization by using postprocedural MR imaging enhancement. Radiology 2009;250:482-7.
31. Weis C, Odermatt EK, Kressler J, et al. Poly(vinyl alcohol) membranes for adhesion prevention. J Biomed Mater Res B Appl Biomater 2004;70:191-202.
32. Hiraizumi Y, Transfeldt EE, Fujimaki E, et al. Application of polyvinyl alcohol hydrogel membrane as anti-adhesive interposition after spinal surgery. Spine (Phila Pa 1976) 1995;20:2272-7.
33. Kobayashi M, Toguchida J, Oka M. Development of the shields for tendon injury repair using polyvinyl alcohol--hydrogel (PVA-H). J Biomed Mater Res 2001;58:344-51.
34. Jiborn H, Ahonen J, Zederfeldt B. Healing of experimental colonic anastomoses. III. Collagen metabolism in the colon after left colon resection. Am J Surg 1980;139:398-405.
35. Lauder CI, Garcea G, Strickland A, et al. Use of a modified chitosan-dextran gel to prevent peritoneal adhesions in a rat model. J Surg Res 2011;171:877-82.
36. Silva SM, Ferreira VM, Feres O, et al. Does metoclopramide impair anastomotic healing of the left colon of rats? Acta Cir Bras 2011;26:297-302.

Part IIb

Colorectal anastomosis: postoperative care

Chapter 6

Polymerase Chain Reaction for Enterococcus faecalis in drain fluid: the first screening test for symptomatic colorectal anastomotic leakage.

The APPEAL-study: Analysis of Parameters Predictive for Evident Anastomotic Leakage.

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ABSTRACT

Purpose: With current diagnostic methods the majority of patients with symptomatic colorectal anastomotic leakage (CAL) is identified approximately one week after operation. The aim of this study is to determine whether Real-Time Polymerase Chain Reaction (RT-PCR) for detection of E. coli and E. faecalis on drain fluid can serve as a screening test for CAL in the early postoperative phase.

Methods: All patients included in this multicenter prospective observational study underwent left-sided colorectal resection for both malignant and benign diseases with construction of an anastomosis. In all patients an intra-abdominal drain was placed during operation. During the first five postoperative days drain fluid was processed for RT-PCR. The quantitative results of the RT-PCR on day 2 to 5 were compared the results of day one in order to detect concentration changes.

Results: In total 243 patients, with both benign and malignant diseases, were included of whom 19 (7,8 %) developed symptomatic CAL. An increase in E. coli concentration was found in significantly more patients with CAL on day four and five ($p=0.0004$; Diagnostic Odds Ratio (DOR) 7.9). For E. faecalis this result was found for days two, three and four ($p< 0.003$) with highest DOR on day three (31.6). Sensitivity and negative predictive value were 92.9 and 98.7 % respectively, virtually ruling out CAL in case of negative test results on the third postoperative day.

Conclusion: Quantitative PCR for E. faecalis performed on drain fluid may be an objective, affordable and fast screening tool for symptomatic colorectal anastomotic leakage.

INTRODUCTION

Despite the vast body of evidence concerning colorectal anastomotic leakage (CAL), it remains a poorly understood complication of colorectal surgery. The reported incidence of CAL is estimated between 2.4 % and 19 % (1-3)] and mortality rates due to sepsis and multiple organ failure are around 15 % in patients who develop CAL [(4)].

With current screening and diagnostic methods the interval between construction of the colorectal anastomosis and diagnosis of leakage varies between 6 and 13 days (5-7)]. Several studies have suggested that delay of diagnosis of CAL is associated with higher mortality rates and that only early management improves clinical outcome (8-10)]. Therefore, new screening methods allowing detection of CAL in the early postoperative phase are needed in addition to current methods.

Morbidity caused by CAL is due to the bacterial load leaking through an anastomotic defect. Gram-negative Escherichia coli (E. coli) and gram-positive Enterococcus faecalis (E. faecalis) belong to the most common species of the colon (11, 12)]. When present in wound fluid obtained from the anastomotic site it means there is contamination from the bowel. Increased concentrations of these bacteria are most likely reflecting an anastomotic defect. Therefore these bacteria might be suited to screen for CAL (13, 14)].

The golden standard for detection of bacterial contamination is culture. However, bacteria present in drain fluid in a collection bag outside the patient may not always be viable, which could render false negative results. In addition, it takes about 48 hours of incubation before bacteria can be identified (14)], which is an unacceptable delay. Real-time polymerase chain reaction (RT-PCR) is an alternative, molecular-based technique that can be used to identify bacterial species. It is faster, more sensitive and less susceptible to contamination than culture and might therefore be a valuable screening tool for CAL. In addition, since virtually every clinical laboratory already has a RT-PCR machine, it is a cheap technique.

The aim of this study is to study whether RT-PCR determination of E. coli and E. faecalis can serve as a screening test for CAL in the early postoperative phase after (left-sided) colorectal surgery.

METHODS

Patients included in the “APPEAL” study received left-sided colorectal resection with construction of an anastomosis and were given an intra-abdominal drain. Seven medical centers in the Netherlands and Belgium participated in this study. The study, registered in the Dutch Trial Register (http://www.trialregister.nl, study number NTR 1258), was approved by the medical ethical committee of all the participating centers, in accordance with the ethical standards of the Helsinki Declaration of 1975, and all patients gave informed consent. Participating centers included patients consecutively between January 2007 and December 2009.

Inclusion and exclusion criteria.

Subsequent patients undergoing left hemicolectomy, sigmoid resection, high anterior resection (HAR; with partial mesorectal excision: PME), low anterior resection (with total mesorectal excision: TME), and subtotal colectomy with ileorectal anastomosis were included. Oncologic resections as well as resections for inflammatory disease were included.

Emergency operations were excluded due to the high probability of coexisting tissue damage and logistical difficulties. Reversals of colostomy were also excluded since the primary disease was already treated. Furthermore, patients under 18 years of age, patients who refused to participate and patients who did not receive a drain were excluded.

Surgical procedure.

The surgical procedure was left to the surgeon's discretion. All patients received preoperative antibiotic prophylaxis and an intra-abdominal drain. Guidelines concerning bowel preparation differed for each centre and were respected. Patients were operated by laparotomy or laparoscopy and the anastomosis was stapled or hand sutured. A diverting stoma was constructed according to the surgeon's preference. To obtain drain fluid, a drain was placed at the anastomotic site and was left in place during the first 5 postoperative days. The drains were all passive and closed drainage systems. The exact type of drain used was left to the surgeon's discretion.

Drain fluid

Drain fluid reservoirs were emptied two times a day with 12 hour intervals, respecting rules of sterility. The evening collection was disposed of. The morning collection was centrifuged for 10 minutes at 2800xg and 4 °C. The supernatant was brought into different cryotubes that were frozen at -80°C to allow PCR analysis in batch.

Real Time-Polymerase Chain Reaction

RT-PCR analysis of the drain fluids was performed in batch for efficiency purposes. The applied technique was described earlier (13)].

DNA isolation

After thawing, each sample was centrifuged at room temperature for 5 min at 100g. Supernatant was diluted 10 times in a total volume of 250 µl and centrifuged at room temperature for 5 min at 8000g. The resulting pellet was resuspended in 180 µl buffer containing 20 mM Tris, 2 mM EDTA, 1% Tween 80 and lysozyme (50 mg/ml) and incubated for 30 min at 37 °C on a shaking device at 600 rpm (Sanyo Orbital Shaker, München, Germany). DNA extraction was performed using a Macherey–Nagel NucleoSpin® Tissue Kit (Clontech Laboratories, Inc., Mountain View, CA, USA). First, 25 µl of protease was added to the sample, followed by incubation at 56 °C for 2 h at 700 rpm in a shaking device (Thermomixer Compact, Eppendorf, Hamburg, Germany). Protocol proceeded according to the

manufacturer's instructions. Finally, template DNA was eluted in nuclease-free water in a total volume of 100 µl.

Semi-quantitative Real-Time PCR

All PCR reactions were performed in a total volume of 25 µl. The PCR-mix for detection of E. coli consisted of 12.5 µl 2× DyNAmo™ HS SYBR® Green mix (Finnzymes Oy, Espoo, Finland), 0.25 µl forward primer (50 pmol/µl), 0.25 µl reverse primer (50 pmol/µl), 0.25 µl
100 nM Fluorescein Calibration Dye (Bio-Rad, Hercules, CA, USA), 5 µl template DNA and 6.75 µl water. In order to detect E. faecalis, a PCR-mix containing 12.5 µl 2× DyNAmo™ HS SYBR® Green mix (Finnzymes Oy), 0.45 µl forward primer (50 pmol/µl), 0.15 µl reverse
primer (50 pmol/µl), 0.25 µl 100 nM Fluorescein Calibration Dye (Bio-Rad), 5 µl template DNA and 6.65 µl water was used. As an extraction process control (internal control) Phocine Herpes Virus (PhHV) was performed with a PCR-mix consisting of 12.5 µl 2× DyNAmo™ HS SYBR® Green mix (Finnzymes Oy), 0.2 µl forward primer (50 pmol/µl), 0.25 µl reverse primer (50 pmol/µl), 0.25 µl 100 nM Fluorescein Calibration Dye (Bio-Rad), 5 µl template DNA and 6.75 µl water. Following primers were used for Real-Time quantitative PCR: E. coli uidA gene forward primer 5'-GGC TTC TGT CAA CGC TGT TT-3', E. coli uidA gene reverse primer 5'-CCC ATG GAA GAG AAA TGG AA-3', E. faecalis 23S rRNA gene forward primer 5'-AGA AAT TCC AAA CGA ACT TG-3', E. faecalis 23S rRNA gene reverse primer 5'-CAG TGC TCT ACC TCC ATC ATT-3', PhHV forward primer 5'-GGG CGA ATC ACA GAT TGA ATC-3', PhHV reverse primer 5'-GCG GTT CCA AAC GTA CCA A-3'. The Bio-Rad IQ5 ICycler (Bio-Rad, Veenendaal, The Netherlands) was used as Real-Time PCR platform and the PCR conditions for E. coli, E. faecalis and PhHV were as follows: a single predenaturation step of 15 min at 95 °C followed by 40 cycles of 15s at 95 °C and 1 min at 59 °C. Finally, the sample temperature was gradually increased to 95 °C in order to generate dissociation curves. These curves were used to assess the specificity of the PCR product. The dissociation temperature was 76.0 °C for the E. coli-specific PCR product and 77.0 °C for the E. faecalis-specific product. The PCR efficiency was calculated using the slope of the standard curve (efficiency=10−1/slope−1).

Standard curves

The semi-quantitative inoculum of indicator organisms potentially present in the peritoneal drain fluid at the time of anastomotic leakage, has been determined by using a reference dilution series of E. coli and E. faecalis inocula. Reference series were produced by spiking 500 µl of culture-negative drain fluid with a 10 log serial dilution of both E. coli and E. faecalis. A standard curve was generated by comparing the Real-Time PCR results (threshold cycle or Ct-value) to the inoculum sizes. The approximate inoculum size of the query patient sample was determined after interpolation of its Ct-value within the standard curve. Patient samples were analyzed in duplicate.

Definitions

The endpoint of the APPEAL-study was symptomatic colorectal anastomotic leakage. This was defined as a clinically manifest insufficiency of the anastomosis leading to a clinical state requiring intervention, confirmed by radiological studies, reoperation or faecal discharge from the drain. Radiologic confirmation of CAL was defined as extravasation of endoluminally administrated water-soluble contrast and/or significant perianastomotic air on computed tomography or X-ray. Radiological studies were not routinely performed, only in case of clinical suspicion of CAL. Interventions to treat CAL consisted of therapeutic drainage (prolonged stay of drain), use of therapeutic antibiotics or a surgical intervention, i.e. construction of a diverting stoma, disconnection of the anastomosis and construction of a new anastomosis or a colostomy, or suturing of the leakage site.

All postoperative fistulas communicating with the surgical anastomosis were classified as a leak. Postoperative abscesses were classified as anastomotic leakage if there was extravasation of enteric contrast on radiological studies, if there was significant perianastomotic air, or if communication with the anastomosis was noted after radiologic drainage.

The bacterial load of drain fluid was expected to rise in case of CAL, therefore an increase detected by RT-PCR was scored positive.

Postoperative mortality was defined as patients that died within 30 days of operation, in hospital and after discharge.

Data collection.

Patients were followed from their pre-operative admission on the ward until the first postoperative follow-up at the outpatient clinic. Demographic data of the patients, operative details, postoperative events, and follow-up data were obtained through a standardized case record form and entered into a database. In case of CAL the postoperative day of diagnosis was noted along with the manifestation of CAL, the diagnostic tool for detection of the leak, and the treatment.

Statistics.

Categorical data are presented as numbers with percentages, numerical data are presented as means ± standard errors of the mean (normally distributed), or medians with interquartile ranges (not normally distributed). Univariate analysis was performed using a chi-square test or Fisher exact test in case of categorical data, and a Mann-Whitney U test in case of numerical data. As test performance indicators sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and diagnostic odds ratio (DOR) were calculated. Calculations were performed using SPSS 20 (SPSS Inc, Chicago, IL, USA).

RESULTS

A total of 243 patients were included. The mean age was 64 ± 12 years, 135 patients (56%) were male and 108 (44%) were female. Thirty-three patients (14%) were treated for inflammatory diseases, 206 patients (84 %) were treated for malignancy, and four patients (2 %) had ischemic colitis. Fifty-six patients (23%) underwent pre-operative radiotherapy, and in 59 patients (25 %) a defunctioning stoma was constructed. A total of 92 (38 %) patients underwent a laparoscopic procedure and 151 patients (62 %) were operated through laparotomy.

***Table 1**. Univariate analysis of baseline characteristics of APPEAL-population.*

Variable	No CAL (n=224)	CAL (n=19)	p-value
Age	64.3 ± 12.0	65.3 ± 13.9	0.765
Gender			
Male	125 (93 %)	10 (7 %)	
Female	99 (92 %)	9 (8 %)	0.789
BMI			
< 25	80 (91 %)	9 (9 %)	
25-30	109 (98 %)	5 (2 %)	
> 30	35 (88 %)	5 (12 %)	0.155
ASA			
1 - 2	173 (93 %)	13 (7 %)	
3 - 4	50 (89 %)	6 (11 %)	0.532
Neoadjuvant radiotherapy			
Yes	51 (91 %)	5 (9 %)	
No	173 (93 %)	14 (7 %)	0.945
Type of resection			
TME / LAR	76 (92%)	7 (8%)	
PME / HAR	55 (95%)	3 (5%)	
Left hemicolectomy	21 (96%)	1 (4%)	
Sigmoid resection	68 (90%)	8 (10%)	
Subtotal colectomy	4 (100%)	0 (0%)	0.727
Height anastomosis			
> 7cm	149 (94 %)	10 (6 %)	
< 7cm	74 (89 %)	9 (11 %)	0.211
Construction anastomosis			
Stapled	178 (93 %)	14 (7 %)	
Handsewn	45 (90 %)	5 (10 %)	0.735
Configuration anastomosis			
End-to-End	57 (86 %)	9 (14 %)	
End-to-Side	16 (94 %)	1 (6 %)	
Side-to-End	122 (94 %)	8 (6 %)	
Side-to-Side	23 (96 %)	1 (4 %)	0.259
Protective ileostomy			
Yes	55 (93 %)	4 (7 %)	
No	167 (92 %)	15 (8 %)	0.933

Nineteen patients (7.8 %) developed clinical CAL. In 9 patients it became manifest as sepsis, in 7 patients as peritonitis, 2 patients developed a pre-sacral abscess and one patient developed an intra-abdominal abscess. In 8 patients the diagnosis was made by CT-scan, in 7 patients by relaparotomy and in 4 patients faecal discharge from the drain occurred. Median interval between operation and confirmation of CAL was 6 days (range 2 – 26 days). Two patients (0,8 %) developed an infection at the drain insertion site, both in the group without CAL. Average hospital stay of patients with CAL was significantly longer (28 ± 22 days vs. 13 ± 13 days (p<0,0001)). In the group of patients with CAL three died (16 %), whereas 6 patients (3 %) died in the group without CAL (p=0.002). Table 1 shows the baseline characteristics of the patients with and without CAL.

Sixty patients received a Penrose drain, all the other patients received a silicone tube drain. Drainage systems were all passive and closed. The production of drain fluid was not constant over time or between patients and varied greatly between 0 and 1500 ml per day per patient (table 2). The difference in production between patients with and without CAL was not significant.

Table 2. *Amount of drain fluid produced in ml per 24 hours versus AL*

24 hour production	CAL	N	Mean	SD	p-value
Day 1	yes	13	121.0	155.2	0.084
	no	196	179.8	172.1	
Day 2	yes	14	79.3	85.0	0.551
	no	194	104.1	133.7	
Day 3	yes	11	94.9	110.5	0.769
	no	177	124.1	182.2	
Day 4	yes	11	129.7	159.3	0.737
	no	162	120.3	149.2	
Day 5	yes	10	91.1	76.7	0.875
	no	134	119.4	151.3	

The quantitative results are depicted in table 3. An increase of E. coli or E. faecalis as detected by RT-PCR was scored positive, whereas no change or a decrease was scored negative. An increase in E. coli concentration was found in significantly more patients with CAL on day four and five (p=0.0004; DOR 7.9). For E. faecalis this result was found for days two, three and four (p< 0.003) with highest DOR on day three (31.6). Sensitivity and negative predictive value were 92.9 and 98.7 % respectively. The results including sensitivity, specificity, PPV, NPV and DOR for E. coli and E. faecalis are depicted in tables 4 and 5 respectively.

Table 3. *Results of the semi-quantitative real-time PCR. The values are presented in colony forming units per milliliter (CFU/ml).*

RT-PCR	CAL Y/N	Day 1	Day 2	Day 3	Day 4	Day 5
E. coli	Y	55	30	55	100000	1000000
(CFU/ml)	N	0	0	0	0	0
E. faecalis	Y	300	7500	75000	75000	100000
(CFU/ml)	N	1000	1000	1000	0	1000

Table 4. *Quantitative increase of E. coli (**table 4**) and E. faecalis (**table 5**) as determined by RT-PCR. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and diagnostic odds ratio (DOR) are shown. All values are accompanied by their 95 % confidence interval (CI).*
** Numbers of PCRs is less than number of included patients due to the APPEAL study´s priority to biochemical analysis, lack of production, accidental drain removal by patient, early intervention for CAL*

Interval	Increase	CAL* Yes	CAL* No	p-value	Sens% 95 % CI	Spec % 95 % CI	PPV % 95 % CI	NPV % 95 % CI	DOR 95 % CI
Day 1 → 2	Yes	3	11	.185	-	-	-	-	-
	No	10	94						
Day 1 → 3	Yes	6	23	.102	-	-	-	-	-
	No	9	91						
Day 1 → 4	Yes	9	16	<.001	69.2	83.5	36.0	95.2	7.9
	No	4	81		38.9–89.6	74.3–89.9	18.7–57.3	87.7–98.5	2.44–5.6
Day 1 → 5	Yes	10	21	<.001	66.7	79.8	32.3	94.3	7.9
	No	5	83		41.7–84.8	71.1–86.4	17.3–51.5	86.6–97.9	2.4–25.6

Table 5.

Interval	Increase	CAL* Yes	CAL* No	p-value	Sens % 95 % CI	Spec % 95 % CI	PPV % 95 % CI	NPV % 95 % CI	DOR 95 % CI
Day 1 → 2	Yes	10	26	.001	71.4	75.9	27.8	95.3	7.9
	No	4	82		45.4 – 88.3	67.1 – 83.0	14.8 – 45.4	87.9 – 98.5	2.3 – 27.3
Day 1 → 3	Yes	13	30	<.001	92.9	70.9	30.2	98.7	31.6
	No	1	73		68.5 – 98.7	61.5 – 78.8	17.7 – 46.3	92.7 – 99.8	4.0 – 252.7
Day 1 → 4	Yes	9	26	.003	75.0	72.6	25.7	95.8	7.9
	No	3	69		46.8 – 91.1	62.9 – 80.6	12.5 – 43.2	88.3 – 99.1	2.0 – 31.8
Day 1 → 5	Yes	7	38	.388	-	-	-	-	-
	No	7	65						

DISCUSSION

Current screening methods for CAL consist of observation of clinical signs and symptoms and blood examination. These methods are not specific for CAL and may lead to various diagnostic procedures to exclude other, less severe, complications instead of ruling out CAL by means of highly specific imaging studies like CT-scan and / or water-soluble contrast radiography (9)]. These additional diagnostics could lead to a delay in diagnosis of CAL(10)]. Therefore, there is a need for a screening method, objective and specific for CAL.

This study shows that the number of patients with increased levels of E. faecalis between postoperative day one and three was significantly higher in case of CAL. This test has the highest DOR (31.6), reflecting the strong association between the test result and CAL. Considering high sensitivity (92.9 %) and NPV (98.7 %), a negative test result virtually rules out CAL at day 3 postoperatively. The false negative (1.3%) rate is far lower than any other reported diagnostic test for CAL. However, since it does not equal zero clinical observation remains important.

Specificity (70.9 %) and PPV (30.2 %) indicate a substantial number of false positive results. This is most likely due to subclinical anastomotic leakage, a long-known phenomenon with a reported incidence of 8 % (15, 16)]. It could also be caused by intraoperatively spill, however, the number of bacteria should have decreased at day three. Regardless of the cause of the false positive results, positive test results should lead to additional imaging. Reported sensitivity and specificity of contrast radiography when performed in case of clinical suspicion are 68 % and 94 % respectively (17)]. When performed routinely, reported sensitivity varies between 20 % and 52 % and specificity is approximately 85 % (18, 19)]. The reported sensitivity of CT-scan in the early postoperative period varies between 15 % to 52 % (17, 20, 21)]. The reported negative predictive value is 73 % and the false negative rates vary between 35 % and 53 % (17, 21)]. Even though sensitity of CT-scan is lower, it is preferable over contrast enema due to the additional information it provides.

As false positive RT-PCR results are most likely due to subclinical anastomotic leakage, CAL demonstrated on CT-scan might also remain subclinical and specific treatment may not be absolutely necessary. However, subclinical leakage is also associated with reduced quality of life and impaired bowel function (16)], perhaps rendering treatment beneficial. The latter remains speculative and requires more research.

The number of PCRs performed, as depicted in the tables, does not add up to the number of included patients. This is due to insufficient production of drain fluid in most cases as illustrated by table 2. The great variability is a drawback of this study that cannot easily be solved. A peritoneal lavage could be a solution, however, this may interfere with the quantitative PCR analysis. In addition, a few samples are missing due to accidental removal by patient, early intervention for CAL and accidental loss of drain fluid either at the ward or at the processing laboratory.

Prophylactic drainage (PD), as performed on patients included in the APPEAL-study, originally aimed to evacuate wound fluid and blood collections from the surgical site to prevent infectious complications and to detect AL by fecal or purulent discharge (22-24). To date, the use of prophylactic drainage remains controversial. Several level 1 studies have shown that PD does not have a beneficial or a detrimental effect on the incidence of AL and on the morbidity afterwards (25-27). A prospective study concerning pelvic anastomosis showed a higher leakage rate after routine irrigation-suction drainage in elective anterior resection (28). A retrospective study showed drainage and the use of a defunctioning stoma to be beneficial in terms of reoperation rates as a result of anastomotic leakage after TME (29). Despite this controversy surrounding the necessity to drain, prophylactic drainage remains common practice in many hospitals, particularly after rectal surgery (30). In addition, the outcome measures used in these studies consist of leakage rates, hospital stay, radiological anastomotic leakage, infectious complications and patient comfort. In this study we have focused on and demonstrated the diagnostic capacity of the drain. Therefore, considering the low complication rate of PD, it should be placed routinely during surgery to allow collection of drain fluid for the first 3 postoperative days. In addition, it does not interfere with ERAS protocols since the results are known at day 3 and the drain can be removed (31).

Screening is defined by the World Health Organization as the systemic application of a test in an asymptomatic population in order to identify abnormalities that suggest presence of disease and refer these patients promptly for diagnosis and treatment (32)]. The APPEAL-study is the first study to define a promising screening tool for symptomatic CAL that is objective, fast, affordable and provides useful information concerning CAL as early as postoperative day three.

CONCLUSION

RT-PCR for E. faecalis performed on drain fluid may be a useful screening tool for symptomatic colorectal anastomotic leakage in the early postoperative phase. Negative test results virtually rule out the presence of CAL. Positive results should lead to highly specific imaging studies for diagnosis of CAL.

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REFERENCES

1. Levack M, Berger D, Sylla P, Rattner D, Bordeianou L. Laparoscopy decreases anastomotic leak rate in sigmoid colectomy for diverticulitis. Arch Surg. 2011 Feb;146(2):207-10.
2. Boccola MA, Buettner PG, Rozen WM, Siu SK, Stevenson AR, Stitz R, et al. Risk factors and outcomes for anastomotic leakage in colorectal surgery: a single-institution analysis of 1576 patients. World J Surg. 2011 Jan;35(1):186-95.
3. Matthiessen P, Hallbook O, Rutegard J, Simert G, Sjodahl R. Defunctioning stoma reduces symptomatic anastomotic leakage after low anterior resection of the rectum for cancer: a randomized multicenter trial. Ann Surg. 2007 Aug;246(2):207-14.
4. Fraccalvieri D, Biondo S, Saez J, Millan M, Kreisler E, Golda T, et al. Management of colorectal anastomotic leakage: differences between salvage and anastomotic takedown. Am J Surg. 2012 Nov;204(5):671-6.
5. Buchs NC, Gervaz P, Secic M, Bucher P, Mugnier-Konrad B, Morel P. Incidence, consequences, and risk factors for anastomotic dehiscence after colorectal surgery: a prospective monocentric study. Int J Colorectal Dis. 2008 Mar;23(3):265-70.
6. Hyman N, Manchester TL, Osler T, Burns B, Cataldo PA. Anastomotic leaks after intestinal anastomosis: it's later than you think. Ann Surg. 2007 Feb;245(2):254-8.
7. Bellows CF, Webber LS, Albo D, Awad S, Berger DH. Early predictors of anastomotic leaks after colectomy. Tech Coloproctol. 2009 Mar;13(1):41-7.
8. Macarthur DC, Nixon SJ, Aitken RJ. Avoidable deaths still occur after large bowel surgery. Scottish Audit of Surgical Mortality, Royal College of Surgeons of Edinburgh. Br J Surg. 1998 Jan;85(1):80-3.
9. Alves A, Panis Y, Pocard M, Regimbeau JM, Valleur P. Management of anastomotic leakage after nondiverted large bowel resection. J Am Coll Surg. 1999 Dec;189(6):554-9.
10. den Dulk M, Noter SL, Hendriks ER, Brouwers MA, van der Vlies CH, Oostenbroek RJ, et al. Improved diagnosis and treatment of anastomotic leakage after colorectal surgery. Eur J Surg Oncol. 2009 Apr;35(4):420-6.
11. Marteau P, Pochart P, Dore J, Bera-Maillet C, Bernalier A, Corthier G. Comparative study of bacterial groups within the human cecal and fecal microbiota. Appl Environ Microbiol. 2001 Oct;67(10):4939-42.
12. Balamurugan R, Rajendiran E, George S, Samuel GV, Ramakrishna BS. Real-time polymerase chain reaction quantification of specific butyrate-producing bacteria, Desulfovibrio and Enterococcus faecalis in the feces of patients with colorectal cancer. J Gastroenterol Hepatol. 2008 Aug;23(8 Pt 1):1298-303.
13. Komen N, Morsink MC, Beiboer S, Miggelbrink A, Willemsen P, van der Harst E, et al. Detection of colon flora in peritoneal drain fluid after colorectal surgery: can RT-PCR play a role in diagnosing anastomotic leakage? J Microbiol Methods. 2009 Oct;79(1):67-70.
14. Fouda E, El Nakeeb A, Magdy A, Hammad EA, Othman G, Farid M. Early detection of anastomotic leakage after elective low anterior resection. J Gastrointest Surg.2011 Jan;15(1):137-44.
15. Goligher JC, Lee PW, Simpkins KC, Lintott DJ. A controlled comparison one- and two-layer techniques of suture for high and low colorectal anastomoses. Br J Surg. 1977 Sep;64(9):609-14.
16. 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 Oct;49(10):1611-9.
17. Doeksen A, Tanis PJ, Wust AF, Vrouenraets BC, van Lanschot JJ, van Tets WF. Radiological evaluation of colorectal anastomoses. Int J Colorectal Dis. 2008 Sep;23(9):863-8.
18. Hoffmann J, Jensen RH, Shokouh-Amiri MH, Damm P. Clinical value of water-soluble contrast enema in assessing the integrity of left colonic anastomoses. J R Coll Surg Edinb. 1988 Feb;33(1):23-4.
19. Akyol AM, McGregor JR, Galloway DJ, George WD. Early postoperative contrast radiology in the assessment of colorectal anastomotic integrity. Int J Colorectal Dis. 1992 Sep;7(3):141-3.
20. Nicksa GA, Dring RV, Johnson KH, Sardella WV, Vignati PV, Cohen JL. Anastomotic leaks: what is the best diagnostic imaging study? Dis Colon Rectum. 2007 Feb;50(2):197-203.
21. Khoury W, Ben-Yehuda A, Ben-Haim M, Klausner JM, Szold O. Abdominal computed tomography for diagnosing postoperative lower gastrointestinal tract leaks. J Gastrointest Surg. 2009 Aug;13(8):1454-8.

22. Averbach AM, Sugarbaker PH. The use of drains in elective surgery for colorectal cancer: always, never or selectively? Tumori. 1995 May-Jun;81(3 Suppl):89-97.
23. Brown SR, Seow-Choen F, Eu KW, Heah SM, Tang CL. A prospective randomised study of drains in infra-peritoneal rectal anastomoses. Tech Coloproctol. 2001 Aug;5(2):89-92.
24. Lennox MS. Prophylactic drainage of colonic anastomoses. Br J Surg. 1984 Jan;71(1):10-1.
25. Merad F, Yahchouchi E, Hay JM, Fingerhut A, Laborde Y, Langlois-Zantain O. Prophylactic abdominal drainage after elective colonic resection and suprapromontory anastomosis: a multicenter study controlled by randomization. French Associations for Surgical Research. Arch Surg. 1998 Mar;133(3):309-14.
26. Jesus EC, Karliczek A, Matos D, Castro AA, Atallah AN. Prophylactic anastomotic drainage for colorectal surgery. Cochrane Database Syst Rev. 2004(4):CD002100.
27. Petrowsky H, Demartines N, Rousson V, Clavien PA. Evidence-based value of prophylactic drainage in gastrointestinal surgery: a systematic review and meta-analyses. Ann Surg. 2004 Dec;240(6):1074-84; discussion 84-5.
28. Yeh CY, Changchien CR, Wang JY, Chen JS, Chen HH, Chiang JM, 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 Jan;241(1):9-13.
29. Peeters KC, Tollenaar RA, Marijnen CA, Klein Kranenbarg E, Steup WH, Wiggers T, et al. Risk factors for anastomotic failure after total mesorectal excision of rectal cancer. Br J Surg. 2005 Feb;92(2):211-6.
30. Karliczek A, Jesus EC, Matos D, Castro AA, Atallah AN, Wiggers T. Drainage or nondrainage in elective colorectal anastomosis: a systematic review and meta-analysis. Colorectal Dis. 2006 May;8(4):259-65.
31. Scatizzi M, Kroning KC, Boddi V, De Prizio M, Feroci F. Fast-track surgery after laparoscopic colorectal surgery: is it feasible in a general surgery unit? Surgery. 2010 Feb;147(2):219-26.
32. WHO. World Health Organization: Cancer. 2011.

Chapter 7

Treatment of colorectal anastomotic leakage:

Results of a questionnaire amongst members of the Dutch Society of Gastrointestinal Surgery

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ABSTRACT

Anastomotic leakage after colorectal surgery is correlated with considerable morbidity and mortality. Although many studies focus on risk factors and detection, studies on 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 < 80 years of age, for ASA3 and/or >80 age of yeas this percentage is 7,3%. For an anastomosis under the promontory 50% of the respondents choose preserving the anastomosis for ASA1-2 compared to 17% for ASA3 and/or >80years of age. 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 >80 years of age 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 prefer to break down the anastomosis. When the patient is ASA3 and/or> 80 years of age 13% prefer 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.

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 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 or 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.

Table 1. Questionnaire containing multiple-choice questions on treatment strategies in CAL.

1. When treating a patient with CAL would you like to be informed on the extent of leakage? Y/N
2. In your opinion would a pre-planned strategy improve outcome compared to ad hoc decision-making? Y/N
3. A deviating ileostomy is preferable over a deviating colostomy. True/False
4. When an intraperitoneal anastomosis is leaking in an ASA 1-2 <80 year patient this anastomosis should be preserved. True/False
5. When an intraperitoneal anastomosis is leaking in an ASA 3 >80 year patient this anastomosis should be preserved. True/False
6. When an extraperitoneal anastomosis is leaking in an ASA 1-2 <80 year patient this anastomosis should be preserved. True/False
7. When an extraperitoneal anastomosis is leaking in an ASA 3 >80 year patient this anastomosis should be preserved. True/False
8. 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
9. 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. b. c. d. e. Idem as question 8
10. Feacal 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
11. Feacal 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. b. c. Idem as question 10

RESULTS

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

General considerations

Prior to any intervention, 54% of the responding surgeons want to be informed on the extent 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

Of the respondents, 27% assume that a leaking anastomosis cranially to the level of the promontory can be preserved in ASA 1-2 patients, <80 years of age. For patients ASA =/> 3 and/or >80 years of age 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 of age.

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 and 40% break down the anastomosis and create a permanent colostomy. In ASA =/> 3 and/or > 80 years of age these percentages are 37% and 63% respectively.

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 of age, these clinical conditions render these numbers 9%, 13% and 74% respectively (figure 1).

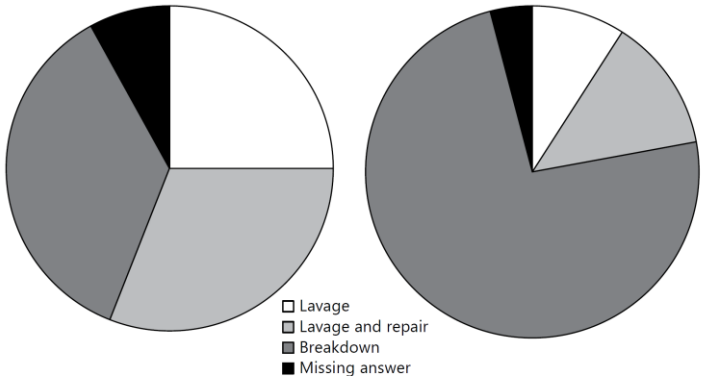

Figure 1. *Overt feacal peritonitis with a small (<30% circumferential) dehiscence: decisions in ASA 1-2 patients <80 years (left), and in ASA 3 patients >80 years (right).*

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 believe 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): p. 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): p. 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): p. 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): p. 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): p. 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): p. 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., Z.H. Krukowski, and A. Munro, Salvage of large bowel anastomotic leaks. Br J Surg, 1999. 86(4): p. 499-500.
14. Rickert, A., et al., Management and outcome of anastomotic leakage after colonic surgery. Colorectal Dis, 2010. 12(10 Online): p. e216-23.
15. Verlaan, T., et al., Early, minimally invasive closure of anastomotic leaks: a new concept. Colorectal Dis, 2011. 13 Suppl 7: p. 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): p. 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): p. 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): p. 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): p. 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): p. 1157-62.
22. Pelloni, A., Colorectal surgery in patients over 80 years old. Hepatogastroenterology, 2012. 59(113): p. 120-3.
23. Reissman, P., F. Agachan, and S.D. Wexner, Outcome of laparoscopic colorectal surgery in older patients. Am Surg, 1996. 62(12): p. 1060-3.

24. Platell, C., et al., The incidence of anastomotic leaks in patients undergoing colorectal surgery. Colorectal Dis, 2007. 9(1): p. 71-9.
25. Brehant, O., et al., Stapled marsupialisation of chronic low rectal anastomotic sinuses. Int J Colorectal Dis, 2009. 24(10): p. 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): p. 288-90.
27. Wind, J., et al., Laparoscopic reintervention for anastomotic leakage after primary laparoscopic colorectal surgery. Br J Surg, 2007. 94(12): p. 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): p. 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): p. 865-72.
32. Alves, A., et al., Management of anastomotic leakage after nondiverted large bowel resection. J Am Coll Surg, 1999. 189(6): p. 554-9.
33. Fraccalvieri, D., et al., Management of colorectal anastomotic leakage: differences between salvage and anastomotic takedown. Am J Surg, 2011 May 18 (Epub ahead of print).

Part IIc

Colorectal anastomosis: risk factors for leakage, and prevention

Chapter 8

Long-term and peri-operative corticosteroids in anastomotic leakage: a prospective study among 259 left-sided colorectal anastomoses

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ABSTRACT

Objective: To determine the risk factors for symptomatic anastomotic leakage(AL) after colorectal resection.

Designs: Review of records of patients who participated in the Analysis of Predictive Parameters for Evident Anastomotic Leakage study.

Setting: Eight health centers.

Patients: Two hundred fifty-nine patients who underwent left-sided colorectal anastomoses.

Intervention: Corticosteroids taken as long-term medication for underlying disease or perioperatively for the prevention of postoperative pulmonary complications.

Main outcome measures: Prospective evaluations for risk factors for symptomatic AL.

Results: In 23% patients a defunctioning stoma was constructed. The incidence of AL was 7.3%. The clinical course of patients undergoing AL showed that in 21% of leaks, the drain indicated leakage, in the remaining patients computed tomography or laparotomy resulted equally often in the detection of AL. In 50% of patients with AL Hartmann's operation was needed. The incidence of AL was significantly higher in patients with pulmonary comorbidity (22.6% leakage), patients taking corticosteroids as chronic medication (50% leakage), and in patients taking corticosteroids peri-operatively (19% leakage). Peri-operative corticosteroids were prescribed in 8% of patients for the prevention of postoperative pulmonary complications.

Conclusions: We found a significantly increased incidence of AL in patients treated with chronic corticosteroids and peri-operative corticosteroids for pulmonary comorbidity. Therefore, we recommend that in this patient category anastomoses should be protected by a diverting stoma, or a Hartmann's procedure should be considered to avoid anastomotic leakage.

INTRODUCTION

Anastomotic leakage (AL) following colorectal resection is a feared complication. The reported incidence of AL is estimated between 3% and 19%[1-5], and when it occurs the mortality is between 10-20%[4,6-8]. There are several basic requirements concerning construction of a colorectal anastomosis; blood flow should be adequate, the anastomosis free of tension, the abdomen free of infectious disease and with minimal contamination. Nevertheless, throughout the years the problem of AL has not diminished[9]. Although accurate prediction of risk is difficult, certain factors are known to contribute to the risk of AL. There is an inverse relationship between the height of the anastomosis from the anal verge and the incidence of AL, extraperitoneal anastomoses carrying the highest risk[10-15]. For these high-risk anastomoses studies have demonstrated the important reduction in mortality and morbidity that can be achieved by the construction of a diverting stoma[4,16,17]. Much research has been done in order to determine additional risk factors for AL. Reported risk factors include male gender[12,13,16], smoking[18], radiotherapy[1,12,19], blood transfusion[1,15,16,20], obesity[5,13], and atherosclerosis[21]. Although corticosteroids are known to impair wound healing, its influence on the healing of colorectal anastomoses is unclear whereas studies report conflicting results[22-25].

The aim of this prospective study was to determine risk factors for clinical AL in patients undergoing left-sided colorectal anastomoses, together with a description of diagnostic and therapeutic approaches in patients having developed AL.

METHODS

Patients included in this study all participated in the Analysis of Predictive Parameters for Evident Anastomotic Leakage (APEPAL) study. In this prospective study all patients undergoing left-sided colorectal resection with construction of an anastomosis were given an intra-abdominal drain. During the first five postoperative days drain fluid was collected for analysis in search for a predictive parameter for AL. Results of drain fluid analysis will be reported separately. Eight centers participated in this study. The study, registered in the Dutch Trial Register (www.trialregister.nl, study number NTR1258), was approved by the medical ethical committee of the participating centers, in accordance with the ethical standards of the Helsinki Declaration of 1975, and all patients gave informed consent. Participating centers included patients consecutively between January 2007 and December 2009; centers stopped including earlier when their target inclusion was fulfilled.

Inclusion criteria

Surgical procedures included left hemicolectomy, sigmoidectomy, high anterior resection or partial meserectal excision (PME), low anterior resection or total mesorectal excision (TME), and subtotal colectomy with ileorectal anastomosis. Oncologic resections as well as resections for inflammatory disease were included. Emergency operations and colostomy reversal were excluded.

Surgical procedure

The surgical procedure was left to the surgeon's discretion. All patients received preoperative antibiotic prophylaxis and an intra-abdominal drain, but guidelines concerning bowel preparation differed per centre. Patients were operated by laparotomy or laparoscopy, the anastomosis was stapled or handsewn, either end-to-end, end-to-side, side-to-end, or side-to-side. A diverting stoma was constructed according to the surgeon's preference.

Definitions

Symptomatic AL, the endpoint of this analysis, was defined as clinically apparent leakage (gas, pus or faecal discharge from the pelvic drain), apparent anastomotic leakage during reoperation, or extravasation of endoluminally administrated water-soluble contrast on computed tomography. Radiological examination was performed only when there was clinical suspicion of anastomotic leakage. All postoperative fistulas communicating with the surgical anastomosis were classified as a leak. Postoperative abscesses were classified as anastomotic leakage if there was extravasation of enteric contrast on an imaging study, there was significant perianastomotic air, or communication with the anastomosis was noted after radiologic drainage. *Asymptomatic AL* was not considered since routine contrast enema was not performed postoperatively.

High anterior resection (HAR) was defined as a colorectal resection with an intraperitoneal anastomis. Low anterior resection (LAR) was defined as a colorectal anastomosis with an extraperitoneal anastomosis.

Data collection

Patients were followed from their pre-operative admission on the ward until the first postoperative follow-up at the outpatient clinic. Demographic data of the patients, operative details, postoperative events, and follow-up data were obtained through a standardized case record form and entered into a database. We used the ICD (International Statistical Classification of Diseases and Related Health Problems, World Health Organization) to define pulmonary and cardiac comorbidity. The diseases included in pulmonary comorbidity are: chronic lower respiratory diseases (J40-J47), lung diseases due to external agents (J60-J70), other respiratory diseases principally affecting the interstitium (J80-J84), other diseases of pleura (J90-J94), other diseases of the respiratory system (J95-J99). The diseases included in cardiac comorbidity are: chronic rheumatic heart diseases (I05-I09), ischaemic heart diseases (I20-I25), pulmonary heart disease and diseases of pulmonary circulation (I26-I28), other forms of heart disease (I29-I52). Use of corticosteroids was subdivided in patients with chronic corticosteroids use for underlying pathology (here called "chronic corticosteroids"), and patients having a corticosteroid scheme prescribed by the anesthesiologist or lung specialist for the reduction of postoperative pulmonary complications starting five days prior to the surgical intervention (here called "peri-operative corticosteroids"). In case of AL the postoperative day of diagnosis was noted

along with the clinical manifestation of AL, the diagnostic tool for leak detection, and the treatment. Postoperative mortality includes all patients who died within 30 days after the operation, both at the hospital as after discharge.

Statistics. Categorical data are presented as numbers with percentages, numerical data are presented as medians with interquartile ranges. Univariate analysis of the differences between patients having a protective ileostomy or not (table 3) was performed using a chi-square test in case of categorical data, and a Mann-Whitney U test in case of numerical data.

Anastomotic leakage binary response (Y/N) was analyzed using logistic regression model, reporting the odds ratios (OR) together with 95% confidence intervals (CI). The univariate and multivariate analyses were conducted with the following covariates: age (categorized at median=65), gender, BMI (categorized at 30), ASA (3,4 vs 1,2), smoking (Y/N), cardiac comorbidity (Y/N), pulmonal comorbidity (Y/N), corticosteroids (chronic, peri-operatively, none), radiotherapy (Y/N), type of resection (LAR, HAR, sigmoidectomy, left hemicolectomy, subtotal colectomy), height of anastomosis (>7cm, <7cm), anastomosis construction (stapled, handsewn), configuration (ETE, ETS, STS, STE), and protective ileostomy (Y/N). In the multivariate analysis the initial model contained all the covariates with grouped type of resection (LAR vs others). Backward elimination procedure was applied to remove non-significant covariates with p to removal ≥0.1.

RESULTS

A total of 259 patients underwent colorectal resection with left-sided anastomosis. Nineteen patients (7.3%) developed clinical AL. Mean age was 64.6 ± 0.75, 144 patients (56%) were male, 115 (44%) were female. Thirty-five patients (13.6%) were treated for inflammatory diseases, 220 patients (84.9%) were treated for malignancy, and four patients (1.5%) had ischemic colitis. Sixty patients (23%) underwent pre-operative radiotherapy, and 89 (34%) anastomoses were situated below the peritoneal reflection. In 60 patients (23%) a defunctioning stoma was constructed.

Anastomotic leakage

Nineteen patients (7.3%) developed clinical AL. The median postoperative day of diagnosis of AL was 6 (4-10). Mortality was significantly increased in patients having undergone AL compared to patients without AL (15.8% versus 2.5%, p-value 0.02). Four patients (21.1%) had a diverting stoma at the time of diagnosis. In three patients AL manifested with a pelvic or intra-abdominal abscess, 7 patients had peritonitis, and 9 patients had signs of sepsis. In 8 patients AL was diagnosed through computed tomography, in 7 patients diagnosis was made during laparotomy, 4 patients had faecal discharge from the drain confirming the diagnosis. In 3 patients treatment consisted of antibiotics, 2 patients had drainage and irrigation of an abscess. Remaining patients were re-operated; four patients had

fecal diversion, two patients had re-anastomosis, and in the remaining eight the anastomosis was converted into end-colostomy. Patients with a diverting ileostomy did not have a clinically lighter presentation of anastomotic leakage nor less invasive treatment of the anastomotic leakage.

Univariate and multivariate analysis

Table 1 shows the result of the univariate analysis for the risk of clinical AL. Gender, BMI, ASA-classification, smoking, pre-operative radiotherapy, height of the anastomosis, type of resection, and construction of a defunctioning stoma were not associated with an increased risk of anastomotic leakage. Two factors were significant in the univariate analysis: pulmonary comorbidity and use of corticosteroids. The incidence of AL was significantly higher in patients taking corticosteroids as chronic medication (50% AL, p-value 0,021) and in patients taking corticosteroid peri-operatively (19% AL, p-value 0.001) compared to patients not taking corticosteroids (5.2% AL). In patients known to have pulmonary comorbidity the incidence of AL was 22.6%; this was 5.3% in patients without pulmonary comorbidity (p-value 0.002). Multivariate analysis was performed, showing a significant result for peri-operative corticosteroids (OR 26.98, SE 30.71, p-value 0.004, 95% CI 2.89-251.10), but a confidence interval so wide due to relatively small quantity of cases that it was chosen to perform a multivariate analysis with chronic corticosteroids and peri-operative steroids combined. From that final multivariate model, it can be concluded that having corticosteroids increased the risk of AL over 7 times (OR 7.52, SE 4.47, p-value 0.001, 95%CI 2.35-24.08). Patients with low anastomosis had a risk of AL greater almost 3 times as compared to patients with high anastomosis (OR 2.98, SE 1.65, p-value 0.049, 95%CI 1.01-8.83).

There was no difference in risk of anastomotic leakage in patients taking corticosteroids between high and low anastomoses.

Table 1. *Univariate analysis of risk factors for anastomotic leakage*

Variable	No AL (n=240)	AL (n=19)	OR	SE	p-value	95% CI
Age	65 (56-73)	68 (53-76)	1.02	0.48	0.963	0.40-2.60
Gender						
Male	134 (93.1%)	10 (6.9%)				
Female	106 (92.2%)	9 (7.8%)	1.14	0.54	0.787	0.44-2.90
BMI	26.3 (0.29)	25.6 (1.1)	0.96	0.06	0.50	0.85-1.06
ASA						
1	64 (97.0%)	2 (3.0%)				
2	119 (91.5%)	11 (8.5%)				
3	54 (90.0%)	6 (10.0%)				
4	2 (100%)	-				
- 1 vs 2			2.96	2.32	0.167	0.64-13.8
- 1 vs 3			3.56	2.98	0.130	0.69-18.3
- 1 vs 4			-	-	-	-
Smoking						
Yes	53 (94.6%)	3 (5.4%)				
No	181 (92.3%)	15 (7.7%)	0.68	0.44	0.558	0.19-2.45

Cardiac comorbidity						
Yes	70 (92.1%)	6 (7.9%)				
No	168 (92.8%)	13 (7.2%)	1.09	0.56	0.864	0.39-2.98
Pulmonary comorbidity						
Yes	24 (77.4%)	7 (22.6%)				
No	214 (94.7%)	12 (5.3%)	4.99	2.59	0.002	1.80-13.85
Steroids						
Yes – long term	3 (50.0%)	3 (50.0%)				
Yes - peri-operatively	17 (81.0%)	4 (19.0%)				
No	218 (94.8%)	12 (5.2%)				
- Long term, yes vs no			4.29	2.70	0.021	1.25-14.76
- Peri-op., yes vs no			18.25	15.85	0.001	3.32-100.15
Radiotherapy						
Yes	55 (91.7%)	5 (8.3%)				
No	184 (92.9%)	14 (7.1%)	1.20	0.65	0.736	0.41-3.48
Type of resection						
LAR	82 (92.1%)	7 (7.9%)				
HAR	57 (95.0%)	3 (5.0%)				
Sigmoidectomy	73 (90.1%)	8 (9.9%)				
Left hemicolectomy	24 (96.0%)	1 (4.0%)				
Subtotal colectomy	4 (100%)	-				
- HAR vs LAR			0.61	0.44	0.497	0.15-2.48
- Sigmoidectomy vs LAR			1.28	0.69	0.645	0.44-3.71
- Left hemicolect. vs LAR			0.48	0.53	0.512	0.06-4.16
- Subtotal colect. vs LAR			-	-	-	-
Height anastomosis						
> 7cm	158 (94.0%)	10 (6.0%)				
< 7cm	80 (89.9%)	9 (10.1%)	1.79	0.86	0.225	0.69-4.58
Stapled	187 (93.0%)	14 (7.0%)				
Handsewn	51 (91.1%)	5 (8.9%)	0.78	0.42	0.464	0.27-2.26
Configuration						
ETE	60 (87.0%)	9 (13.0%)				
ETS	17 (94.4%)	1 (5.6%)				
STE	128 (94.1%)	8 (5.9%)				
STS	26 (96.3%)	1 (3.7%)				
- ETS vs ETE			0.41	0.44	0.407	0.05-3.42
- STS vs ETE			0.26	0.28	0.219	0.03-2.20
- STE vs ETE			0.43	0.22	0.095	0.16-1.16
Protective ileostomy						
Yes	56 (93.3%)	4 (6.7%)				
No	180 (92.3%)	15 (7.7%)	0.86	0.50	0.799	0.27-2.70

Characteristics of patients with and without a defunctioning ileostomy are demonstrated in table 2. Significantly more patients with preoperative radiotherapy and low anastomoses or low anterior resections had a diverting stoma. A diverting stoma was equally constructed in patients receiving corticosteroids or not receiving corticosteroids.

DISCUSSION

Risk-assessment for anastomotic leakage remains an important aspect, since it could lead to better management of high-risk patients. For extraperitoneal anastomoses, which often include extensive

surgical resection and neoadjuvant radiotherapy, it is known that the risk of AL is increased but that the construction of a diverting stoma lowers morbidity and mortality in case of AL[4,16,17]. The benefit of a diverting stoma outweighs the morbidity it includes, since the important complications of clinical AL can be avoided in high-risk groups. However, risk-assessment and knowledge of risk factors is essential in the choice for a diverting stoma.

***Table 2**. Distribution of variables between patients with and without defunctioning ileostomy*

Variable	Without ileostomy (n=195)	With ileostomy (n=60)	p-value
Age	65 (57-74)	66 (53-72)	0.45
Gender			
Male	104 (73.2%)	38 (26.8%)	
Female	91 (80.5%)	22 (19.5%)	0.17
BMI			
< 30	154 (77.4%)	45 (22.6%)	
> 30	29 (67.4%)	14 (32.6%)	0.17
ASA			
1 - 2	149 (76.8%)	45 (23.2%)	
3 - 4	46 (75.4%)	15 (24.6%)	0.82
Smoking			
Yes	40 (72.7%)	15 (27.3%)	
No	150 (76.9%)	45 (23.1%)	0.52
Pulmonary comorbidity			
Yes	26 (89.3%)	5 (16.1%)	
No	169 (75.4%)	55 (24.6%)	0.30
Corticosteroids			
Yes – long term	6 (100%)	0 (-)	
Yes - peri-operatively	19 (90.5%)	2 (9.5%)	
No	170 (74.6%)	58 (25.4%)	0.12
Radiotherapy			
Yes	20 (33.9%)	39 (66.1%)	
No	175 (89.3%)	21 (10.7%)	0.00
Type of resection			
LAR	38 (43.7%)	49 (56.3%)	
HAR	51 (86.4%)	8 (13.6%)	
Sigmoidectomy	78 (96.3%)	3 (3.7%)	
Left hemicolectomy	25 (100%)	-	
Subtotal colectomy	4 (100%)	-	0.00
Height anastomosis			
> 7cm	154 (92.8%)	12 (7.2%)	
< 7cm	40 (45.5%)	48 (54.5%)	0.00

In this prospective study the incidence of clinical AL was 7.5% among 259 left-sided colorectal anastomoses, and mortality rate in patients with AL was 15.8%. These high incidences are in line with percentages of AL and associated mortality reported in literature[1,4,5,12], and again emphasize the importance of this complication in colorectal surgery. The clinical course of patients undergoing AL showed that majority of patients had signs of sepsis or peritonitis. In 21% of leaks the drain indicated

leakage, in the remaining patients computed tomography or laparotomy resulted equally often in the detection of AL. In 50% of patients with AL Hartmann's operation was needed.

In this series in 26% of patients a diverting stoma was constructed, significantly more often in high-risk patients having undergone radiotherapy and with low anastomoses after TME surgery. In univariate analysis low anastomoses did not have an increased risk of anastomotic leakage, however in the multivariate analysis low anastomoses did increase the risk of anastomotic leakage (p-value 0.049). Having a non-significant effect in a univariate analysis and a significant effect in multivariate analysis is due to an interaction effect between factors. First, there is an interaction between the height of anastomosis and a protective ileostomy, with 80% of protective ileostomies in low anastomoses. Second, there is also an interaction with steroids: over 90% of patients with stoma don't have steroids. Therefore in the multivariate analysis when looking at the effect of the height of anastomosis in patients not taking steroids the risk of leakage will be higher in low anastomoses.

In patients using corticosteroids (chronic use of corticosteroids or peri-operative use of corticosteroids) risk of AL was significantly increased. It is known that corticosteroids impair wound healing by decreasing activation and infiltration of inflammatory cells. These inflammatory cells, macrophages and polymorph leucocytes, are essential in the first phase of wound healing[26]. Additionally, corticosteroids inhibit the expression of growth factors and matrix proteins, such as collagen synthesis[26]. Known complications of glucocorticoids are gastrointestinal bleeding, peptic ulcer perforation, and sigmoid diverticular perforation[27,28], as well as postoperative complications as wound infection and wound dehiscence[29-31].

Despite these effects on wound healing in general, conflicting results are found in literature concerning the effect of corticosteroids on healing of colorectal anastomoses. Majority of experimental studies have shown less breaking strength and collagen concentrations in anastomoses of animals treated with steroids[32-37], although some have found equal healing[38,39]. On the contrary, only a minority of clinical studies have found corticosteroids to be a risk factor for AL[22,23,40,41]. Among these is one prospective study of patients with colorectal carcinoma; other studies are retrospective, have only included patients with Crohn's disease, or have looked at postoperative complications in general and not specifically anastomotic leakage. Most clinical studies however, have failed to demonstrate a significant relation between corticosteroids and impaired wound healing after colorectal surgery[14,24,25,42-47]. Unfortunately, again the majority of studies are retrospective, the inclusion criteria of these clinical studies were broad, often only including patients with Crohn's disease, and in a substantial part of these studies postoperative complications in general were taken as outcome measure, and AL was not specifically addressed.

To our knowledge, this is the first study searching for risk factors of AL that not only included chronic use of corticosteroids, but also separately focused on corticosteroids prescribed peri-operatively for

the reduction of postoperative pulmonary complications. In their systematic review Smetana et al.[48] have shown that chronic obstructive pulmonary disease (COPD) is an important independent risk factor for postoperative pulmonary complications, as are specific surgical interventions including abdominal surgery and duration of surgery longer than 2.5 hours. Therefore, the Dutch guidelines for the prevention of postoperative pulmonary complications advise peri-operative corticosteroids for patients having newly diagnosed COPD, unstable COPD, or severe COPD, and undergoing extensive surgical interventions[49]. In these patients it is advised to start five days prior to surgery with 30mg of prednisone/day, which can be ended or gradually reduced 2-3 days postoperatively.

In our study peri-operative corticosteroids were prescribed to eight% of the study population, and to our knowledge this is the first study to demonstrate a significant relation between patients having peri-operative corticosteroid treatment and clinical AL. However, apparently in the surgeon's view peri-operative use of steroids is not considered a substantial risk factor for AL, as these patients did not receive a diverting stoma more often than patients without use of corticosteroids.

In conclusion, our results show that the construction of a diverting stoma in patients with extraperitoneal anastomoses, who have often undergone pre-operative radiotherapy and include extensive total mesorectal excision surgery, is effective in reducing the risk of AL. However, in this prospective study we did find a significantly increased incidence of AL in patients with chronic corticosteroids and peri-operative corticosteroids for pulmonary comorbidity. Therefore, we recommend that in this patient category anastomoses should be protected by a diverting stoma, or, in the case of chronic corticosteroids, a Hartmann's procedure should also be considered to avoid the morbidity and strongly increased mortality associated with AL.

REFERENCES

1. Alves A, Panis Y, Trancart D, et al. Factors associated with clinically significant anastomotic leakage after large bowel resection: multivariate analysis of 707 patients. World J Surg 2002;26:499-502.
2. Hyman N, Manchester TL, Osler T, et al. Anastomotic leaks after intestinal anastomosis: it's later than you think. Ann Surg 2007;245:254-8.
3. Matthiessen P, Hallbook O, Rutegard J, et al. Defunctioning stoma reduces symptomatic anastomotic leakage after low anterior resection of the rectum for cancer: a randomized multicenter trial. Ann Surg 2007;246:207-14.
4. Peeters KC, Tollenaar RA, Marijnen CA, et al. Risk factors for anastomotic failure after total mesorectal excision of rectal cancer. Br J Surg 2005;92:211-6.
5. Komen N, Dijk JW, Lalmahomed Z, et al. After-hours colorectal surgery: a risk factor for anastomotic leakage. Int J Colorectal Dis 2009;24:789-95.
6. Alberts JC, Parvaiz A, Moran BJ. Predicting risk and diminishing the consequences of anastomotic dehiscence following rectal resection. Colorectal Dis 2003;5:478-82.
7. Branagan G, Finnis D, Wessex Colorectal Cancer Audit Working G. Prognosis after anastomotic leakage in colorectal surgery. Dis Colon Rectum 2005;48:1021-6.
8. Fielding LP, Stewart-Brown S, Blesovsky L, et al. Anastomotic integrity after operations for large-bowel cancer: a multicentre study. Br Med J 1980;281:411-4.
9. den Dulk M, Marijnen CA, Collette L, et al. Multicentre analysis of oncological and survival outcomes following anastomotic leakage after rectal cancer surgery. Br J Surg 2009;96:1066-75.
10. Detry RJ, Kartheuser A, Delriviere L, et al. Use of the circular stapler in 1000 consecutive colorectal anastomoses: experience of one surgical team. Surgery 1995;117:140-5.
11. Mann B, Kleinschmidt S, Stremmel W. Prospective study of hand-sutured anastomosis after colorectal resection. Br J Surg 1996;83:29-31.
12. Matthiessen P, Hallbook O, Andersson M, et al. Risk factors for anastomotic leakage after anterior resection of the rectum. Colorectal Dis 2004;6:462-9.
13. Rullier E, Laurent C, Garrelon JL, et al. Risk factors for anastomotic leakage after resection of rectal cancer. Br J Surg 1998;85:355-8.
14. Vignali A, Fazio VW, Lavery IC, et al. Factors associated with the occurrence of leaks in stapled rectal anastomoses: a review of 1,014 patients. J Am Coll Surg 1997;185:105-13.
15. Yeh CY, Changchien CR, Wang JY, 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;241:9-13.
16. Law WL, Chu KW. Anterior resection for rectal cancer with mesorectal excision: a prospective evaluation of 622 patients. Ann Surg 2004;240:260-8.
17. Tan WS, Tang CL, Shi L, et al. Meta-analysis of defunctioning stomas in low anterior resection for rectal cancer. Br J Surg 2009;96:462-72.
18. Sorensen LT, Jorgensen T, Kirkeby LT, et al. Smoking and alcohol abuse are major risk factors for anastomotic leakage in colorectal surgery. Br J Surg 1999;86:927-31.
19. Eriksen MT, Wibe A, Norstein J, et al. Anastomotic leakage following routine mesorectal excision for rectal cancer in a national cohort of patients. Colorectal Dis 2005;7:51-7.
20. Makela JT, Kiviniemi H, Laitinen S. Risk factors for anastomotic leakage after left-sided colorectal resection with rectal anastomosis. Dis Colon Rectum 2003;46:653-60.
21. Komen N, Klitsie P, Dijk JW, et al. Calcium score: a new risk factor for colorectal anastomotic leakage. Am J Surg 2010.
22. Konishi T, Watanabe T, Kishimoto J, et al. Risk factors for anastomotic leakage after surgery for colorectal cancer: results of prospective surveillance. J Am Coll Surg 2006;202:439-44.
23. Post S, Betzler M, von Ditfurth B, et al. Risks of intestinal anastomoses in Crohn's disease. Ann Surg 1991;213:37-42.

24. Tresallet C, Royer B, Godiris-Petit G, et al. Effect of systemic corticosteroids on elective left-sided colorectal resection with colorectal anastomosis. Am J Surg 2008;195:447-51.
25. Jex RK, van Heerden JA, Wolff BG, et al. Gastrointestinal anastomoses. Factors affecting early complications. Ann Surg 1987;206:138-41.
26. Schacke H, Docke WD, Asadullah K. Mechanisms involved in the side effects of glucocorticoids. Pharmacol Ther 2002;96:23-43.
27. Weiner HL, Rezai AR, Cooper PR. Sigmoid diverticular perforation in neurosurgical patients receiving high-dose corticosteroids. Neurosurgery 1993;33:40-3.
28. Mpofu S, Mpofu CM, Hutchinson D, et al. Steroids, non-steroidal anti-inflammatory drugs, and sigmoid diverticular abscess perforation in rheumatic conditions. Ann Rheum Dis 2004;63:588-90.
29. De Vivo A, Mancuso A, Giacobbe A, et al. Wound length and corticosteroid administration as risk factors for surgical-site complications following cesarean section. Acta Obstet Gynecol Scand 2010;89:355-9.
30. Steingrimsson S, Gottfredsson M, Kristinsson KG, et al. Deep sternal wound infections following open heart surgery in Iceland: a population-based study. Scand Cardiovasc J 2008;42:208-13.
31. Busti AJ, Hooper JS, Amaya CJ, et al. Effects of perioperative antiinflammatory and immunomodulating therapy on surgical wound healing. Pharmacotherapy 2005;25:1566-91.
32. Cali RL, Smyrk TC, Blatchford GJ, et al. Effect of prostaglandin E1 and steroid on healing colonic anastomoses. Dis Colon Rectum 1993;36:1148-51.
33. Del Rio JV, Beck DE, Opelka FG. Chronic perioperative steroids and colonic anastomotic healing in rats. J Surg Res 1996;66:138-42.
34. Furst MB, Stromberg BV, Blatchford GJ, et al. Colonic anastomoses: bursting strength after corticosteroid treatment. Dis Colon Rectum 1994;37:12-5.
35. Phillips JD, Kim CS, Fonkalsrud EW, et al. Effects of chronic corticosteroids and vitamin A on the healing of intestinal anastomoses. Am J Surg 1992;163:71-7.
36. Polat A, Nayci A, Polat G, et al. Dexamethasone down-regulates endothelial expression of intercellular adhesion molecule and impairs the healing of bowel anastomoses. Eur J Surg 2002;168:500-6.
37. Mantzoros I, Kanellos I, Demetriades H, et al. Effects of steroid on the healing of colonic anastomoses in the rat. Tech Coloproctol 2004;8 Suppl 1:s180-3.
38. Mastboom WJ, Hendriks T, de Man BM, et al. Influence of methylprednisolone on the healing of intestinal anastomoses in rats. Br J Surg 1991;78:54-6.
39. Eubanks TR, Greenberg JJ, Dobrin PB, et al. The effects of different corticosteroids on the healing colon anastomosis and cecum in a rat model. Am Surg 1997;63:266-9.
40. Golub R, Golub RW, Cantu R, Jr., et al. A multivariate analysis of factors contributing to leakage of intestinal anastomoses. J Am Coll Surg 1997;184:364-72.
41. Yamamoto T, Allan RN, Keighley MR. Risk factors for intra-abdominal sepsis after surgery in Crohn's disease. Dis Colon Rectum 2000;43:1141-5.
42. Allsop JR, Lee EC. Factors which influenced postoperative complications in patients with ulcerative colitis or Crohn's disease of the colon on corticosteroids. Gut 1978;19:729-34.
43. Bruewer M, Utech M, Rijcken EJ, et al. Preoperative steroid administration: effect on morbidity among patients undergoing intestinal bowel resection for Crohns disease. World J Surg 2003;27:1306-10.
44. Colombel JF, Loftus EV, Jr., Tremaine WJ, et al. Early postoperative complications are not increased in patients with Crohn's disease treated perioperatively with infliximab or immunosuppressive therapy. Am J Gastroenterol 2004;99:878-83.
45. Heimann TM, Greenstein AJ, Mechanic L, et al. Early complications following surgical treatment for Crohn's disease. Ann Surg 1985;201:494-8.
46. Knudsen L, Christiansen L, Jarnum S. Early complications in patients previously treated with corticosteroids. Scand J Gastroenterol Suppl 1976;37:123-8.
47. Lipska MA, Bissett IP, Parry BR, et al. Anastomotic leakage after lower gastrointestinal anastomosis: men are at a higher risk. ANZ J Surg 2006;76:579-85.

48. Smetana GW, Lawrence VA, Cornell JE, et al. Preoperative pulmonary risk stratification for noncardiothoracic surgery: systematic review for the American College of Physicians. Ann Intern Med 2006;144:581-95.
49. Dutch Society for Anesthesiology. Guideline: Prevention of peri-operative pulmonary complications in non-pulmonary surgery in patients with an increased risk of pulmonary complications; 2007.

Chapter 9

Calcium score: a new risk factor for colorectal anastomotic leakage

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ABSTRACT

Background: Anastomotic leakage (AL) is the most feared complication of colorectal surgery. Atherosclerosis is suggested to have a detrimental effect on anastomotic healing. This study aimed to analyze the calcium score, a measure for atherosclerosis, as a risk factor for AL.

Study design: The calcium scores of colorectal patients operated on in 2 Dutch university medical centers were determined using a computed tomography scan and calcium scoring software. The aorta, common iliac arteries, internal and external iliac arteries were studied. Additionally, patient- and operation-related factors were scored.

Results: A total of 122 patients were included. In patients with AL, calcium scores were significantly higher in the left common iliac artery (561.4 vs 156.0, *P* = .028), right common iliac artery (542.0 vs 144.4, *P* = .041), both common iliac arteries together (1,103.3 vs 301.9, *P* = .046), and the left internal iliac artery (716.3 vs 35.3, *P* = .044).

Conclusion: Patients with higher calcium scores in the iliacal arteries have an increased leakage risk.

INTRODUCTION

Anastomotic leakage (AL) is the most feared complication in colorectal surgery. Aiming to assess the risk for anastomotic leakage, many studies analyzing potential risk factors have been reported. Factors like diverticular disease[1], rectal resection[2], urgent operation[3], smoking[4], body mass index (BMI)[5], sex[6], use of steroids[7] radio- and/or chemotherapy[6], American Society of Anesthesiologists (ASA) score[8], a history of cardiac and vascular disease[9] sutured or stapled anastomosis[10], prophylactic drainage[11] and operating time[6] are considered risk factors. However, despite this knowledge, leakage rates still are high, varying between 2% and 24%[12–16] with high mortality and morbidity rates. This suggests that risk factors for AL remain to be discovered.

Ischemia is considered an etiologic factor for AL. At the anastomotic site, local vascular supply is disrupted because of vessel injury, thrombosis, and tissue compression by sutures or staplers or by mobilization of the intestinal limbs. Surgery activates a cascade of events, including platelet degranulation and the release of complement, kinins, and chemotactic factors, which lead to a migration of neutrophils, lymphocytes, macrophages, and fibroblasts into the anastomotic site. This state of higher metabolic activity and higher oxygen demand combined with a decreased vascular supply causes the anastomosis to be hypoxic compared with normal tissue[17]. Atherosclerosis is a known cause of tissue ischemia[18,19] and is suggested to have a detrimental effect on anastomotic healing[20]. At present, it is possible to quantify the atherosclerotic calcifications on computed tomography (CT) images by means of calcium scoring software. It allows measurement of the calcium mass, calcium volume, number of calcifications, and the calcium score. The latter represents the total atherosclerotic load in the analyzed trajectory[21,22]. With this tool, the study of atherosclerosis as a risk factor for anastomotic leakage is possible. The aim of this study was to analyze the calcium score as a risk factor for anastomotic leakage. It is hypothesized that higher calcium scores are predictive for higher leakage rates.

METHODS

All patients who received a primary colorectal anastomosis, irrespective of indication, during elective or emergency surgery at the Erasmus MC between 2002 and 2006 and at the UMCG between 2005 and 2007 were selected by operation code. Patients within this selection whom received a preoperative contrast-enhanced CT scan with a slice thickness of 5 mm were included. The calcium scores were determined in the following segments of the aortoiliac trajectory: the aorta starting from the T12-L1 level, left and right common iliac arteries, left and right internal iliac arteries, and the left and right external iliac arteries. Scoring was performed with a lower threshold of 500 Hounsfield units using the following software: Siemens Calcium Score (Syngo CT 2006G-W; Siemens, Forcheim, Germany). Together with the calcium score, this software allows measurement of the calcium mass,

the calcium volume, and the number of calcifications in a designated trajectory. To describe the studied population, after CT scan analysis, patient- and operation-related factors were scored (ie, age, use of antihypertensive drugs and statins, smoking, cardiac comorbidity, history of vascular disease, diabetes mellitus, sex, BMI, use of steroids, type of anastomosis, urgent vs elective operation, type of operation, prophylactic drainage, ASA score, neoadjuvant therapy, approach, stapled vs hand-sutured, and time under anesthesia respectively). The primary outcome measure was clinically manifest anastomotic leakage, confirmed by imaging or re-laparotomy. Whether leakage occurred or not was determined after CT scan analysis and after the search for patient- and operation-related factors to prevent bias. The median and mean values were compared between groups with and without AL by means of the Mann-Whitney *U* test or chi-square test in univariate analysis. Multiple regression analysis was performed for the calcium score, calcium mass, and calcium volume separately, with factors that were significant in univariate analysis and consisted of multiple logistic regression with backwards elimination. In the final model, multiple logistic regression with backwards elimination of all factors, significant or nonsignificant in univariate analysis, was performed. Statistical analysis was performed with SPSS 12.0 (SPSS Inc, Chicago, IL).

RESULTS

A total of 122 patients were included of whom 11 (9%) developed anastomotic leakage. In both the group with and without leakage, 3 patients died (27% vs 2.7% [*P* = .004]). None of the scored patient- and operation-related factors were significantly different in univariate analysis as depicted in Table 1.

Table 1. *Univariate analysis of patient and operation related factors.*

	Factor	AL	No AL	p-value
Hospital	EMC	7 (9%)	66 (91%)	1·000
	UMCG	4 (8%)	45 (92%)	
BMI (kg/m^2) *		24·6 ± 2·7	25·5 ± 4·2	0·454
Gender (M/F)	Male	5 (7%)	66 (93%)	0·563
	Female	6 (12%)	45 (88%)	
Use of steroids†	Yes	3 (27%)	8 (73%)	0·099
	No	8 (7%)	102 (93%)	
ASA-score†	1	5 (10%)	45 (90%)	0·492
	2	4 (8%)	45 (92%)	
	3	1 (6%)	16 (94%)	
	4	1 (33%)	2 (67%)	
Neoadjuvant radiotherapy	Yes	1 (5%)	19 (95%)	0·796
	No	10 (10%)	92 (90%)	
Anastomotic configuration†	End to End	3 (20%)	12 (80%)	0·334
	End to Side	0 (0%)	9 (100%)	
	Side to End	2 (6%)	31 (94%)	
	Side to Side	5 (10%)	46 (90%)	

Type of operation‡	Right sided	3 (9%)	29 (91%)	0·974
	Left sided	5 (9%)	48 (91%)	
	Rectum	3 (8%)	34 (92%)	
Approach	Laparotomy	10 (10%)	95 (90%)	0·976
	Laparoscopy	1 (6%)	16 (94%)	
Stapled vs. hand sutured	Stapled	2 (4%)	46 (96%)	0·237
	Sutured	9 (12%)	65 (88%)	
Urgent vs. Elective†	Urgent	1 (6%)	15 (94%)	1·000
	Elective	9 (9%)	96 (91%)	
Prophylactic drainage	Yes	3 (7%)	37 (93%)	0·943
	No	8 (10%)	74 (90%)	
Time under anaesthesia (minutes)		257·7 ± 58·0	250·8 ± 95·7	0·526
Age (years)		60·3 ± 12·4	59·9 ± 16·5	0·841
Anti-hypertensive medication*	Yes	3 (11%)	25 (89%)	0·790
	No	6 (7%)	82 (93%)	
Use of statins*	Yes	2 (14%)	12 (86%)	0·659
	No	7 (7%)	95 (93%)	
History of vascular disease*	Yes	3 (14%)	19 (86%)	0·600
	No	7 (7%)	88 (93%)	
Cardiac comorbidity*	Yes	3 (12%)	21 (88%)	0·713
	No	7 (7%)	86 (93%)	
Smoker*	Yes	3 (14%)	18 (86%)	0·801
	No	7 (9%)	68 (91%)	
Diabetes Mellitus*	Yes	1 (10%)	9 (90%)	1·000
	No	9 (8%)	98 (92%)	

Age, BMI and time under anesthesia are expressed in means and standard deviation.
**BMI is Body Mass Index in kg/m2. †Data does not ad up to 122 because of occasional missing data. ‡Right sided includes ileocecal resection and right hemicolectomy. Left sided includes left Hemicolectomy and sigmoid resection. Rectum includes total mesorectal excision (TME) and rectosigmoid resection.*

The number of calcified lesions in the right common iliac artery was significantly different between patients with and without leakage. Differences in calcium volume were significant for the total trajectory, the left common iliac artery, the right common iliac artery, both common iliac arteries together, and the left internal iliac artery. Differences in calcium mass were significant for the total trajectory, the aorta, the left common iliac artery, the right common iliac artery, both common iliac arteries together, and the left internal iliac artery. Differences in the calcium score were significant for the left common iliac artery, the right common iliac artery, both common iliac arteries together, and the left internal iliac artery. The results of the analyses are depicted in Tables 2 to 5. In some patients, the CT scan started below the T12-L1 level or ended prematurely. Therefore, not all trajectories could be scored and the number of scored patients does not always add up to 122.

Table 2. *Number of calcified lesions per trajectory. AL = Anastomotic Leakage; N = the number of patients; Mean = mean number of lesions; SD = standard deviation.*

		Number of lesions			
Trajectory	**AL**	**N**	**Mean**	**SD**	**p-value**
Total trajectory	yes	11	19,7	17,1	0·067
	no	105	9·2	12·7	
Aorta	yes	11	10·4	10·0	0·076
	no	109	5·4	8·5	
Left common iliac artery	yes	11	3·3	3·2	0·072
	no	108	1·7	3·0	
Right common iliac artery	yes	11	4·7	4·5	**0·036**
	no	108	1·6	2·6	
Left internal iliac artery	yes	11	1·5	1·6	0·060
	no	106	0·7	1·4	
Left external iliac artery	yes	11	0·3	0·9	0·963
	no	106	0·1	0·5	
Right internal iliac artery	yes	11	1·4	1·7	0·184
	no	107	0·6	1·3	
Right external iliac artery	yes	11	1·3	3·1	0·222
	no	107	0·1	0·4	
Left and right common iliac arteries	Yes	11	8·0	7·6	0·076
	no	108	3·3	5·4	
Left and right internal iliac arteries	yes	11	2·8	3·2	0·128
	no	106	1·3	2·5	

Table 3. *Calcium volume per trajectory. AL = Anastomotic Leakage; N = the number of patients; Mean = mean calcium volume; SD = standard deviation.*

		Calcium volume			
Trajectory	**AL**	**N**	**Mean**	**SD**	**p-value**
Total trajectory	yes	11	1750·6	1902·8	0·043
	no	105	520·8	1098·6	
Aorta	yes	11	1030·8	1351·3	0·057
	no	109	376·2	814·7	
Left common iliac artery	yes	11	333·0	358·2	0·025
	no	108	82·2	169·6	
Right common iliac artery	yes	11	290·4	287·2	0·040
	no	108	75·5	187·9	
Left internal iliac artery	yes	11	443·4	1360·6	0·049
	no	106	16·1	44·5	
Left external iliac artery	yes	11	0·6	2·1	0·985
	no	106	2·4	12·9	
Right internal iliac artery	yes	11	35·0	56·5	0·280
	no	107	20·9	78·8	
Right external iliac artery	yes	11	10·2	31·5	0·275
	no	107	4·8	24·1	
Left and right common iliac arteries	yes	11	623·5	604·7	0·041
	no	108	157·7	335·2	
Left and right internal iliac arteries	yes	11	478·4	1376·7	0·165
	no	106	36·9	116·2	

Table 4. *Calcium mass per trajectory. AL = Anastomotic Leakage; N = the number of patients; Mean = mean calcium mass; SD = standard deviation.*

Calcium mass					
Trajectory	**AL**	**N**	**Mean**	**SD**	**p-value**
Total trajectory	yes	10	1322·3	1241·4	0·014
	no	103	377·0	769·9	
Aorta	yes	10	755·2	856·0	0·023
	no	107	261·7	540·1	
Left common iliac artery	yes	10	267·8	255·1	0·010
	no	107	65·0	133·5	
Right common iliac artery	yes	10	247·0	224·0	0·014
	no	107	57·8	139·8	
Left internal iliac artery	yes	10	323·9	919·7	0·022
	no	105	13·7	34·8	
Left external iliac artery	yes	10	0·9	2·8	0·946
	no	105	2·1	10·6	
Right internal iliac artery	yes	10	33·4	48·2	0·155
	no	106	16·3	57·0	
Right external iliac artery	yes	10	9·9	27·8	0·223
	no	106	3·5	16·9	
Left and right common iliac arteries	yes	10	514·8	447·7	0·014
	no	107	122·9	257·2	
Left and right internal iliac arteries	yes	10	357·3	937·1	0·083
	no	105	29·8	87·3	

Table 5. *Calcium score per trajectory. AL = Anastomotic Leakage; N = the number of patients; Mean = mean calcium score; SD = standard deviation.*

Calcium score					
Trajectory	**AL**	**N**	**Mean**	**SD**	**p-value**
Total trajectory	yes	11	2716·8	2904·5	0·052
	no	105	896·8	1798·1	
Aorta	yes	11	1489·4	2054·2	0·122
	no	109	618·5	1248·4	
Left common iliac artery	yes	11	561·4	571·4	0·028
	no	108	156·0	318·3	
Right common iliac artery	yes	11	542·0	538·7	0·041
	no	107	144·4	337·2	
Left internal iliac artery	yes	11	716·3	2116·1	0·044
	no	106	35·3	87·4	
Left external iliac artery	yes	11	2·4	7·9	0·985
	no	106	5·4	25·8	
Right internal iliac artery	yes	11	78·0	117·8	0·232
	no	107	39·7	132·0	
Right external iliac artery	yes	11	26·9	79·0	0·267
	no	107	8·3	38·2	
Left and right common iliac arteries	yes	11	1103·3	1056·6	0·046
	no	107	301·9	623·8	
Left and right internal iliac arteries	yes	11	794·2	2162·0	0·144
	no	106	74·6	209·1	

Multiple regression analysis as described in the methods section was performed for the calcium score, mass, and volume in the right and left common iliac arteries together. All 3 parameters were independent risk factors for anastomotic leakage (Table 6).

Table 6. *Results of multivariate analysis performed for calcium score, -mass and volume in the right and left common iliac arteries together.*

Multiple regression analyses			
Right and left common iliac arteries	**OR**	**95 % CI**	**p-value**
Calcium score	1·001	1·000 – 1·002	0·003
Calcium mass	1·003	1·001 – 1·004	0·001
Calcium volume	1·002	1·001 – 1·003	0·002

Each parameter is an independent risk factor for AL. Odds ratio's (OR) show that an increase of one unit of calcium score, -mass or –volume leads to an increased risk for AL of 0.1%·,0.3% and 0.2% respectively.

DISCUSSION

AL is the most feared complication of colorectal surgery for which the construction of a diverting stoma (DS) is the most common strategy. Some studies recommend routine DS construction[14]. However, because DS is associated with considerable morbidity, an impact on quality of life, and mortality after stoma closure[23–27], a more selective approach is warranted. Knowledge of risk factors is required to perform an educated risk assessment preoperatively, allowing a tailor-made decision whether or not to construct DS. Atherosclerosis may have a detrimental effect on anastomotic healing because it can lead to ischemia of the intestinal limbs of anastomosis. Therefore, it can be a risk factor that was still unaddressed. In this study, quantification tools for atherosclerosis (ie, calcium score, mass, and volume) were used to analyze the potential association between anastomotic leakage and atherosclerosis. By means of multivariate analysis, this study has shown that the mean calcium load, expressed as calcium score, mass, and volume, determined in the common iliac arteries is an independent risk factor for AL. Consequently, these tools can and should be used in the decision-making process of whether or not to construct an anastomosis and/or DS. Many risk factors for AL have been reported in the literature, and the majority has been analyzed in this study. No statistically significant differences were found between the groups with and without leakage. The 2 groups are similar except for the calcium score, calcium mass, and volume. This enforces our finding; however, it raises questions on whether the studied population represents the overall population. In addition, univariate analysis has shown the calcium score determined in only the left internal iliac artery to be significantly higher in patients with AL compared with patients without AL. However, this finding cannot be explained anatomically or physiologically. Therefore, multiple regression analysis was not performed for this segment. To address these questions and the

small number of patients with AL, a prospective study with larger patient numbers should be performed.

The calcium (Agatson) score is the product of the area of calcification (mm^2) and its radiodensity (Hounsfield units). It is commonly used in studies on atherosclerosis with regard to the coronary arteries. However, controversy remains on whether the total atherosclerotic load is represented. Studies have been published showing the calcium score to represent the entire atherosclerotic load, meaning the noncalcified as well as the calcified plaques[22]. However, a more recent publication suggests that this may not be true and that the calcium score is an underestimation of the real atherosclerotic load[28]. Whether or not the total atherosclerotic load is represented by the calcium score does not affect the results of this study addressing the association between atherosclerotic calcifications and AL. This association indicates that macroangiopathy (ie, calcifications within the aortoiliac trajectory), is a predictor for AL.

The software used in this study was designed to measure calcium volume and calcium mass parallel to the calcium score. For both parameters, a similar association with leakage was found as for the calcium score (Tables 3 and 4). In addition, differences in calcium mass were significant for the total trajectory and aorta as well. Differences in calcium volume were different for the total trajectory as well. Particularly the association between calcium mass and AL is an interesting finding in view of the interchangeability between different labels of CT scanners. Because a constant mass of calcium should yield similar results in different CT scanners, this parameter is best suited to detect differences between systems. The determination of calcium mass allows the comparison of calcium loads quantified with different systems. The results of this study indicate that the calcium mass does not necessarily have to be determined in the common iliac arteries, allowing certain flexibility in scanning protocols. The number of calcifications does not appear to be a significant factor, the difference is only significant in the right common iliac artery. This is understandable considering a certain score, mass, or volume of calcium can contain multiple small lesions or few larger lesions. Multiple regression analysis was performed for the 2 common iliac arteries together because these were significant for the calcium score, mass, and volume. The odds ratios (Table 6) showed that an increase of 1 U of calcium score, mass, or volume led to an increased risk for AL of 0.1%, 0.3% and 0.2%, respectively. The difference between patients with and without AL for the calcium score was 801.4, calcium mass 391.9, and calcium volume 465.8 (Tables 3–5). This means an 80% (0.1 x 801.4) increased risk for AL based on the calcium score, 118% (0.3 x 391.9) increased risk for AL based on calcium mass, and 93% (0.2 x 465.8) increased risk for AL based on calcium volume. The quantification of atherosclerotic calcifications as described in this study requires CT imaging of the abdomen. Because abdominal CT scan still is the principle staging tool for colorectal cancer, obtaining information on atherosclerotic calcifications does not require additional imaging[29,30].

However, for rectal cancer, according to the European guidelines, only an upper-abdominal CT scan is indicated to search for liver metastasis [31]. This means that for quantification of atherosclerotic calcifications in the (common-) iliac arteries additional imaging is required. However, considering the relatively low cost and speed of CT scan, this is acceptable.

CONCLUSION

This study has shown that atherosclerotic calcifications in the left and right common iliac arteries, expressed as calcium score, mass, and volume, are an independent risk factor for colorectal anastomotic leakage. An increase of 1 U of calcium score, mass, or volume leads to an increased risk for AL of 0.1%, 0.3% and 0.2%, respectively. These parameters can be used in a preoperative risk assessment for anastomotic leakage, allowing tailor-made decisions on the construction of an anastomosis and/or a protective or definite stoma.

REFERENCES

1. Platell C, Barwood N, Dorfmann G, et al. The incidence of anastomotic leaks in patients undergoing colorectal surgery. Colorectal Dis 2007;9:71–9.
2. Buchs NC, Gervaz P, Secic M, et al. Incidence, consequences, and risk factors for anastomotic dehiscence after colorectal surgery: a prospective monocentric study. Int J Colorectal Dis 2007;23:265–70.
3. Choi HK, Law WL, Ho JW. Leakage after resection and intraperitoneal anastomosis for colorectal malignancy: analysis of risk factors. Dis Colon Rectum 2006;49:1719 –25.
4. Sorensen LT, Jorgensen T, Kirkeby LT, et al. Smoking and alcohol abuse are major risk factors for anastomotic leakage in colorectal surgery. Br J Surg 1999;86:927–31.
5. Nickelsen TN, Jorgensen T, Kronborg O. Lifestyle and 30-day complications to surgery for colorectal cancer. Acta Oncol 2005;44:218–23.
6. Matthiessen P, Hallbook O, Andersson M, et al. Risk factors for anastomotic leakage after anterior resection of the rectum. Colorectal Dis 2004;6:462–9.
7. Konishi T, Watanabe T, Kishimoto J, et al. Risk factors for anastomotic leakage after surgery for colorectal cancer: results of prospective surveillance. J Am Coll Surg 2006;202:439–44.
8. Alves A, Panis Y, Trancart D, et al. Factors associated with clinically significant anastomotic leakage after large bowel resection: multivariate analysis of 707 patients. World J Surg 2002;26:499 –502.
9. Makela JT, Kiviniemi H, Laitinen S. Risk factors for anastomotic leakage after left-sided colorectal resection with rectal anastomosis. Dis Colon Rectum 2003;46:653– 60.
10. Lustosa SA, Matos D, Atallah AN, et al. Stapled versus handsewn methods for colorectal anastomosis surgery. Cochrane Database Syst Rev 2001;3:CD003144.
11. Jesus EC, Karliczek A, Matos D, et al. Prophylactic anastomotic drainage for colorectal surgery. Cochrane Database Syst Rev 2004;4: CD002100.
12. Hagmuller E, Lorenz D, Werthmann K, et al. [Uses and risks of drainage following elective colon resection. A prospective, randomized and controlled clinical study] nutzen und Risiken einer Drainage nach elektiven Colonresektionen. Eine prospektive, randomisierte und kontrollierte klinische Studie. Chirurg 1990;61:266 –71.
13. Hyman N, Manchester TL, Osler T, et al. Anastomotic leaks after intestinal anastomosis: it's later than you think. Ann Surg 2007;245: 254–8.
14. Matthiessen P, Hallbook O, Rutegard J, et al. Defunctioning stoma reduces symptomatic anastomotic leakage after low anterior resection of the rectum for cancer: a randomized multicenter trial. Ann Surg 2007;246:207–14.
15. Sagar PM, Couse N, Kerin M, et al. Randomized trial of drainage of colorectal anastomosis. Br J Surg 1993;80:769 –71.
16. Komen N, Dijk JW, Lalmahomed Z, et al. After-hours colorectal surgery: a risk factor for anastomotic leakage. Int J Colorectal Dis 2009;24:789 –95.
17. Chang N, Goodson WH 3rd, Gottrup F, et al. Direct measurement of wound and tissue oxygen tension in postoperative patients. Ann Surg 1983;197:470–8.
18. Scharff JR, Longo WE, Vartanian SM, et al. Ischemic colitis: spectrum of disease and outcome. Surgery 2003;134:624 –9; [Discussion: 629–630].
19. Greenwald DA, Brandt LJ, Reinus JF. Ischemic bowel disease in the elderly. Gastroenterol Clin North Am 2001;30:445–73.
20. Foster ME, Brennan SS, Morgan A, et al. Colonic ischaemia and anastomotic healing. Eur Surg Res 1985;17:133–9.
21. Greenland P, Bonow RO, Brundage BH, et al, American College of Cardiology Foundation Clinical Expert Consensus Task Force (ACCF/ AHA Writing Committee to Update the 2000 Expert Consensus Document on Electron Beam Computed Tomography), Society of Atherosclerosis Imaging and Prevention, Society of Cardiovascular Computed Tomography. ACCF/AHA 2007 clinical expert consensus document on coronary artery calcium scoring by computed tomography in global cardiovascular risk assessment and in

evaluation of patients with chest pain: a report of the American College of Cardiology Foundation Clinical Expert Consensus Task Force (ACCF/AHA Writing Committee to Update the 2000 expert consensus document on electron beam computed tomography) developed in collaboration with the Society of Atherosclerosis Imaging and Prevention and the Society of Cardiovascular Computed Tomography. J Am Coll Cardiol 2007;49:378 – 402.

22. Rumberger JA, Simons DB, Fitzpatrick LA, et al. Coronary artery calcium area by electron-beam computed tomography and coronary atherosclerotic plaque area. A histopathologic correlative study. Circulation 1995;92:2157– 62.
23. Engel J, Kerr J, Schlesinger-Raab A, et al. Quality of life in rectal cancer patients: a four-year prospective study. Ann Surg 2003;238: 203–13.
24. Gunnarsson U, Karlbom U, Docker M, et al. Proctocolectomy and pelvic pouch—is a diverting stoma dangerous for the patient? Colorectal Dis 2004;6:23–27.
25. Hallbook O, Matthiessen P, Leinskold T, et al. Safety of the temporary loop ileostomy. Colorectal Dis 2002;4:361– 4.
26. Gastinger I, Marusch F, Steinert R, et al, Working Group 'Colon/Rectum Carcinoma'. Protective defunctioning stoma in low anterior resection for rectal carcinoma. Br J Surg 2005;92:1137– 42.
27. Guenaga KF, Lustosa SA, Saad SS, et al. Ileostomy or colostomy for temporary decompression of colorectal anastomosis. Cochrane Database Syst Rev 2007;1:CD004647.
28. Henneman MM, Schuijf JD, Pundziute G, et al. Noninvasive evaluation with multislice computed tomography in suspected acute coronary syndrome: plaque morphology on multislice computed tomography versus coronary calcium score. J Am Coll Cardiol 2008;52:216 –22.
29. Van Cutsem EJ, Oliveira J. Advanced colorectal cancer: ESMO clinical recommendations for diagnosis, treatment and follow-up. Ann Oncol 2008;19(Suppl 2):ii33– 4.
30. Van Cutsem EJ, Oliveira J. Colon cancer: ESMO clinical recommendationsfor diagnosis, adjuvant treatment and follow-up. Ann Oncol 2008;19(suppl 2):ii29 –30.
31. Glimelius B, Oliveira J. Rectal cancer: ESMO clinical recommendations for diagnosis, treatment and follow-up. Ann Oncol 2008;19(Suppl 2): ii31–2.

Chapter 10

Prevention of leakage by sealing colon anastomosis:

experimental study in a mouse model

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ABSTRACT

Introduction: In colorectal surgery, anastomotic leakage (AL) is the most important complication. Sealants, applied around the colon anastomosis, may help prevent AL by giving the anastomosis time to heal by mechanically supporting the anastomosis and preventing bacteria leaking into the peritoneal cavity. The aim of this study is to compare commercially available sealants on their efficacy of preventing leakage in a validated mouse model for AL.

Methods: Six sealants (Evicel, Omnex, VascuSeal, PleuraSeal, BioGlue, Colle Chirurgicale Cardial) were applied around an anastomosis constructed with five interrupted sutures in mice, and compared to a control group without sealant. Outcome measures were AL, anastomotic bursting pressure (ABP), and death.

Results: In the control group there was a 40% death rate with a 50% rate of AL. None of the sealants were able to diminish the rate of AL. Furthermore, use of the majority of sealants resulted in failure to thrive, increased rates of ileus, and higher mortality rates.

Conclusion: If sealing of a colorectal anastomosis could achieve a reduction of incidence of clinical AL this would be a promising tool of prevention of leakage in colorectal surgery. In this study we found no evidence that sealants reduce leakage rates in a mouse model for AL. However, the negative results of this study make us emphasize the need of systemic research, investigating histologic tissue reaction of the bowel to different sealants, the capacity of sealants to form a watertight barrier, their time of degradation, and finally their results in large animal models for AL.

INTRODUCTION

In the field of colorectal surgery, anastomotic leakage (AL) is the most important complication[1,2]. Incidence of AL has gone unchanged for many years, with high mortality (10 to 20%), and often need of second surgery, increased rate of subsequent complications, and prolonged hospitalization[3-6]. A major problem of AL is timing of the diagnosis due to lack of sensitive and specific diagnostic tools. This increases the morbidity of AL, due to the delay in diagnosis and subsequent therapy in symptomatic, ill patients[3,7,8]. In some patient categories alertness for AL is raised, thanks to known risk factors for AL such as low anastomosis[9-11], male gender[9-12], smoking[13,14] and corticosteroid use[15]. Despite higher vigilance in patients with risk factors for AL, and the use of deviating stomas in low anastomoses[16], a tool for primary prevention of leakage of a colorectal anastomosis is not yet clinically available.

Different approaches to AL prevention have been investigated, such as omental wrapping[17], staple line reinforcement[18], intraluminal devices[19], and sealing[20-23]. None have yet shown convincing results or achieved broad implementation. Sealants, applied around the colon anastomosis, may help prevent AL by giving the anastomosis time to heal by mechanically supporting the anastomosis and preventing bacteria leaking into the peritoneal cavity. Some sealants have been tested in an experimental setting, however with different models and outcome measures, making it difficult to evaluate their safety and benefits in colorectal surgery, and their use in a clinical setting remains rare.

Prevention of AL should be a priority in colorectal surgery considering the potential benefits in morbidity and mortality. Sealing with tissue adhesives may be an effective technique in this field. The aim of this study is to compare a number of available sealants on their efficacy of preventing leakage in a validated mouse model for colorectal AL.

METHODS

Leakage model

Within this research group an animal model was developed for AL. In this model, described by Komen et al.[24], approximately 40% of the animals will develop AL in seven days based on technical failure by creating an anastomosis with five full-thickness interrupted sutures, compared to a standard, non-leaky, anastomosis constructed with 12 full-thickness interrupted sutures. C57BL6-mice were used since they are considered to be more sensitive to infections than rats[25]. Outcome measures are AL, anastomotic bursting pressure (ABP), and death.

Anesthesia and operation

Before and after the intervention standard mouse chow and water were supplied ad libitum. The intervention consisted of anesthetizing the mouse (nose mask, FiO2 60%, isoflurane 2%), shaving,

and disinfecting the abdomen. The abdomen was entered through a 3-cm midline incision. On the ascending colon (one centimeter aborally to the cecum), the bowel was transected without damaging the vessels. An end-to-end anastomosis was constructed with 5 interrupted full-thickness sutures (Dafilon 8-0; B. Braun Melsungen, Germany). In the study groups a sealant was applied around the anastomosis (extraluminally), using the minimum quantity necessary to cover it circularly. The colon was repositioned and the abdominal wall and skin are both closed with a continuous suture (Safil 5-0 B. Braun). All intra-abdominal manipulations were done with microscope to ensure optimal vision. After the operation, the mice were examined daily for signs of AL, and their weight noted. When mice died before day 7, necropsy was performed aiming to determine the cause of death.

Measurements at day 7

After seven days the experiment was ended. The mice were anesthetized and re-laparotomy performed. The abdominal cavity was examined for abscesses or signs of fecal peritonitis, regarded as a manifestation of AL. Then the anastomotic bursting pressure (ABP) was determined: a canula was inserted proximal of the anastomotic site; the bowel was ligated distally to the anastomosis and proximally over the canula. Air was injected into the isolated anastomotic segment and the pressure monitored. The pressure at the point of rupture of the anastomosis represented ABP. After completing the ABP test the animal was sacrificed.

In case of death before day 7 a necropsy was performed. In case of unethical sickness relaparotomy was performed before day 7.

Study groups

Six different sealants were tested, from each of the existing sealant categories: fibrin sealants, cyanoacrylate sealants, polyethylene glycol sealants, and albumin-based sealants[26]. Their properties are described beneath. All groups contained eight mice, with a control group containing 16 mice. The Evicel experiment was performed separately, and contained 14 mice with 14 controls.

1. Evicel (Ethicon Inc, Johnson & Johnson, Sommervile, NJ) is a human fibrin sealant indicated as an adjunct to hemostasis. It initiates the last phase of physiological blood coagulation: thrombin activates the conversion of fibrinogen into fibrin. Factor XIIIa, which is activated form factor XIII by thrombin, crosslinks fibrin. Fibrin sealants are metabolized in the same way as endogenous fibrin, by fibrinolysis and phagocytosis.
2. Omnex (Ethicon, USA) is a (synthetic) cyanoacrylate sealants consisting of a blend of two monomers, 2-octyl cyanoacrylate and butyl lactoyl cyanoacrylate. The sealant polymerizes to form a flexible, strong film adherent to the tissue. Omnex biodegrades in approximately 36 months[27].

3. VascuSeal (Covidien, Mansfield, MA) is a 100% synthetic polyethylene glycol based hydrogel sealant. When mixed together, the precursors cross link to form the surgical sealant, visible through a blue coloration. The polymer hydrolyzes over seven days liberating polyethylene glycol molecules, which are cleared by the kidneys.
4. PleuraSeal (Covidien, USA) is also a synthetic, polyethylene glycol based hydrogel sealant. It is similar to VascuSeal, except for later absorption in approximately four to eight weeks. It has been withdrawn from commerce since this experiment, due to a higher than anticipated persistent air leak rate and inconsistent efficacy at interim results of a clinical study[27].
5. BioGlue (CryoLife Inc, Kennesaw, GA) is an albumin-based surgical adhesive. It is composed of purified bovine serum albumin (BSA) and glutaraldehyde. BioGlue makes a mechanical seal after crosslinking when being mixed, bonding tissues and sealing defects.
6. Colle chirurgicale Cardial (Cardial-Bard, St Etienne France) is an albumin-based sealant, consisting of resorcin-gelatin glue with formaldehyde-glutaraldehyde polymerizing agent. The polymer is applied on the surface to be glued; the polymerizing agent is added afterwards with a syringe.

RESULTS

Application was only possible when the polymerizing or crosslinking agent was mixed in the syringe or at the tip, making a semi-liquid gel-like substance when applied on the bowel, which stayed in place. The only sealant in which we could not achieve this was Cardial Colle Chirurgicale, being two completely fluid components that had to be applied on the bowel one after the other. This technique does not make a ‘sticky’ solution and therefore could not be applied at the correct position. For this reason the experiment with Cardial Colle Chirurgicale was aborted after surgery of four mice out of ethical considerations. The easiest application of sealants was through the help of an air-assisted applicator (Evicel, VascuSeal, PleuraSeal).

In the control group there was a 40% death rate with a 50% rate of AL (10% abscess, 40% peritonitis). In this group there was no observation of mechanical ileus, there was a weight gain after three days, and the mean ABP was 134.6 mmHg (SEM 12.45). None of the sealants were able to diminish the rate of AL. Evicel showed similar results as the control group: weight gain after 4 days, 43% AL, ABP was 118 mmHg (SEM 16.8). However 1 mouse developed ileus (7%). Omnex, VascuSeal and Cardial Colle Chirurgicale showed similar results considering the rate of AL and death (0% AL in the uncomplete Cardial-group with 4 mice), but significantly more ileus (figure 2) and higher mortality (figure 3). In two mice of the Cardial-group mascroscopic hepatic tissue damage was visible. PleuraSeal and BioGlue had a 100% death rate. During necropsy, in some mice origin of death could not be determined anymore.

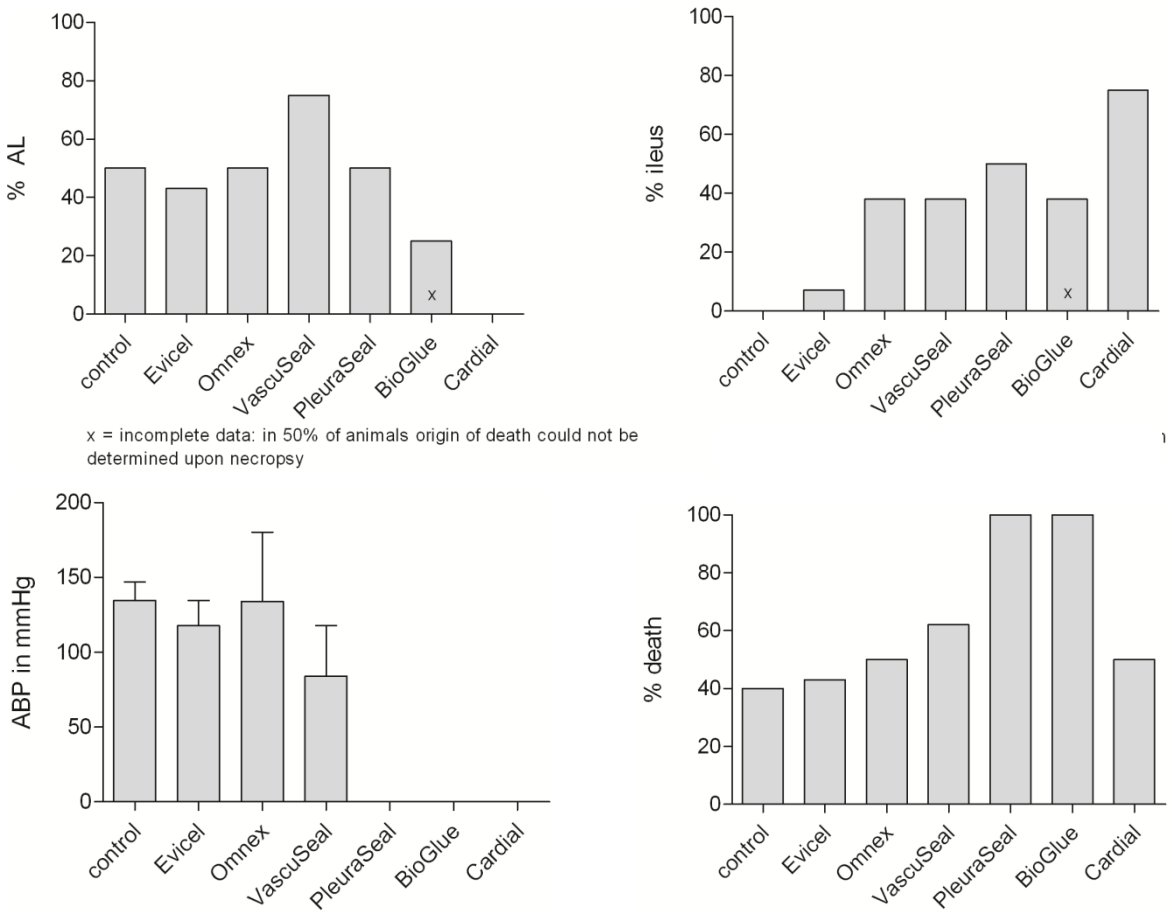

***Figure 1**. Percentage of AL, ileus, death, and anastomotic bursting pressure (ABP, in mmHg, no significant differences between groups (Mann Whitney U test)).*

Rates of AL, ileus, death, and results of ABP for each group are shown in figure 1 to 4. In conclusion, the sealants tested in this study seem to worsen morbidity and mortality in a mouse-model for colonic anastomotic leakage, with the exception of Evicel fibrin sealant which gave similar results as the control group.

DISCUSSION

Prevention of complications is something every surgeon aims for. Disinfection, preoperative prophylactic antibiotics, and choice of suture material aim to prevent wound infection; rapid mobilization and analgesia aim to prevent postoperative ileus; subcutaneous heparin aims to prevent thrombosis and emboli. Anastomotic leakage (AL) is the most feared after colorectal surgery due to its increased rate of subsequent complications, need of re-intervention, prolonged hospitalization, and high mortality (10-20%)[3-6]. A tool of prevention of leakage of bowel content into the abdominal

cavity, therefore significantly lowering the morbidity of AL, would be a reassurance for surgeon and patient, significantly lowering hospital costs and mortality.

Several techniques have been tested to date. Merad et al. performed a randomized controlled trial in 1998 on omentoplasty to prevent AL. No difference between groups was found[17]. Several intraluminal devices have been tested, such as the Coloshield or C-Seal (Polyganics, Groningen, the Netherlands)[28,29]. There are only few clinical studies with these devices, some with promising results; however they are small and have not brought the convincing results needed for broad implementation[19]. A temporary protective stoma has been shown to reduce clinical AL after low anterior resection[16]. However, a temporary protective stoma is also related to complications and associated morbidity, requires re-intervention for its closure, or is not closed at all due to complications and increased morbidity encountered during the postoperative phase[30-32]. Therefore it is only indicated in situations of high risk of AL.

Sealants, applied around the colon anastomosis, may help prevent AL by giving the anastomosis time to heal by mechanically supporting the anastomosis and preventing any apparent leaks. In other fields of surgery sealants have been tested clinically, such as for (cardio)vascular anastomoses with positive results[33-35], in pancreatic surgery without any benefit on pancreatic leaks[36,37], in thoracic surgery with inconsistent results regarding diminishing air leaks after pulmonary resection[38-42], and one randomized study in bariatric surgery where fibrin sealing of staple lines has not shown superiority[43].

The optimal sealant should break down so that no foreign body remains, not hindering the natural healing process. Four large categories of sealants exist[26]: fibrin sealants, cyanoacrylate sealants, polyethylene glycol sealants, and albumin-based sealants. The majority of clinical experience exists with fibrin sealants: they do not impair wound healing and degrade quickly, however do not have the properties for a watertight seal that can last for at least one week. Cyanoacrylate makes a stronger, watertight seal. However it takes a long time to degrade and most cyanoacrylate sealants are intended only for extracorporeal use in skin approximation. Polyethylene glycol is a non-toxic, biocompatible hydrogel that mechanically bonds to the tissue forming a flexible bond, staying intact from a few days to several weeks. Albumin-based sealants contain formaldehyde (toxic) or glutaraldehyde (non-toxic) polymerizing agents. They are very solid, but increase the risk of causing a strong inflammation reaction, especially when based on formaldehyde. They are mostly used in arterial wall repair.

In this experiment we used sealants out of each of these groups. There is no tissue adhesive that has been developed for sealing of gastro-intestinal anastomoses; the existing sealants we used are intended for vascular sealing, pleural sealing, or arterial wall repair. We believe surgical sealants should be tested in a situation where the risk of an inadequate anastomosis exists. The perfect

anastomosis that will heal without (micro)leaks is not a problem in colorectal surgery, and does not need sealing. Therefore, the tested hypothesis is that if a (micro)defect exists or occurs within the first days, the healing-process can still continue with help of the watertight seal around it. In the model we used we know approximately 60-70% of anastomoses will heal properly, leaving 30-40% of the anastomoses with abscesses or leakage within 7 days. In our opinion this is a correct model for sealant testing: sealants should not make any difference in the anastomoses that heal properly (or potentially make them a bit stronger). However they should prove their use in insufficient anastomoses, for this is the indication for which they are studied.

The fibrin glue used in this study indeed showed no complications related to toxicity, however it did not diminish the risk of AL. Omnex (cyanoacrylate) showed similar incidences of AL and mortality as the control group; however there was also a 40% ileus-rate, showing the glue generates a reaction at the site of the bowel resulting in obstruction. VascuSeal (polyethylene glycol, absorption within 1 week) showed an even higher risk for AL, and also a 40% rate of ileus. PleuraSeal (polyethylene glycol, absorption 4-8 weeks, withdrawn from market) resulted in a 100% death rate, with at least 40% AL and 40% ileus, considering the difficulty of determining cause of death in necropsies. This also applied for BioGlue (albumin-based), showing both AL and ileus, but most of all a 100% death rate. Cardial Colle chirurgicale (albumin-based) is composed of the polymerizing agent formaldehyde. This liquid must be dripped on the polymer without applying it on living tissue due to its reported toxicity[44]. Two or three drops being sufficient for one cm^2 [44], one can imagine that its application is almost impossible in a mouse model. Considering this the experiment with Cardial Colle Chirurgicale was ended after difficult application in the first four mice, out of ethical considerations. Liver damage was seen in two out or four mice on postoperative day 7, and an 80% ileus rate.

In conclusion, the results for each of the included sealants used in this experiment are grim.

Until now, most experiments on the sealing of colon anastomosis have large variations in methodology and outcome measures. Some studies have used a normally healing anastomosis, others a model with insufficient anastomosis (less sutures, chemo/radiotherapy, ischemia, peritonitis etc). Majority of studies with a fibrin sealant on a sufficient anastomosis found a higher ABP in the fibrin sealant group[45-49]. In studies with insufficient anastomoses and fibrin sealant, three studies from Kanellos et al. found less AL and higher ABP with a fibrin sealant[50-52], however three studies by van der Ham found no AL in all groups, and no improvement of ABP after fibrin sealing[49,53,54]. One study with a cyanoacrylate sealing on a sufficient anastomosis found no AL, but more strictures, less ABP, and more inflammation in the cyanoacrylate group[55]. Three studies with cyanoacrylate and insufficient anastomoses found no differences in AL, ABP was inferior or equal, and there was more inflammation in the cyanoacrylate sealant group[22,55,56]. One study with a polyethylene glycol sealant

and one study with an albumin-based sealant on a sufficient anastomosis found no differences in AL or ABP[21,57].

Almost all studies mentioned above are rat studies. Pommergaard et al. showed, in a recent review on experimental anastomotic leakage models, that mouse or pig models seem superior to the rat, since the rat seems less sensitive to infection, therefore creating a leaking anastomosis with clinical consequences is difficult to achieve in the rat[25]. However, the use of sealants in mice with devices that are made for humans is also considered not ideal. Application and amount of sealant applied is difficult; therefore rat or pig studies may be superior for this type of research.

This study shows that sealants are unsuccessful in lowering the incidence of colon AL in mice, and that the majority of sealants increase morbidity and mortality, with progressive weight loss of mice and ileus. The exact bowel tissue reaction to different sealants should be investigated with histologic evaluation, to determine which sealants do not impair wound healing and do not cause strictures, thus identifying potential sealants for colorectal surgery for additional research.

In conclusion, if sealing of a colorectal anastomosis could achieve a reduction of incidence of clinical AL this would be a tremendous tool of prevention of leakage in colorectal surgery. In this study we found no evidence that sealants reduce leakage rates in a mouse model for colon AL. However, the negative results of this study make us emphasize the need of systemic research, investigating histologic tissue reaction of the bowel to different sealants, the capacity of sealants to form a watertight barrier, their time of degradation, and finally their results in large animal models for AL.

REFERENCES

1. Alves A, Panis Y, Pocard M, et al. Management of anastomotic leakage after nondiverted large bowel resection. J Am Coll Surg 1999;189:554-9.
2. Buchs NC, Gervaz P, Secic M, et al. Incidence, consequences, and risk factors for anastomotic dehiscence after colorectal surgery: a prospective monocentric study. Int J Colorectal Dis 2008;23:265-70.
3. Alberts JC, Parvaiz A, Moran BJ. Predicting risk and diminishing the consequences of anastomotic dehiscence following rectal resection. Colorectal Dis 2003;5:478-82.
4. Branagan G, Finnis D. Prognosis after anastomotic leakage in colorectal surgery. Dis Colon Rectum 2005;48:1021-6.
5. Fielding LP, Stewart-Brown S, Blesovsky L, et al. Anastomotic integrity after operations for large-bowel cancer: a multicentre study. Br Med J 1980;281:411-4.
6. Fraccalvieri D, Biondo S, Saez J, et al. Management of colorectal anastomotic leakage: differences between salvage and anastomotic takedown. Am J Surg 2011.
7. Bellows CF, Webber LS, Albo D, et al. Early predictors of anastomotic leaks after colectomy. Tech Coloproctol 2009;13:41-7.
8. Hyman N, Manchester TL, Osler T, et al. Anastomotic leaks after intestinal anastomosis: it's later than you think. Ann Surg 2007;245:254-8.
9. Law WL, Chu KW. Anterior resection for rectal cancer with mesorectal excision: a prospective evaluation of 622 patients. Ann Surg 2004;240:260-8.
10. Matthiessen P, Hallbook O, Andersson M, et al. Risk factors for anastomotic leakage after anterior resection of the rectum. Colorectal Dis 2004;6:462-9.
11. Rullier E, Laurent C, Garrelon JL, et al. Risk factors for anastomotic leakage after resection of rectal cancer. Br J Surg 1998;85:355-8.
12. Eriksen MT, Wibe A, Norstein J, et al. Anastomotic leakage following routine mesorectal excision for rectal cancer in a national cohort of patients. Colorectal Dis 2005;7:51-7.
13. Bertelsen CA, Andreasen AH, Jorgensen T, et al. Anastomotic leakage after anterior resection for rectal cancer: risk factors. Colorectal Dis 2010;12:37-43.
14. Sorensen LT, Jorgensen T, Kirkeby LT, et al. Smoking and alcohol abuse are major risk factors for anastomotic leakage in colorectal surgery. Br J Surg 1999;86:927-31.
15. Slieker JC, Komen NA, Mannaerts GH, et al. Long-term and Perioperative Corticosteroids in Anastomotic Leakage: A Prospective Study of 259 Left-Sided Colorectal Anastomoses. Arch Surg 2012.
16. Montedori A, Cirocchi R, Farinella E, et al. Covering ileo- or colostomy in anterior resection for rectal carcinoma. Cochrane Database Syst Rev 2010:CD006878.
17. Merad F, Hay JM, Fingerhut A, et al. Omentoplasty in the prevention of anastomotic leakage after colonic or rectal resection: a prospective randomized study in 712 patients. French Associations for Surgical Research. Ann Surg 1998;227:179-86.
18. Cheragwandi A, Nieuwenhuis DH, Gagner M, et al. An update of available innovative staple line reinforcement materials in colorectal surgery. Surg Technol Int 2008;17:131-7.
19. Morks AN, Havenga K, Ploeg RJ. Can intraluminal devices prevent or reduce colorectal anastomotic leakage: a review. World J Gastroenterol 2011;17:4461-9.
20. Bae KB, Kim SH, Jung SJ, et al. Cyanoacrylate for colonic anastomosis; is it safe? Int J Colorectal Dis 2010;25:601-6.
21. Giuratrabocchetta S, Rinaldi M, Cuccia F, et al. Protection of intestinal anastomosis with biological glues: an experimental randomized controlled trial. Tech Coloproctol 2011;15:153-8.
22. Nursal TZ, Anarat R, Bircan S, et al. The effect of tissue adhesive, octyl-cyanoacrylate, on the healing of experimental high-risk and normal colonic anastomoses. Am J Surg 2004;187:28-32.
23. van der Ham AC, Kort WJ, Weijma IM, et al. Effect of fibrin sealant on the healing colonic anastomosis in the rat. Br J Surg 1991;78:49-53.

24. Komen N, van der Wal HC, Ditzel M, et al. Colorectal anastomotic leakage: a new experimental model. J Surg Res 2009;155:7-12.
25. Pommergaard HC, Rosenberg J, Schumacher-Petersen C, et al. Choosing the best animal species to mimic clinical colon anastomotic leakage in humans: a qualitative systematic review. Eur Surg Res 2011;47:173-81.
26. Reece TB, Maxey TS, Kron IL. A prospectus on tissue adhesives. Am J Surg 2001;182:40S-4S.
27. . (Accessed at http://www.covidien.com/recall/pages.aspx)
28. Kolkert JL, Havenga K, ten Cate Hoedemaker HO, et al. Protection of stapled colorectal anastomoses with a biodegradable device: the C-Seal feasibility study. Am J Surg 2011;201:754-8.
29. Ravo B. Intracolonic bypass procedure. Dis Colon Rectum 1997;40:628-9.
30. Chow A, Tilney HS, Paraskeva P, et al. The morbidity surrounding reversal of defunctioning ileostomies: a systematic review of 48 studies including 6,107 cases. Int J Colorectal Dis 2009;24:711-23.
31. David GG, Slavin JP, Willmott S, et al. Loop ileostomy following anterior resection: is it really temporary? Colorectal Dis 2010;12:428-32.
32. den Dulk M, Smit M, Peeters KC, 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;8:297-303.
33. DeAnda A, Jr., Elefteriades JA, Hasaniya NW, et al. Improving outcomes through the use of surgical sealants for anastomotic sealing during cardiovascular surgery. J Card Surg 2009;24:325-33.
34. Schenk WG, 3rd, Burks SG, Gagne PJ, et al. Fibrin sealant improves hemostasis in peripheral vascular surgery: a randomized prospective trial. Ann Surg 2003;237:871-6; discussion 6.
35. Shireman PK, Greisler HP. Fibrin sealant in vascular surgery: a review. J Long Term Eff Med Implants 1998;8:117-32.
36. Fingerhut A, Veyrie N, Ata T, et al. Use of sealants in pancreatic surgery: critical appraisal of the literature. Dig Surg 2009;26:7-14.
37. Schulick RD, Yoshimura K. Stents, glue, etc.: is anything proven to help prevent pancreatic leaks/fistulae? J Gastrointest Surg 2009;13:1184-6.
38. D'Andrilli A, Andreetti C, Ibrahim M, et al. A prospective randomized study to assess the efficacy of a surgical sealant to treat air leaks in lung surgery. Eur J Cardiothorac Surg 2009;35:817-20; discussion 20-1.
39. De Leyn P, Muller MR, Oosterhuis JW, et al. Prospective European multicenter randomized trial of PleuraSeal for control of air leaks after elective pulmonary resection. J Thorac Cardiovasc Surg 2011;141:881-7.
40. Gonfiotti A, Santini PF, Jaus M, et al. Safety and effectiveness of a new fibrin pleural air leak sealant: a multicenter, controlled, prospective, parallel-group, randomized clinical trial. Ann Thorac Surg 2011;92:1217-24; discussion 24-5.
41. Malapert G, Hanna HA, Pages PB, et al. Surgical sealant for the prevention of prolonged air leak after lung resection: meta-analysis. Ann Thorac Surg 2010;90:1779-85.
42. Tan C, Utley M, Paschalides C, et al. A prospective randomized controlled study to assess the effectiveness of CoSeal(R) to seal air leaks in lung surgery. Eur J Cardiothorac Surg 2011;40:304-8.
43. Silecchia G, Boru CE, Mouiel J, et al. The use of fibrin sealant to prevent major complications following laparoscopic gastric bypass: results of a multicenter, randomized trial. Surg Endosc 2008;22:2492-7.
44. Bachet J. Dissections aigues de l'aorte: traitement. EM-Consulte 2004;1:324-64.
45. Akgun A, Kuru S, Uraldi C, et al. Early effects of fibrin sealant on colonic anastomosis in rats: an experimental and case-control study. Tech Coloproctol 2006;10:208-14.
46. Girgin S, Ozturk H, Gedik E, et al. Effect of a 50-Hz Sinusoidal Electromagnetic Field on the Integrity of Experimental Colonic Anastomoses Covered with Fibrin Glue. Adv Clin Exp Med 2009;18:13-8.
47. Kanellos I, Mantzoros I, Goulimaris I, et al. Effects of the use of fibrin glue around the colonic anastomosis of the rat. Tech Coloproctol 2003;7:82-4.
48. Subhas G, Bhullar JS, Cook J, et al. Topical gentamicin does not provide any additional anastomotic strength when combined with fibrin glue. Am J Surg 2011;201:339-43.

49. van der Ham AC, Kort WJ, Weijma IM, et al. Transient protection of incomplete colonic anastomoses with fibrin sealant: an experimental study in the rat. J Surg Res 1993;55:256-60.
50. Kanellos D, Blouhos K, Pramateftakis MG, et al. Effect of 5-fluorouracil plus interferon on the integrity of colonic anastomoses covering with fibrin glue. World J Surg 2007;31:186-91.
51. Kanellos I, Christoforidis E, Kanellos D, et al. The healing of colon anastomosis covered with fibrin glue after early postoperative intraperitoneal chemotherapy. Tech Coloproctol 2006;10:115-20.
52. Kanellos I, Mantzoros I, Demetriades H, et al. Healing of colon anastomoses covered with fibrin glue after immediate postoperative intraperitoneal administration of 5-fluorouracil. Dis Colon Rectum 2004;47:510-5.
53. van der Ham AC, Kort WJ, Weijma IM, et al. Healing of ischemic colonic anastomosis: fibrin sealant does not improve wound healing. Dis Colon Rectum 1992;35:884-91.
54. van der Ham AC, Kort WJ, Weijma IM, et al. Effect of fibrin sealant on the integrity of colonic anastomoses in rats with faecal peritonitis. Eur J Surg 1993;159:425-32.
55. Irkorucu O, Ucan BH, Cakmak GK, et al. Effect of 2-octyl-cyanoacrylate on ischemic anastomosis of the left colon. J Invest Surg 2009;22:188-94.
56. Kayaoglu HA, Ersoy OF, Ozkan N, et al. Effect of n-butyl-2-cyanoacrylate on high-risk colonic anastomoses. Kaohsiung J Med Sci 2009;25:177-83.
57. Yol S, Tekin A, Yilmaz H, et al. Effects of platelet rich plasma on colonic anastomosis. J Surg Res 2008;146:190-4.

Part III

Optimizing colorectal laparoscopy

Chapter 11

Training in laparoscopic colorectal surgery: a new educational model using specially embalmed human anatomical specimen

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ABSTRACT

Introduction: With an increasing percentage of colorectal resections performed through laparoscopy nowadays, more emphasis has come on training 'before the job' of operative skills including the comprehension of specific laparoscopic surgical anatomy. As integration of technical skills with correct interpretation of the anatomical image must be incorporated in laparoscopic training, a human specimen training model with special attention for surgical anatomy was developed.

Methods: The new embalming method Anubifix™ combines long-term high-quality embalming of human bodies with almost normal flexibility and plasticity, that can be kept operational as long as conventionally embalmed human specimens. A colorectal training model was created in a specimen in which anatomical landmarks of colorectal anatomy were permanently coloured to explore laparoscopic colorectal anatomy in a skills-training setting. Airtight closure of the abdominal wall permits the creation of a pneumoperitoneum. Residents were asked to test the model by mobilizing small and large bowel, and expose the central vessels and ureters. Afterwards they were asked to fill out a questionnaire with eight questions regarding the model.

Results: Eleven surgical residents in their first and second year of training participated. The questionnaire showed a majority of residents considered the model to be representative for the real situation and superior to animal models or virtual reality simulators, improving knowledge of three-dimensional anatomy and laparoscopic skills.

Conclusion: The new training model for laparoscopic colorectal surgery proved to be a high quality tool, concentrating on laparoscopic colorectal anatomy in a skills-training setting. We believe it may be a valuable adjunct to residency training programs, based on the principle of 'training before the job'.

INTRODUCTION

An increasing percentage of colorectal resections are performed through laparoscopy nowadays[1,2]. Therefore, more emphasis has come on the achievement of the necessary laparoscopic skills during residency, reducing iatrogenic complications. Recognition of complex surgical anatomy, specific cognitive and motor skills, hand-eye coordination, adjustment to the loss of a degree of tactile feedback, and image interpretation, are the principal skills to be acquired by the novice laparoscopic surgeon. Many different training models for laparoscopy have been studied, varying from box and virtual reality simulators, animal models, and human bodies donated for science. These different training models are all individually useful in training specific aspects of laparoscopy. Box trainers or virtual reality simulators are well suited for training technical skills and hand-eye coordination but lack training of tissue handling, surgical field interpretation and anatomical recognition. Animal models are superior for the latter, however they have strong ethical and financial restrictions, and the anatomical situation differs. The abdominal wall of conventionally embalmed human anatomical specimen is too rigid to create a pneumoperitoneum, and fresh-frozen specimen or specimen embalmed via the Thiel method cannot be kept operational for a long period making them less suitable for creating training models (fresh-frozen for 1-2 days; Thiel for 3-6 months).

In addition to training surgical skills, the training of surgical anatomy has also been highlighted the past years. Problem-based surgical anatomy courses have been developed for residents[3], in the Netherlands even resulting in a national institute for the development and teaching surgical anatomy: the Lowlands Institute for Surgical Anatomy (LISA).

During colorectal laparoscopy, combining cognitive and motor skills with anatomical recognition is challenging for the resident, but nonetheless essential for a successful procedure. We aimed to develop a training model for laparoscopic colorectal surgery using human bodies donated for science treated with a new embalming method keeping tissues flexible and soft. In such model, education of laparoscopic cognitive and motor skills can be combined with laparoscopic surgical anatomy.

METHODS

Model:

An anatomic specimen embalmed by means of the Anubifix™ method was used. This embalming technique is based on a new pre-rinsing method combined with a normal 4% formaldehyde fixation solution. In contrast to conventional embalming methods, Anubifix™ embalming does hardly result in a decrease of flexibility or plasticity. Furthermore this result is accomplished without impairing the quality and duration of conservation. Anubifix™ embalming results in a preserved range of motion of joints and flexibility of the abdominal wall combined with ‘tissue tactility’ comparable to fresh frozen tissues, this all in contrast to conventional embalming methods.

After the embalming phase a midline laparotomy of 20 centimetres was performed. Specific aspects of colorectal anatomy were dissected and marked (aorta and iliac arteries (dark red), superior mesenteric artery/vein and its branches (red/blue), inferior mesenteric artery/vein and its branches (red/blue), gonadal arteries (purple), ureters(yellow)). Colouring of vessels and ureters was performed circumferentially with a specially developed paint: formaldehyde proof paint (FPP™). After dissection and colouring, the abdominal muscle wall was separated from on-laying fat and skin, and closed with running sutures. A rectangular sheet of synthetic butyl rubber measuring 26 x 6cm with a circular hole at the level of the umbilicus was sutured on top of the sutured muscle wall, analogous to an on-lay mesh for incisional hernia, after which the skin was closed with running sutures. The use of a butyl rubber sheet results in airtight closure of the abdominal wall permitting the creation of a pneumoperitoneum despite the prior abdominal opening. A 10mm trocar was placed at the umbilicus through which a 30º scope was placed. A standard set of laparoscopic instruments was used. Four 5mm trocars were placed in the right and left upper quadrants. Pneumoperitoneum was achieved with a continuous flow of CO_2 with the pressure set between 12-15 mmHg, i.e. comparable to the *in vivo* situation.

Training course:

Surgical residents following the mandatory national LISA course module: 'Surgical Anatomy of the Colon and Rectum' were asked to participate. The LISA course presented here was given in the SkillsLab of the Erasmus University Medical Center, Rotterdam, a clinical training center including six modern equipped laparoscopic working stations, a microsurgical lab, and three fully equipped dissection rooms.

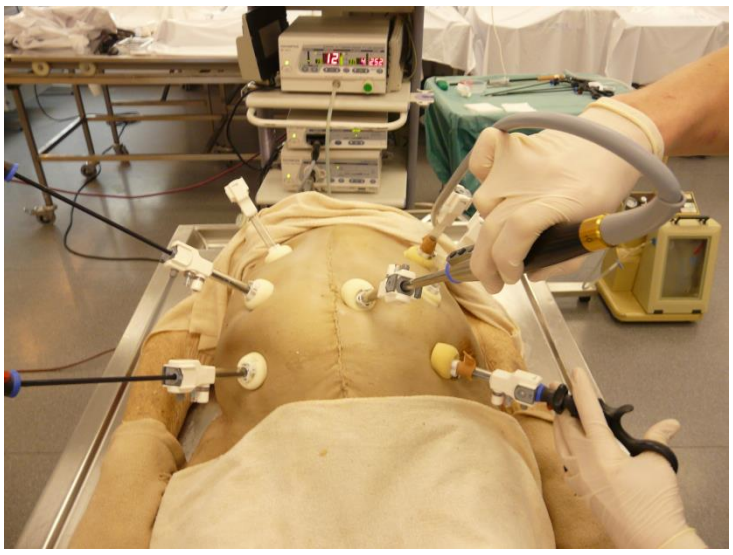

Figure 2. *Anubifix™ model laparoscopic colorectal surgery*

In the present study, each resident alternated in the role of operating surgeon and first assistant using the model as described above. They were asked to mobilize the small bowel to the left or to the right depending on what side of the colorectal anatomy was to be exposed. Next, the left- and right-sided anatomy was explored, defining segmental colonic anatomy and exposing central vessels and ureters, helped by the colouring and supervised by a faculty member (surgeon as well as anatomist).

Outcome measures:

Following the course, a standardized, anonymous questionnaire was given to analyze the relevance of the course by means of eight questions represented in figure 1.

Table 1. *Questionnaire following the course. Data were collected using the Likert scale (1 = strongly disagree; 2 = disagree; 3 = neither agree nor disagree; 4 = agree; 5 = strongly agree).*

- The tissue quality is representative for the real situation
- The colour quality is representative for the real situation
- The operative tactility is representative for the real situation
- This model helps me improve my knowledge of anatomy for laparoscopic colorectal resection
- This model helps me improve my laparoscopic skills
- This laparoscopic model is superior to an animal model
- This laparoscopic model is superior to virtual reality simulators
- The course on laparoscopic surgical anatomy was useful
- I would like to see this laparoscopic model implemented in the LISA surgical anatomy course

RESULTS

Images are illustrating the result of the model: the model at the outside (figure 2), the right-sided anatomy (figures 3 and 4), and the left-sided anatomy (figures 5 and 6).

Participants were asked to answer eight questions regarding their perceptions of this model for training colorectal laparoscopy focussing on: the opinion of the participants on the quality of the tissue and the operative tactility, the improvement of anatomical knowledge and laparoscopic skills, the comparison to animal models and virtual reality models, and on the utility of implementing this model in a course for surgical anatomy (figure 1). Eleven surgical residents participated and filled in the questionnaire. Residents had not yet performed laparoscopic colectomies themselves, however all residents had box training and virtual reality experience.

The results, as can be found in figure 7, show that the majority of residents believed that (1) the quality of the tissue is representative for the real situation, (2) the model is superior to animal models of virtual reality simulators, and (3) that the model helps in improving knowledge of three-dimensional anatomy and laparoscopic skills.

Figure 3. *Cecum with ileocolic artery (red), ileocolic vein (blue), right ureter (yellow), right gonadal artery (purple)*

Figure 4. *Hepatic flexure with medial colic artery (red), and superior mesenteric vein (blue)*

Figure 5. *Aorta (dark red), inferior mesenteric artery with ascending and descending branch (red), inferior mesenteric vein (blue), left ureter (yellow), and left gonadal artery (purple)*

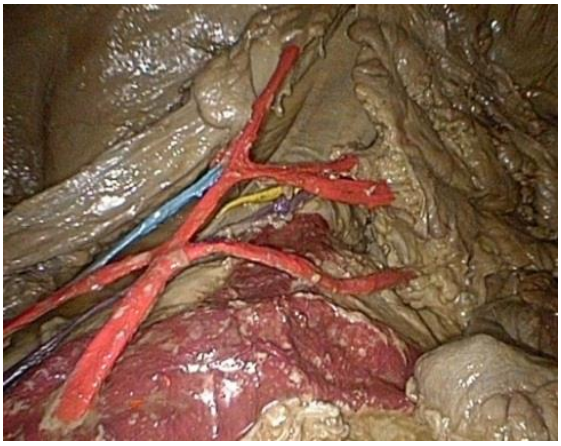

Figure 6. *Aorta and iliac arteries (dark red), inferior mesenteric artery with descending branch, sigmoid arteries, and superior rectal artery (red), inferior mesenteric vein (blue), left ureter (yellow), left gonadal artery (purple)*

DISCUSSION

The initial concerns on laparoscopic colorectal surgery regarding safety, degree of oncologic resection, and tumour recurrence, are shown to be unfounded[4-6], and nowadays an increasing percentage of all colorectal resections is performed through laparoscopic surgery[1,2]. Laparoscopic colorectal resection has become a successful common surgical procedure as it has many advantages over conventional surgery, including less postoperative pain, earlier recovery of bowel function, less blood loss, and shorter hospital stay[5,7-9].

However, it remains a technically challenging procedure, and a more and more prominent role has been ascribed to training 'before the job'. The recognition of the relatively long and technically demanding learning curve has led to, for example, the NICE guidelines recommending that laparoscopic surgery should only be performed by surgeons who have completed appropriate training and who perform this procedure often enough to maintain competence[10]. In a study performed by Hwang et al. difficulties in laparoscopic performance were shown during the early period of training; an average of approximately twenty seconds and two to three errors were required for one grasp[11]. Such results emphasize the need for training residents in a safe tension- and blame free environment outside the operating room.

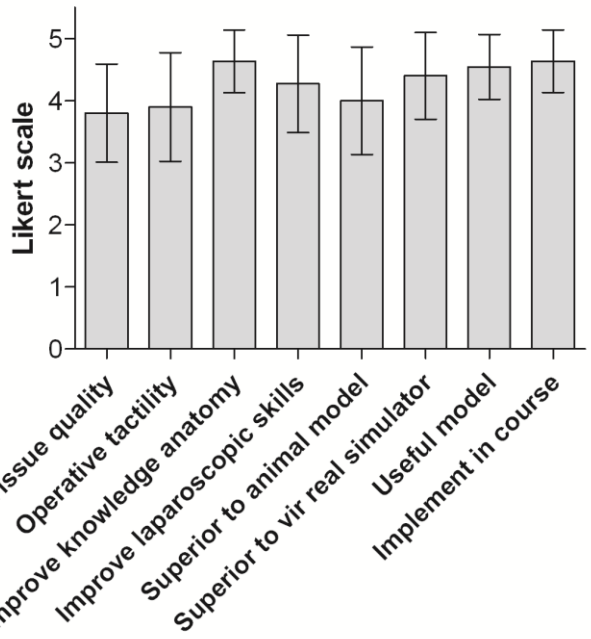

Figure 7. *Results of the questionnaire of participants having tested the Anubifix™ model on laparoscopic colorectal surgery (mean ± standard deviation)*

Currently, different devices and models exist for training purposes, being (1) box-trainers and virtual reality simulators, (2) animal models, and (3) models using embalmed anatomical specimens. The first, box-trainers and virtual reality simulators, are particularly useful for learning basic optical and manipulative skills. Studies have shown that simulation-based training can be successful in achieving transfer of skills from the training institute to the operative setting[12]. However, not all studies have found a universal improvement for the trained groups; some outcome measures were found to be unchanged after training with a box-trainer or virtual reality simulator. A study by Kimura et al. showed that training with a virtual reality simulator or a box-training was not immediately helpful for shortening the operating time of laparoscopic cholecystectomy[13]; another study indicated that simulator training did not provide skills for the operating room[14]. A possible explanation is that

although box- or virtual reality simulators largely focus on technical skills, the acquisition of technical skills is only one aspect of laparoscopic training. Laparoscopic surgery not only requires optical and manipulative skills, but also additional cognitive and motor skills with the requirement of long periods of continuous concentration, anatomical image interpretation and adjustment to the loss of a degree of tactile feedback and altered anatomical view[15]. These difficult laparoscopic requirements need to be practised and automated in order to perform a successful procedure.

The second, animal models, offer the possibility to combine technical skills with image interpretation and adjustment to the loss of a degree of tactile feedback under physiologic conditions. However, animal models have important disadvantages: different anatomy, high costs, and furthermore in a number of countries there is active ethical opposition combined with prohibitive legislation against animal models.

The third, models using embalmed anatomic specimens, have the advantage of combining human anatomy, including the experience of normal dimensions, (almost) normal tissue handling and the experience of normal instruments of choice. The absence of active bleeding can be an issue, although the importance of active bleeding in a training model can be questioned. Until now the most important disadvantage of anatomic specimen models was the conventional embalming method resulting in stiffness and rigidity, hence making it impossible to create a pneumoperitoneum necessary to create an appropriate working space. This problem can be solved by using fresh cadavers or Thiel-embalmed cadavers, but those can only be used for a short period of time (one day; 3-6 months). The new embalming method Anubifix™, invented in the Anatomy department of the Erasmus University Medical Center, offers a series of possibilities as it combines long-term high-quality embalming with normal flexibility and plasticity. Because Anubifix™ specimen can be kept operational as long as conventional specimens, unique training models can be made that can be used for many years. In this way the time invested in making such models is returned in having a useful model for training surgical procedures for years, particularly in comparison to Thiel-embalmed human bodies.

Anatomy courses during residency are gaining more importance, as it is crucial for young residents to have an excellent knowledge of 3D anatomy of the surgical field. Therefore short courses at the dissection room during the first years of residency are highly valuable to make teaching afterwards at the operating room most efficient possible. Since a large part of interventions are performed by laparoscopy nowadays, we realized that open anatomy teaching in human anatomical specimen is clearly no longer sufficient. This is the primary goal of this model: integration of technical skills with correct interpretation of the anatomical image This is lacking in box-trainers or virtual reality simulators, while recognition of anatomical landmarks is difficult but essential in laparoscopy. In the training-model described here, anatomical landmarks were permanently coloured, with a specially

developed formaldehyde proof paint, to offer the possibility to explore laparoscopic colorectal anatomy in a skills-training setting. We asked eleven residents in their first years of residency to test the model by exploring anatomy, defining segmental colonic anatomy and exposing the central vessels and ureters. Results show that the majority of residents found the quality of the tissue representative for the real situation, the model superior to animal models of virtual reality simulators, and useful for improving knowledge of anatomy and laparoscopic skills.

Chang et al. showed the majority of residents do not choose to practice in a training-lab although their hospital offers such facility, due to lack of time[16]. We chose to incorporate this model in the Lowlands Institute for Surgical Anatomy (LISA) - course. LISA is a Dutch national institute concentrating on surgical anatomy courses for residents. In this institute, all eight Dutch University Medical Centers cooperate in postgraduate training and education in surgical anatomy. In 2004 the Dutch Association of Surgery (NVvH), made the LISA courses obligatory for all surgical residents in the Netherlands. The LISA course is given several times a year to residents related to their different phases of training in general surgery to enhance their anatomic knowledge, aiming for applied surgical anatomy education. The involvement of surgeon and anatomist is considered an essential element of its success.

Traditionally surgical skills training took place in the operating room; nowadays complex combination of laparoscopic cognitive and motor skills, altered anatomical image interpretation, and adjustment to the loss of a degree of tactile feedback calls for training-models. Until now the importance of training 'before the job' of laparoscopic anatomical skills has always been underestimated and this competence had to be acquired on the patient, which is undesirable and responsible for exaggerated long learning curves. We have presented a new training method developed on embalmed human specimen through which is it possible to practice laparoscopic skills as well as laparoscopic surgical anatomy for laparoscopic colorectal surgery. We propose a standardized integration of laparoscopic Anubifix™ embalmed human-models in the mandatory surgical anatomy courses in the Netherlands.

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REFERENCES

1. Buchanan GN, Malik A, Parvaiz A, et al. Laparoscopic resection for colorectal cancer. Br J Surg 2008;95:893-902.
2. Lim SB, Choi HS, Jeong SY, et al. Feasibility of laparoscopic techniques as the surgical approach of choice for primary colorectal cancer: an analysis of 570 consecutive cases. Surg Endosc 2008;22:2588-95.
3. Mattingly MW, Dean RE, Carrow R, et al. Problem-based anatomy for surgical residents. Curr Surg 2000;57:377-80.
4. Guillou PJ, Quirke P, Thorpe H, et al. Short-term endpoints of conventional versus laparoscopic-assisted surgery in patients with colorectal cancer (MRC CLASICC trial): multicentre, randomised controlled trial. Lancet 2005;365:1718-26.
5. Clinical Outcomes of Surgical Therapy Study G. A comparison of laparoscopically assisted and open colectomy for colon cancer. N Engl J Med 2004;350:2050-9.
6. Lacy AM, Garcia-Valdecasas JC, Delgado S, et al. Laparoscopy-assisted colectomy versus open colectomy for treatment of non-metastatic colon cancer: a randomised trial. Lancet 2002;359:2224-9.
7. Breukink S, Pierie J, Wiggers T. Laparoscopic versus open total mesorectal excision for rectal cancer. Cochrane Database Syst Rev 2006:CD005200.
8. Reza MM, Blasco JA, Andradas E, et al. Systematic review of laparoscopic versus open surgery for colorectal cancer. Br J Surg 2006;93:921-8.
9. Veldkamp R, Kuhry E, Hop WC, et al. Laparoscopic surgery versus open surgery for colon cancer: short-term outcomes of a randomised trial. Lancet Oncol 2005;6:477-84.
10. (NICE) NIfHaCE. Laparoscopic Surgery for Colorectal Cancer. Technology Appraisal Guidence 105 2006;August.
11. Hwang MR, Seo GJ, Yoo SB, et al. Learning curve of assistants in laparoscopic colorectal surgery: overcoming mirror imaging. Surg Endosc 2010.
12. Sturm LP, Windsor JA, Cosman PH, et al. A systematic review of skills transfer after surgical simulation training. Ann Surg 2008;248:166-79.
13. Kimura T, Kawabe A, Suzuki K, et al. Usefulness of a virtual reality simulator or training box for endoscopic surgery training. Surg Endosc 2006;20:656-9.
14. Ahlberg G, Heikkinen T, Iselius L, et al. Does training in a virtual reality simulator improve surgical performance? Surg Endosc 2002;16:126-9.
15. Way LW, Stewart L, Gantert W, et al. Causes and prevention of laparoscopic bile duct injuries: analysis of 252 cases from a human factors and cognitive psychology perspective. Ann Surg 2003;237:460-9.
16. Chang L, Petros J, Hess DT, et al. Integrating simulation into a surgical residency program: is voluntary participation effective? Surg Endosc 2007;21:418-21.

Chapter 12

Bowel preparation prior to laparoscopic colorectal resection:

what is the current practice?

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ABSTRACT

Background: Much has been published on the role of mechanical bowel preparation (MBP) in open colorectal resection; however current literature shows little evidence on the use of MBP prior to laparoscopic colorectal resections. In contrast to open procedures, MBP could influence the diameter of the bowel and thus the exposure of the surgical field in laparoscopy. This study aimed to assess the current practice of Dutch laparoscopic surgeons regarding MBP prior to colorectal resections.

Methods: In January 2010 members of the Dutch Association for Endoscopic Surgery were invited to fill out an online questionnaire investigating whether MBP is prescribed prior to laparoscopic colorectal surgery, and which considerations are taken into account when choosing or omitting MBP.

Results: The 82 (49%) returned questionnaires showed that 20% of respondents prescribe MBP prior to colonic resections, while 63% prescribe MBP prior to rectal resections. The most common reasons for giving MBP were the construction of a protective ileostoma (22%), improvement of the surgical field exposure (16%), and 'other reasons' specified by free text (21%). The three most common reasons for conversion were inadequate surgical field exposure (88%), locally advanced tumour (68%), and adhesions (29%). Concerning the question which stages of the operation are influenced by MBP 29% of respondents believed the diameter of the small bowel was influenced by MBP, 29% indicated that the exposure of the surgical field was influenced by MBP, and 52% did not believe that any of the stages of the operation were influenced by MBP.

Conclusion: The results of this questionnaire indicate that the implementation of MBP in laparoscopic colorectal surgery is based on individual preferences in the Netherlands. This emphasizes the need of new studies investigating the role of MBP on surgical field exposure in colorectal laparoscopic surgery.

INTRODUCTION

The introduction of laparoscopic procedures has led to an important progress in colorectal surgery. Not only does this technique achieve similar long-term results as the conventional open procedure, short-term results have been shown to be superior[1-4]. These include less postoperative pain, earlier recovery of bowel function, less blood loss, and shorter hospital stay. In case of colorectal cancer, which is the third most common cancer in the developed world, colorectal resection is the only curative treatment and short-term advantages obtained by laparoscopy represent an important difference for the operated patient. Long-term results, defined as disease-free survival, do not differ between patients operated through laparotomy or laparoscopy[2,3].

Thorough mechanical cleansing of the bowel has long been considered essential prior to colorectal operations[5-7]. One believed an empty bowel would diminish the risk of anastomotic leakage and septic complications. However, during the last decade several studies have been conducted investigating the use of mechanical bowel preparation (MBP). Most recent randomized controlled trials and meta-analyses uniformly conclude that there is no advantage of MBP prior to colorectal resections, finding equal or lower rates of anastomotic leakage and septic complications in patients without MBP compared to patients with pre-operative MBP[8-17]. However, these studies have not included patients operated by means of minimally invasive techniques, and therefore this conclusion cannot be extrapolated to laparoscopic surgery. Logically, one does not expect the effect of MBP on anastomotic leakage and other septic complications to be different between patients with a laparoscopic or open approach. However, the effect of bowel preparation on the volume of the bowel, and thus on exposure, could play an important role in the course of the laparoscopic intervention itself. Contradictory opinions are found in literature concerning this subject[12,16,18], and very few studies have investigated the role of MBP prior to laparoscopic interventions[19,20]. To evaluate the current practice among Dutch laparoscopic gastrointestinal surgeons we performed a questionnaire survey. The aim of this questionnaire was to investigate whether MBP is prescribed prior to laparoscopic colorectal surgery, and which considerations are taken into account when choosing or omitting MBP.

METHODS

The Dutch Society for Endoscopic Surgery (NVEC, Nederlandse Vereniging Endoscopische Chirurgie) was contacted and asked to participate in the study by sharing their members' contact information. In January 2010 members from the NVEC were invited by e-mail to fill out an online questionnaire on MBP prior to laparoscopic procedures. The target group of this study comprised surgeons performing laparoscopic colorectal surgery. The answers were automatically submitted online at the end of the

questionnaire. After two weeks the questionnaire was again sent to the members who had not yet responded.

The questionnaire consisted of 10 questions; 4 open and 6 multiple-choice questions. Of these 6 multiple-choice questions 4 could be answered with ‘‘other’’ and specified with free text. Answers specified by free text were reviewed for validity (i.e. not just one letter or incoherent text).

Surgeons were asked whether they use MBP for laparoscopic procedures, what type of MBP they use, for what reason they use it, and what aspects of the procedure could be influenced by MBP. Because of the interest of this study in surgical field exposure, major reasons for conversion were asked, as well as the degree of Trendelenburg-positioning of the patient.

Table 1 shows a summarized version of the questionnaire. Results are presented as percentages or medians with inter-quartile ranges.

Table 1. *Summarized version of the questionnaire*.

- What is your surgical field of interest?
- How many laparoscopic colonic- or rectal resections do you perform per month?
- Do you subscribe MBP to your patient prior to laparoscopic colonic resections?
- If yes: What MBP do you subscribe?
- Do you subscribe MBP to your patient prior to laparoscopic rectal resections?
- If yes: What MBP do you subscribe?
- Why do you use MBP? (more than 1)
  - this is according to the guideline of the department
  - to improve exposure of the surgical field
  - to diminish postoperative septic complications
  - I do not use MBP
  - other:
- How many degrees Trendelenburg do you position your patient?
- What are your 3 major reasons for conversion?
  - adhesions
  - locally advanced tumour
  - inadequate surgical field exposure
  - difficult localization of the tumour
  - intra-abdominal haemorrhage or injury to organs
  - technical difficulties
  - patient obesity
  - other:
- Do you feel MBP can influence: (more than 1)
  - the diameter of the small bowel
  - the ease of mobilizing the small bowel
  - operation time
  - exposure of the surgical field
  - risk of conversion
  - none of mentioned above
  - other:

RESULTS

The NVEC has 247 members. Fifty-three surgeons not performing general surgery or gastro-intestinal surgery were not contacted (mostly gynaecologists, urologists, and thoracic surgeons). The online survey was sent to the remaining 194 members.

Thirty-five members did not receive it due to incorrect e-mail addresses (defined as emails that could not be delivered due to errors in the address or non-existing addresses), or responded that they did not perform gastro-intestinal surgery. Of the 169 laparoscopic surgeons that received the online survey, 82 responded (49%). In 84.1% of respondents lower gastro-intestinal surgery was included in their field of interest, 15.9% indicated that their field of interest was upper gastro-intestinal surgery. The median quantity of colorectal resections performed per month was 5 (3-7).

Twenty percent of respondents declared to give MBP prior to laparoscopic colorectal resections, while 63% of respondents declared to give MBP prior to laparoscopic rectal resections. The distribution of the different types of MBP can be found in figures 1 and 2. The median percentage Trendelenburg positioning of the patient was 30º (26.5º - 42.5º).

Of the 63% of respondents giving MBP, most common reasons for giving MBP are shown in figure 3. The construction of a protective ileostoma, not intending to leave a 'filled' colon, was the most frequent answer (22%), followed by 'other reasons' and free text (21%), and improvement of the surgical field exposure (16%). The two most frequent text when choosing 'other reasons' was (1) better handling of the bowel when it is empty and (2) easier introduction of the stapler. The three most common reasons for conversion were inadequate surgical field exposure (88%), locally advanced tumour (68%), and adhesions (29%) (figure 4). Concerning the question which stages of the operation are influenced by MBP, 52% of respondents believed that MBP does not influence any stage of the operation. Twenty-nine per cent of respondents thought that the diameter of the small bowel was influenced by MBP, and 29% indicated that the exposure of the surgical field was influenced by MBP (figure 5).

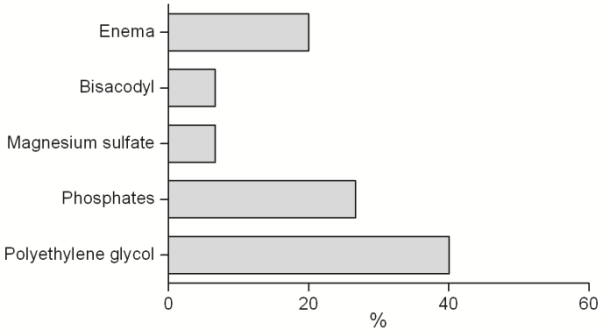


Figure 1. *MBP used prior to colonic resection*

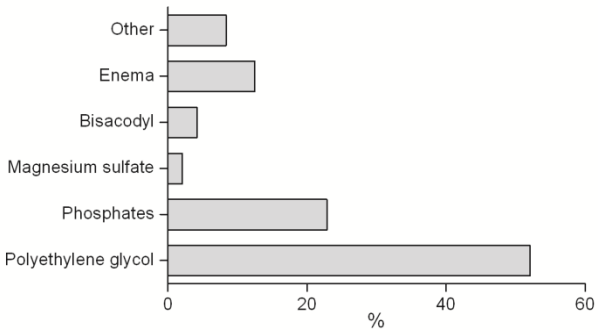


Figure 2. *MBP used prior to rectal resection*

DISCUSSION

Due to strong evidence that MBP does not lower the risk of anastomotic leakage and other septic complications in elective colorectal surgery[8-17], its standardized use has been abandoned in many centres. However, no studies regarding MBP have yet been conducted focusing on patients operated by means of minimally invasive techniques. In the Netherlands a significant part of colorectal resections are performed through laparoscopy nowadays, and the improved short-term results (less postoperative pain, earlier recovery of bowel function, less blood loss, shorter hospital stay) and similar disease-free survival rates have resulted in the important increase of laparoscopic procedures[1-4].

In our opinion the results of studies on MBP and infectious complications can also be applied to laparoscopic surgery; however the effect of MBP on the volume of the bowel and its competition with the insufflated CO^2 influencing exposure could play an important role in the course of the laparoscopic intervention itself. Evidence-based guidelines concerning this issue are lacking, and contradictory opinions are found in literature concerning this subject.

Figure 3. *"Why do you use MBP?"*

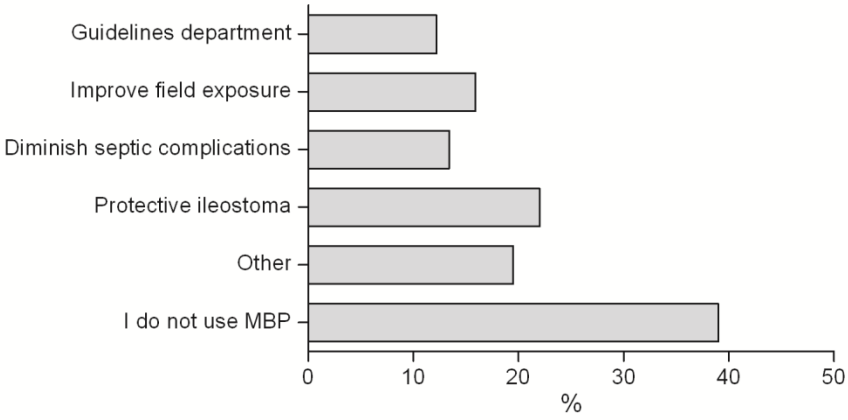


Figure 4. *"What are your major reasons for conversion?"*

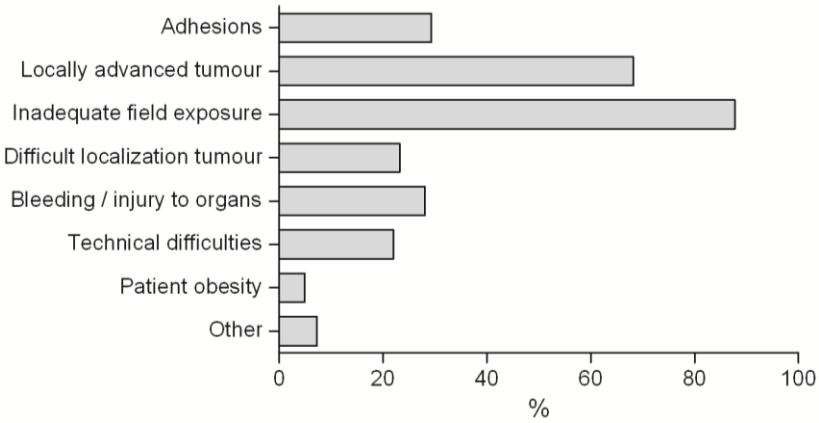
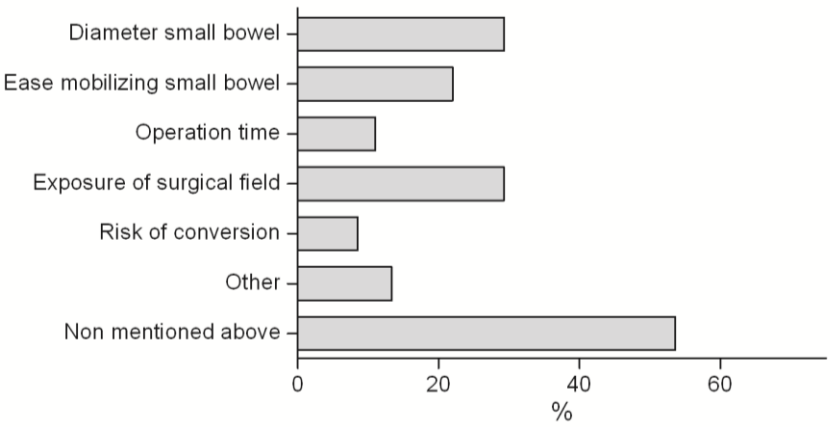


Figure 5*. "Do you feel MBP influences..:"*



Guenaga and coworkers mention in their Cochrane review that it has been argued that it is easier to perform laparoscopic surgery if the bowel contains solid matter in order to use gravity to obtain better overview[12]. Slim and coworkers state in a meta-analysis that MBP usually results in dilated bowel which could hamper laparoscopic vision and make mobilization of the intestines more difficult[16]. Cheung and coworkers have described their results of a questionnaire on the technique of laparoscopic total mesorectal excision[18]. They find that most surgeons apply MBP routinely for different reasons, and that reduction of intestinal volume to facilitate laparoscopic exposure appears to be a specific incentive.

Two studies in literature evaluated the effect of MBP on exposure in gynaecologic laparoscopy. In the first study, performed by Muzii et al., patients were randomized between pre-operative MBP (90ml sodium phosphate) and no MBP; the endpoint was the appropriateness of the surgical field as judged by the surgeon on a scale going from poor to excellent in five steps. No advantage of MBP on the evaluation of the surgical field could be demonstrated[19]. Another randomized trial, performed by Yang et al., divided patients in two groups. The first group received MBP through oral sodium phosphate solution; the second group received only a sodium phosphate enema. Assessment of the quality of the surgical field and bowel characteristics was performed using a surgeon questionnaire with Likert and visual analog scales. No significant differences were observed between the 2 groups in evaluation of the surgical field, bowel handling, degree of bowel preparation, or surgical difficulty[21].

The results of this questionnaire show that bowel preparation is still frequently used in laparoscopic colorectal procedures in the Netherlands, mostly in rectal resection. Sixteen per cent of respondents prescribe MBP prior to surgery in order to improve surgical field exposure; on the other hand inadequate surgical field exposure was by far the most common reason for conversion (88%). Almost a third of the respondents felt MBP might influence the diameter of the small bowel and the exposure; this can be placed in either a positive or a negative perspective since some feel MBP results in an emptied bowel and some in a bowel filled with liquid or gas bowel contents[22].

The most important limitation of this questionnaire is the response rate of 49%. A low response rate to questionnaires is a well-known problem, and to make the chances of response as high a possible we sent an online questionnaire by email, made it as short as possible (10 questions), and with automatic sending of the results at the end of the questionnaire. Another limitation is the fact that ideally all Dutch surgeons performing laparoscopic gastro-intestinal procedures should have been contacted, however from a practical point of view that is not feasible. We have chosen to send this questionnaire through the Dutch Association of Endoscopic Surgery since that provided us an email-list of Dutch surgeons with particular interest for laparoscopic surgery.

A different questionnaire was performed by Wells et al., amongst 110 members of the Society of Gynecologic Oncologists of Canada to assess the practice pattern and beliefs on MBP[23]. The results show that half of the respondents routinely use MBP for gynaecologic oncologic surgery (laparotomy and laparoscopy). The most common reasons for using MBP were to decrease risk of anastomotic leak and improve visualization.

To present, no evidence exists on the role of MBP on the diameter of the bowel and exposure in colorectal laparoscopy. To achieve optimal exposure in laparoscopic colorectal surgery, the small bowel has to be mobilized cranially. Several aspects can influence the ease of mobilizing the small bowel: the degree of muscle relaxation and Trendelenburg-position, the thickness of the omentum and mesocolon of the small bowel (related to Body Mass Index), and the diameter of the small bowel. The first aspect is in the hands of both surgeon and anaesthetist; the second aspect is patient-dependent and cannot be influenced. Concerning the diameter and contents of the small bowel and the ease in which it can be mobilized only little is known. Whether a completely emptied bowel is preferable over normal stool contents in order to use gravity remains an unanswered question until now. Furthermore, it is questionable whether MBP can achieve a complete emptied bowel at all, or whether it will result in a more voluminous small bowel due to inadequate bowel cleansing and liquid or gas bowel contents[22]. The latter could also be influenced by the type of MBP being administrated and patient compliance.

The scarce quantity of studies regarding the subject of MBP in laparoscopy indicates the following: (1) Questionnaires regarding MBP indicate a number of laparoscopic surgeons use MBP with the aim to improve surgical field exposure (this study,[23]). (2) Randomized studies on MBP in gynecologic laparoscopy seem to conclude that there is no amelioration of surgical field exposure with MBP. The difficulty in these studies is the outcome measure, which is the evaluation of the surgical field using a surgeon questionnaire[19,21].

In conclusion, the results of this questionnaire show that the indication of MBP in laparoscopic colorectal surgery is undefined in the Netherlands. A review of literature shows the influence of MBP on diameter of the bowel and thus laparoscopic vision is not clear. Studies investigating the role of MBP on intestinal volume and surgical field exposure in colorectal laparoscopic surgery are necessary.

REFERENCES

1. Breukink S, Pierie J, Wiggers T. Laparoscopic versus open total mesorectal excision for rectal cancer. Cochrane Database Syst Rev 2006:CD005200.
2. Clinical Outcomes of Surgical Therapy Study G. A comparison of laparoscopically assisted and open colectomy for colon cancer. N Engl J Med 2004;350:2050-9.
3. Reza MM, Blasco JA, Andradas E, et al. Systematic review of laparoscopic versus open surgery for colorectal cancer. Br J Surg 2006;93:921-8.
4. Veldkamp R, Kuhry E, Hop WC, et al. Laparoscopic surgery versus open surgery for colon cancer: short-term outcomes of a randomised trial. Lancet Oncol 2005;6:477-84.
5. Chung RS, Gurll NJ, Berglund EM. A controlled clinical trial of whole gut lavage as a method of bowel preparation for colonic operations. Am J Surg 1979;137:75-81.
6. Dunphy JE. Preoperative preparation of the colon and other factors affecting anastomotic healing. Cancer 1971;28:181-2.
7. Nichols RL, Condon RE. Preoperative preparation of the colon. Surg Gynecol Obstet 1971;132:323-37.
8. Bretagnol F, Alves A, Ricci A, et al. Rectal cancer surgery without mechanical bowel preparation. Br J Surg 2007;94:1266-71.
9. Bucher P, Gervaz P, Soravia C, et al. Randomized clinical trial of mechanical bowel preparation versus no preparation before elective left-sided colorectal surgery. Br J Surg 2005;92:409-14.
10. Contant CM, Hop WC, van't Sant HP, et al. Mechanical bowel preparation for elective colorectal surgery: a multicentre randomised trial. Lancet 2007;370:2112-7.
11. Fa-Si-Oen P, Roumen R, Buitenweg J, et al. Mechanical bowel preparation or not? Outcome of a multicenter, randomized trial in elective open colon surgery. Dis Colon Rectum 2005;48:1509-16.
12. Guenaga KK, Matos D, Wille-Jorgensen P. Mechanical bowel preparation for elective colorectal surgery. Cochrane Database Syst Rev 2009:CD001544.
13. Jung B, Pahlman L, Nystrom PO, et al. Multicentre randomized clinical trial of mechanical bowel preparation in elective colonic resection. Br J Surg 2007;94:689-95.
14. Pena-Soria MJ, Mayol JM, Anula R, et al. Single-blinded randomized trial of mechanical bowel preparation for colon surgery with primary intraperitoneal anastomosis. J Gastrointest Surg 2008;12:2103-8; discussion 8-9.
15. Ram E, Sherman Y, Weil R, et al. Is mechanical bowel preparation mandatory for elective colon surgery? A prospective randomized study. Arch Surg 2005;140:285-8.
16. Slim K, Vicaut E, Panis Y, et al. Meta-analysis of randomized clinical trials of colorectal surgery with or without mechanical bowel preparation. Br J Surg 2004;91:1125-30.
17. Zmora O, Mahajna A, Bar-Zakai B, et al. Is mechanical bowel preparation mandatory for left-sided colonic anastomosis? Results of a prospective randomized trial. Tech Coloproctol 2006;10:131-5.
18. Cheung YM, Lange MM, Buunen M, et al. Current technique of laparoscopic total mesorectal excision (TME): an international questionnaire among 368 surgeons. Surg Endosc 2009.
19. Muzii L, Angioli R, Zullo MA, et al. Bowel preparation for gynecological surgery. Crit Rev Oncol Hematol 2003;48:311-5.
20. Zmora O, Lebedyev A, Hoffman A, et al. Laparoscopic colectomy without mechanical bowel preparation. Int J Colorectal Dis 2006;21:683-7.
21. Yang LC, Arden D, Lee TT, et al. Mechanical bowel preparation for gynecologic laparoscopy: a prospective randomized trial of oral sodium phosphate solution vs single sodium phosphate enema. J Minim Invasive Gynecol 2011;18:149-56.
22. Mahajna A, Krausz M, Rosin D, et al. Bowel preparation is associated with spillage of bowel contents in colorectal surgery. Dis Colon Rectum 2005;48:1626-31.
23. Wells T, Plante M, McAlpine JN. Preoperative Bowel Preparation in Gynecologic Oncology: A Review of Practice Patterns and an Impetus to Change. Int J Gynecol Cancer 2011.

Chapter 13

Optimizing working-space in laparoscopy: measuring the effect of mechanical bowel preparation in a porcine model

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ABSTRACT

Background: Adequate working space is a prerequisite for safe and efficient minimal access surgery. No objective data exist in literature about the effect of mechanical bowel preparation (MBP) on working space in laparoscopic surgery. We objectively measured this effect with computed tomography in a porcine laparoscopy model.

Methods: Using standardized anesthesia, twelve 20kg pigs without MBP and eight 20kg pigs with MBP were studied with computed tomography at intra-abdominal pressure (IAP) levels of 0, 5, 10 and 15mm Hg. Volumes and dimensions of the pneumoperitoneum were measured on reconstructed CT-images and compared between the pigs with and those without MBP.

Results: A reproducible and statistically significant increase of around 500ml in pneumoperitoneum volume was found in the MBP group at all levels of IAP. This represents a 43% relative increase at a pneumoperitoneum pressure of 5 mm Hg, 21% at IAP 10mm Hg and 18% at IAP 15mm Hg. Peak inspiratory pressure was lower at IAP 0 and 5mm Hg in the MBP group. Antero-posterior diameter in the group with MBP was lower at 0 mmHg, but abdominal dimensions were similar in both groups at all other IAPs. This shows the gain in working space is due to a diminished volume of the intra-abdominal content and not to compression or displacement of the bowel.

Conclusion: MBP increases working space by reducing bowel content. Especially at low intra-abdominal working pressures the increase in working space associated with MBP could represent an important benefit in challenging laparoscopic surgery.

INTRODUCTION

The introduction of laparoscopic procedures has led to important progress in colorectal surgery. Short-term results have been shown to be superior, including less postoperative pain, earlier recovery of bowel function, less blood loss, and shorter hospital stay[1-4]. Long-term results, defined as disease-free survival, do not differ between patients operated by means of laparotomy or laparoscopy[1,3]. However, despite the short-term advantages, laparoscopy also has negative aspects. It has a longer learning curve[5] , increases operating-times and -costs[2,3] and it has the disadvantages of a CO_2 pneumoperitoneum[6-18]. Various solutions have been proposed to overcome the consequences of CO_2 pneumoperitoneum[19-23,24] . Nevertheless, obtaining enough working space is essential for good view and handling of instruments[25-27].

Several factors influence working space, e.g. age and size of the patient, obesity, bowel content, pneumoperitoneum-pressure, positioning of the patient, use of systemic neuromuscular blocking agents and ventilation settings[28]. Whether preoperative mechanical bowel preparation (MBP) influences working space has not been established[29,30]. However, several randomized controlled trials and meta-analyses have been conducted on MBP prior to colorectal operations, investigating its influence on anastomotic leakage and septic complications. The vast majority of studies conclude there is no advantage of MBP prior to colorectal resections regarding the aforementioned complications[31-38].

The aim of this study was to investigate in a porcine model whether MBP has a positive influence on working space during laparoscopy.

METHODS

Animals

Twenty female Landrace pigs, weighing approximately 20kg, were studied: eight pigs received MBP while 12 pigs did not. The study was approved by the institutional animal ethics committee.

Mechanical Bowel Preparation

In the MBP group food was withheld and replaced by water ad libitum and sweetened water at 30 hours before the experiment. Animals were placed in cages without floor-coverage. At 24 hours and 8 hours before surgery, 20ml of sodium phosphate was administered orally, followed by 100ml of water. Pigs in the non MBP group were fed ad libitum until premedication.

Anaesthesia

All pigs were subjected to the same anesthesia protocol as described earlier by the authors[28]. After premedication with midazolam and ketamine in the animal housing facility, animals were brought to the laboratory and intubated. Maintenance anaesthesia consisted of sufentanil and propofol. No neuromuscular blocking agents were used for these experiments. Artificial ventilation was volume-

controlled(10ml/kg), with a positive end expiratory pressure (PEEP) set at 5cm H_2O. Only the respirator frequency was adjusted when End-Tidal CO_2 ($ETCO_2$) rose above 7kPa. Arterial and venous access was established. Heart rate, blood pressure, respiratory rate, peak inspiratory pressure (PIP) and $ETCO_2$ were measured continuously. A 5mm radially expanding trocar (Versastep®, Covidien, Dublin, Ireland) was placed in the supra-umbilical midline. Its correct intra-abdominal position was verified endoscopically (Storz Telepack®, Tuttlingen, Germany, 5mm 30° telescope).

Study protocol

With stable cardiorespiratory parameters, the pig was transported to the CT-scanner (Somatom Definition Flash Dual Source®, Siemens Healthcare, Erlangen, Germany). After installation of the pig on the scanning-tray, an electronic CO_2 insufflator (Endoflator®, Storz) was attached to the abdominal trocar. Breath-hold end-expiratory Computed Tomography (CT) of thorax and abdomen, lasting ca. 5 seconds, was performed at intra-abdominal pressures (IAP) of 0, 5, 10 and 15mm Hg. At each pressure-level, a stabilization period of 5 minutes was taken into account and cardiorespiratory parameters were documented. After finishing the scans, the pig was euthanized.

Outcome measurements

Body weight as well as the total length of the first 5 lumbar vertebral bodies in a sagittal CT midline plane was measured. This CT length was measured to get an objective measure for the size of the pig, not dependent on food-status like the weight[39]. All pigs had 6 lumbar vertebrae, but the physiologic lordosis made measuring of the length of the first 5 lumbar vertebrae easiest and most reproducible. Intra-abdominal volume of pneumoperitoneum was calculated with the Syngo 3D volume-module of a Siemens Navigator® workstation using a dataset of 5mm slices. With the definition of appropriate thresholds, semi-automatic detection of CO_2 in the abdomen was done on transverse slices [40]. These could be integrated to a total volume of pneumoperitoneum. All volumes were visually checked for inadvertent inclusion of air in the bowel (figures 1a and b).

In a sagittal midline plane maximum external antero-posterior diameter of the abdomen and maximum distance between the upper border of the pubic symphysis and the highest diaphragmatic peritoneal lining was measured on CT-images at all levels of IAP. In a coronal plane the maximum external transverse diameter was measured (figure 1a and b).

Statistics

Normality of the data was confirmed by means of visual assessment and Kolmogorov Smirnov testing. Data are presented as means with standard errors of the mean. Differences between groups were assessed using an independent samples t- test. A p-value lower than 0.05 was considered significant.

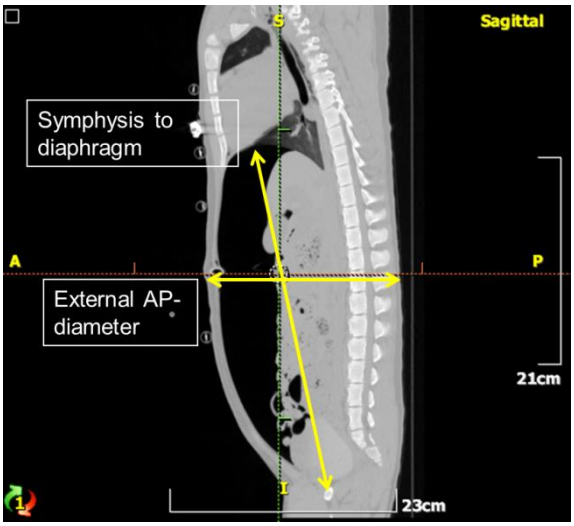

***Figure 1a**. Anteroposterior (AP) diameter and 'symphysis to diaphragm'-measurements.*

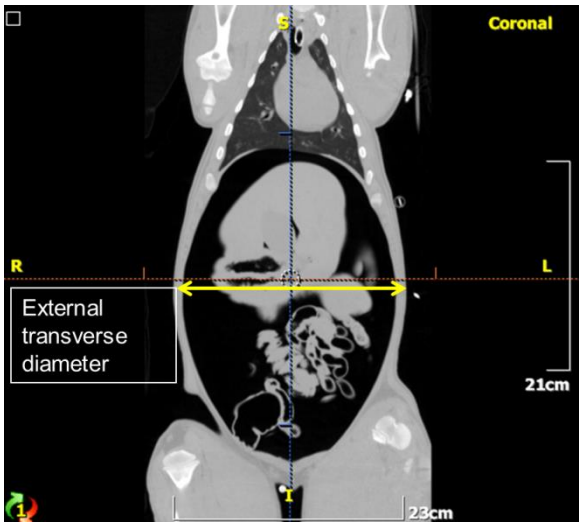

***Figure 1b**. External transverse diameter*

RESULTS

One pig in the non MBP group died during surgical preparation leaving the data of 19 pigs eligible for analysis. There was no statistically significant difference in body weight or in length of the first five lumbar vertebrae between the non-MBP and the MBP group but mean body weight was 1.2kg lower in the MBP group (Table 1). Cardiorespiratory parameters are shown in table 2. Changes in respiratory rate to compensate for hypercapnia were made in 3 pigs in the non-MBP group (average increase 10 breaths/min) and 5 pigs in the MBP group (average increase 14 breaths/min). PIP was significantly lower in the MBP group at IAP of 0 and 5 mmHg. This reduction in PIP disappeared at IAPs of 10 and 15 mm Hg.

When comparing the CT pneumoperitoneum volumes at different IAPs between groups, pigs in the MBP group had a significantly higher pneumoperitoneum volume, gaining approximately 500ml at each IAP level (table 3). The relative increase associated with MBP was 43% at IAP 5mm Hg, 21% at 10mm Hg, and 18% at 15mm Hg. The pneumoperitoneum volume attained at IAP 10mm Hg with MBP was similar to the volume at IAP 15mm Hg without MBP.

The dimensions of the abdomen are presented in table 4. As can be seen, a difference in antero-posterior diameter of the abdomen exists between the non-MBP and MBP group only in the non-insufflated state. There were no significant differences in transverse diameter or symphysis-to-diaphragm distance of the abdomen between the non-MBP and MBP group.

Table 1. *Body weight and length of first 5 lumbar vertebrae*

	Non MBP Mean(SEM)	**MBP** Mean(SEM)	**p-value**
Weight (kg)	22.7 (0.65)	21.5 (0.47)	0.15
Length vertebrae(cm)	11.77 (0.10)	11.87 (0.09)	0.50

MBP: mechanical bowel preparation, SEM: standard error of the mean

Table 2. *Cardiorespiratory parameters (mean values)*

IAP	**0 mmHg**		**5 mmHg**		**10 mmHg**		**15 mmHg**	
	MBP-	MBP+	MBP-	MBP+	MBP-	MBP+	MBP-	MBP+
MAP	80.3	94.4	79.2	96.3	79.7	91.4	85.5	88.9
HR	83.7	88.1	81.1	76.0	83.3	78.0	88.4	81.4
RR	29.6	28.8	29.6	28.8	30.5	28.8	31.4	32.5
PIP	19.2	16.8*	19.0	16.8*	22.3	21.1	28.1	27.4
$ETCO_2$	5.8	5.8	5.9	6.2	6.3	6.6	6.5	6.6

IAP: intra-abdominal pressure, MBP: mechanical bowel preparation, MAP: mean arterial blood pressure (mmHg), HR: heart rate (beats/min), RR: respiratory rate (breaths/min),
PIP: peak inspiratory pressure (cm H_2O), $ETCO_2$: End-tidal CO_2 (kPa).
**: a significant difference exists in PIP between non-MBP and MBP pigs at 0mm Hg (p-value 0.02) and 5mm Hg (p-value 0.03) (unpaired t-test).*

Table 3. *Volumes of pneumoperitoneum in ml*

IAP	**Non MBP** Mean (SEM)	**MBP** Mean (SEM)	**Mean difference** (% increase)	**p-value**
0 mmHg	11 (7)	21 (2)	9	0.27
5 mmHg	1271 (138)	1823 (130)	551 (43.4%)	0.01
10 mmHg	2459 (131)	2968 (165)	509 (20.7%)	0.03
15 mmHg	2919 (140)	3438 (167)	519 (17.8%)	0.03

IAP: intra-abdominal pressure, MBP: mechanical bowel preparation, SEM: standard error of the mean

DISCUSSION

The standard use of MBP has been largely abandoned, since studies have proven its use does not diminish the risk of anastomotic leakage or wound infections[31-38]. However, the relationship between MBP and working space in laparoscopic surgery is still matter of debate. The two level 1A studies on MBP in open colorectal surgery have contradictory discussions on the theoretical influence of MBP in laparoscopy. It has been argued that it is easier to perform laparoscopic surgery if the bowel contains solid matter in order to use gravity to obtain better overview[35], or that MBP results in dilated bowel which could hamper laparoscopic vision and make mobilization of the intestines more difficult[37].

Table 4. *Dimensions of the abdomen in centimeters*

		Non MBP	MBP	p-value
	IAP	Mean (SEM)	Mean (SEM)	
External AP diameter	0 mmHg	15.4 (0.37)	13.5 (0.30)	0.02
	5 mmHg	18.5 (0.36)	17.9 (0.42)	NS
	10 mmHg	20.6 (0.29)	19.8 (0.43)	NS
	15 mmHg	21.4 (0.29)	20.7 (0.41)	NS
External transverse diameter	0 mmHg	25.4 (0.53)	24.4 (0.24)	NS
	5 mmHg	25.4 (0.51)	24.3 (0.28)	NS
	10 mmHg	25.0 (0.46)	24.3 (0.31)	NS
	15 mmHg	24.9 (0.45)	24.3 (0.26)	NS
Symphysis to diaphragm distance	0 mmHg	36.2 (0.47)	36.3 (0.43)	NS
	5 mmHg	36.8 (0.36)	37.2 (0.48)	NS
	10 mmHg	37.7 (0.40)	38.1 (0.55)	NS
	15 mmHg	38.0 (0.39)	38.4 (0.45)	NS

IAP: intra-abdominal pressure, AP: antero-posterior, MBP: mechanical bowel preparation

Only a few studies have evaluated the effect of MBP on exposure in gynaecologic laparoscopy. In the first study, performed by Muzii et al., patients were randomized between pre-operative MBP (sodium phosphate) and no MBP; the endpoint was the appropriateness of the surgical field as judged by the surgeon on a scale going from poor to excellent in five steps[29]. No advantage of MBP on the evaluation of the surgical field could be demonstrated. Another randomized trial, performed by Yang et al., divided patients undergoing gynaecologic laparoscopy in two groups[30]. The first group received MBP through oral sodium phosphate solution; the second group received only a sodium phosphate enema. Assessment of the quality of the surgical field and bowel characteristics was performed using a surgeon questionnaire with Likert and visual analog scales. No significant differences were observed between the 2 groups in evaluation of the surgical field, bowel handling, degree of bowel preparation, or surgical difficulty.

Two additional surveys (laparoscopic colon and rectum surgery, and laparoscopic gynaecology) show MBP is still used for different reasons in these fields of laparoscopy[41,42]. One of these reasons is the possible influence MBP could have on surgical field exposure. All these studies reflect individual preferences rather than evidence based practice. Moreover, the surgeon's evaluation of the working space may be too subjective to detect significant differences in outcome.

For this reason we conducted this animal study, aiming to investigate whether MBP has an influence on laparoscopic working space. The results show a significant increase in pneumoperitoneum volume in the group receiving MBP pre-operatively. This gain in pneumoperitoneum volume of 500ml CO_2 is

independent of the pressure of pneumoperitoneum, and represents a relative increase of 43% at 5mm Hg and 21% at 10mm Hg and 18% at 15mm Hg. Consequently, with pre-operative MBP the same volume of pneumoperitoneum can be obtained at lower IAPs (table 3).

Concordantly, mechanical ventilation is easier in MBP pigs at low pneumoperitoneum pressures (diminished peak inspiratory pressure at 0 and 5 mmHg in the MBP group, table 2). Antero-posterior diameter in the group with MBP was lower at 0 mmHg, but abdominal dimensions were similar in both groups at all other IAPs. This shows the gain in working space is due to a diminished volume of the intra-abdominal content and not to compression or displacement of the bowel (table 4).

In this animal study our choice for MBP was sodium phosphate. The most commonly prescribed preparations for bowel cleaning in humans are sodium phosphate (90ml), poly-ethylene glycol (PEG, 4L), and magnesium citrate (300mL). Literature shows sodium phosphate has the highest patient compliance, and least residual stool[43] [44,45] In animals orogastric intubation is required to administer large volumes of lavage solution over several minutes, leading to discomfort, struggling, and apparent increased stress[46]. Sodium phosphate is a low-volume, hyperosmolar, buffered saline laxative that osmotically draws water into the gastrointestinal tract lumen. It relies on osmotic action to draw plasma water into the colon to soften and flush faecal material out of the colon[44,45]. Its use for mechanical bowel preparation in pigs prior to colonoscopy is shown by Pfeffer et al.[47] .

A difference between the two groups of pigs, except for MBP, is the duration of fasting. Food was withheld from pigs receiving MBP beginning the day before the experiment. Whether this also influences the volume of intra-abdominal content or might have caused the 1.2kg difference in mean body weight has not been investigated in this study. This raises the question of the necessity of MBP. In a blinded, randomized controlled trial in gynaecologic laparoscopic surgery for benign disease, a 7-day low fiber diet gave as good exposure as PEG (scored by the surgeon) but was far better tolerated[48].

In conclusion, MBP prior to laparoscopy in pigs results in an increased volume of CO_2 pneumoperitoneum irrespective of IAP. This could represent an important benefit in technically challenging intestinal and non-intestinal laparoscopic surgery. The relative gain in volume of CO_2 pneumoperitoneum by MBP is highest at lower insufflation pressures, which can be helpful in low-pressure laparoscopic surgery, as is custom in pediatric surgery.

Further studies are necessary to investigate whether a similar effect could be obtained with more patient-friendly bowel preparations such as low-fiber diet.

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REFERENCES

1. A comparison of laparoscopically assisted and open colectomy for colon cancer. N Engl J Med 2004;350:2050-9.
2. Breukink S, Pierie J, Wiggers T. Laparoscopic versus open total mesorectal excision for rectal cancer. Cochrane Database Syst Rev 2006:CD005200.
3. Reza MM, Blasco JA, Andradas E, et al. Systematic review of laparoscopic versus open surgery for colorectal cancer. Br J Surg 2006;93:921-8.
4. Veldkamp R, Kuhry E, Hop WC, et al. Laparoscopic surgery versus open surgery for colon cancer: short-term outcomes of a randomised trial. Lancet Oncol 2005;6:477-84.
5. Schlachta CM, Mamazza J, Seshadri PA, et al. Defining a learning curve for laparoscopic colorectal resections. Dis Colon Rectum 2001;44:217-22.
6. Blobner M, Bogdanski R, Kochs E, et al. Effects of intraabdominally insufflated carbon dioxide and elevated intraabdominal pressure on splanchnic circulation: an experimental study in pigs. Anesthesiology 1998;89:475-82.
7. Burgos FJ, Saenz J, Correa C, et al. Changes in visceral flow induced by laparoscopic and open living-donor nephrectomy: experimental model. Transplant Proc 2009;41:2491-2.
8. Caldwell CB, Ricotta JJ. Changes in visceral blood flow with elevated intraabdominal pressure. J Surg Res 1987;43:14-20.
9. Gupta A, Watson DI. Effect of laparoscopy on immune function. Br J Surg 2001;88:1296-306.
10. Hirvonen EA, Poikolainen EO, Paakkonen ME, et al. The adverse hemodynamic effects of anesthesia, head-up tilt, and carbon dioxide pneumoperitoneum during laparoscopic cholecystectomy. Surg Endosc 2000;14:272-7.
11. Jakimowicz J, Stultiens G, Smulders F. Laparoscopic insufflation of the abdomen reduces portal venous flow. Surg Endosc 1998;12:129-32.
12. Koivusalo AM, Lindgren L. Respiratory mechanics during laparoscopic cholecystectomy. Anesth Analg 1999;89:800.
13. Neudecker J, Sauerland S, Neugebauer E, et al. The European Association for Endoscopic Surgery clinical practice guideline on the pneumoperitoneum for laparoscopic surgery. Surg Endosc 2002;16:1121-43.
14. Sammour T, Mittal A, Loveday BP, et al. Systematic review of oxidative stress associated with pneumoperitoneum. Br J Surg 2009;96:836-50.
15. Schilling MK, Redaelli C, Krahenbuhl L, et al. Splanchnic microcirculatory changes during CO2 laparoscopy. J Am Coll Surg 1997;184:378-82.
16. Yasir M, Mehta KS, Banday VH, et al. Evaluation of post operative shoulder tip pain in low pressure versus standard pressure pneumoperitoneum during laparoscopic cholecystectomy. Surgeon 2012;10:71-4.
17. Reintam Blaser A, Bloechlinger S. Should we be worried about disturbed sympathovagal balance during laparoscopic cholecystectomy? Minerva Anestesiol 2010;76:876-8.
18. Ure BM, Suempelmann R, Metzelder MM, et al. Physiological responses to endoscopic surgery in children. Seminars in pediatric surgery 2007;16:217-23.
19. Balick-Weber CC, Nicolas P, Hedreville-Montout M, et al. Respiratory and haemodynamic effects of volume-controlled vs pressure-controlled ventilation during laparoscopy: a cross-over study with echocardiographic assessment. Br J Anaesth 2007;99:429-35.
20. Chassard D, Berrada K, Tournadre J, et al. The effects of neuromuscular block on peak airway pressure and abdominal elastance during pneumoperitoneum. Anesth Analg 1996;82:525-7.
21. Dexter SP, Vucevic M, Gibson J, et al. Hemodynamic consequences of high- and low-pressure capnoperitoneum during laparoscopic cholecystectomy. Surg Endosc 1999;13:376-81.
22. Gurusamy KS, Samraj K, Davidson BR. Abdominal lift for laparoscopic cholecystectomy. Cochrane Database Syst Rev 2008:CD006574.
23. Gurusamy KS, Samraj K, Davidson BR. Low pressure versus standard pressure pneumoperitoneum in laparoscopic cholecystectomy. Cochrane Database Syst Rev 2009:CD006930.

24. Wong YT, Shah PC, Birkett DH, et al. Peritoneal pH during laparoscopy is dependent on ambient gas environment: helium and nitrous oxide do not cause peritoneal acidosis. Surg Endosc 2005;19:60-4.
25. Emam TA, Hanna GB, Kimber C, et al. Effect of intracorporeal-extracorporeal instrument length ratio on endoscopic task performance and surgeon movements. Arch Surg 2000;135:62-5; discussion 6.
26. Frede T, Stock C, Renner C, et al. Geometry of laparoscopic suturing and knotting techniques. J Endourol 1999;13:191-8.
27. Hanna GB, Shimi S, Cuschieri A. Influence of direction of view, target-to-endoscope distance and manipulation angle on endoscopic knot tying. Br J Surg 1997;84:1460-4.
28. Vlot J. Optimizing working-space in porcine laparoscopy: CT measurement of the effects of intra-abdominal pressure. Surg Endosc 2012;Submitted.
29. Muzii L, Angioli R, Zullo MA, et al. Bowel preparation for gynecological surgery. Crit Rev Oncol Hematol 2003;48:311-5.
30. Yang LC, Arden D, Lee TT, et al. Mechanical bowel preparation for gynecologic laparoscopy: a prospective randomized trial of oral sodium phosphate solution vs single sodium phosphate enema. J Minim Invasive Gynecol 2011;18:149-56.
31. Bretagnol F, Alves A, Ricci A, et al. Rectal cancer surgery without mechanical bowel preparation. Br J Surg 2007;94:1266-71.
32. Bucher P, Gervaz P, Soravia C, et al. Randomized clinical trial of mechanical bowel preparation versus no preparation before elective left-sided colorectal surgery. Br J Surg 2005;92:409-14.
33. Contant CM, Hop WC, van't Sant HP, et al. Mechanical bowel preparation for elective colorectal surgery: a multicentre randomised trial. Lancet 2007;370:2112-7.
34. Fa-Si-Oen P, Roumen R, Buitenweg J, et al. Mechanical bowel preparation or not? Outcome of a multicenter, randomized trial in elective open colon surgery. Dis Colon Rectum 2005;48:1509-16.
35. Guenaga KK, Matos D, Wille-Jorgensen P. Mechanical bowel preparation for elective colorectal surgery. Cochrane Database Syst Rev 2009:CD001544.
36. Jung B, Pahlman L, Nystrom PO, et al. Multicentre randomized clinical trial of mechanical bowel preparation in elective colonic resection. Br J Surg 2007;94:689-95.
37. Slim K, Vicaut E, Panis Y, et al. Meta-analysis of randomized clinical trials of colorectal surgery with or without mechanical bowel preparation. Br J Surg 2004;91:1125-30.
38. Zmora O, Lebedyev A, Hoffman A, et al. Laparoscopic colectomy without mechanical bowel preparation. Int J Colorectal Dis 2006;21:683-7.
39. King JWB, Roberts RC. Carcass length in the bacon pig; its association with vertebrae numbers and prediction from radiographs of the young pig. Animal production 1960;2:59-65.
40. Cai W, Tabbara M, Takata N, et al. MDCT for automated detection and measurement of pneumothoraces in trauma patients. AJR Am J Roentgenol 2009;192:830-6.
41. Slieker JC, van't Sant HP, Vlot J, et al. Bowel preparation prior to laparoscopic colorectal resection: what is the current practice? J Laparoendosc Adv Surg Tech A 2011;21:899-903.
42. Wells T, Plante M, McAlpine JN. Preoperative bowel preparation in gynecologic oncology: a review of practice patterns and an impetus to change. Int J Gynecol Cancer 2011;21:1135-42.
43. Hara AK, Kuo MD, Blevins M, et al. National CT colonography trial (ACRIN 6664): comparison of three full-laxative bowel preparations in more than 2500 average-risk patients. AJR Am J Roentgenol 2011;196:1076-82.
44. Hsu CW, Imperiale TF. Meta-analysis and cost comparison of polyethylene glycol lavage versus sodium phosphate for colonoscopy preparation. Gastrointest Endosc 1998;48:276-82.
45. Law WL, Choi HK, Chu KW, et al. Bowel preparation for colonoscopy: a randomized controlled trial comparing polyethylene glycol solution, one dose and two doses of oral sodium phosphate solution. Asian J Surg 2004;27:120-4.
46. Daugherty MA, Leib MS, Rossmeisl JH, et al. Safety and efficacy of oral low-volume sodium phosphate bowel preparation for colonoscopy in dogs. J Vet Intern Med 2008;22:31-6.

47. Pfeffer J, Grinshpon R, Rex D, et al. The Aer-O-Scope: proof of the concept of a pneumatic, skill-independent, self-propelling, self-navigating colonoscope in a pig model. Endoscopy 2006;38:144-8.
48. Lijoi D, Ferrero S, Mistrangelo E, et al. Bowel preparation before laparoscopic gynaecological surgery in benign conditions using a 1-week low fibre diet: a surgeon blind, randomized and controlled trial. Arch Gynecol Obstet 2009;280:713-8.

Chapter 14

Summary, discussion and future perspectives

Leakage of anastomosis is a complication every colorectal surgeon aims to prevent. It can convert an elective procedure with the patient leaving the hospital in approximately four days, eating, little pain, small scars, and in case of a protective stoma the admission date for its rapid closure, into a procedure followed by an emergency reoperation with a patient leaving the hospital after several months, weakened, denutritioned, with an infected wound and an end colostomy having the intrinsic risk of never being closed.

COLORECTAL ANATOMY AND TYPE OF COLORECTAL RESECTION

An important part of short-term outcome after colon or rectum resections is defined by the vascularization of the remaining tissue after completing the resection. In addition, in case of procedures for malignancies it is also the vascularization, with lymph nodes, that defines the extent of the resection. Leaving poorly-vascularized tissue after intestinal resection is a catastrophical situation in colorectal surgery, especially in case of creating an anastomosis. Wound healing in the bowel demands adequate perfusion, and even a small anastomotic defect can lead to abscess formation or peritonitis. These two complications are coupled with increased morbidity, which especially in case of peritonitis will have many negative consequences.

Knowledge of vascularisation and innervation is crucial for good outcome in colorectal surgery. Particularly the oncological principles of resection must be known, together with their implications regarding vascular resection and possibilities of intestinal reconstruction[1, 2]. The major arterial vessels supplying the segment of the colon containing the tumor should be excised at their origins, but this should be done so that devascularization is prevented. The ability of prediction of lymphatic drainage of colon tumor cells is a limitation in defining the ideal extent of colon resection. Attempts have been made to provide lymphatic mapping through sentinel node detection for tailored mesocolon-resection instead of en bloc mesenteric resection with central vascular ligation. However this technique is not yet validated in literature[3]. Similarly, the risk of aberrant lymphatic drainage of early stage tumors is unknown, for example in cecum cancer considering the general 6.1% risk of lymph node metastasis along the right middle colic artery[4]. A randomized study of hemicolectomy versus segmental colectomy of left colonic carcinoma performed in 1994 showed equal median survival rates, however recent studies are lacking[5]. In theory a more limited resection would reduce the risk of unnecessary devascularisation and ischemic complications, as well as denervation and interference with bowel motility. However, the priority of colonic resection is represented by the oncological completeness, and large mesocolon resection remains the standard until better predicition of lymphatic drainage is available.

One of the debates is the level of arterial ligation in case of rectal cancer. In 1908 Miles proposed the “low tie” technique through division of the superior rectal artery just distally to the origin of the left

colic artery, with removal of lymph nodes following the arterial supply[6]. During the same period Moynihan was in favor of the "high tie" technique: resection of the inferior mesenteric artery at its origin including all lymph nodes following this arterial supply within the resection[7]. Advantage of the low tie technique is that it leaves an intact vascularization to the splenic flexure and descending colon that will be anastomosed. A restriction of this technique might be tension on the descending colon due to the fixation of the mesentery, which can be a reason to perform a high tie. Whether a high tie will result in increased survival due to increased harvesting of lymph nodes does not seem to be the case, but is not fully studied[8]. One study investigating the difference in AL between preservation of the ascending left colic artery vs high tie in low anterior resection did not found any significant differences, however with a low number of patients[9]. Our study, described in **Chapter 3**, examined the blood flow of the residual intestine after rectal resection, comparing high tie and low tie. Results show better vascularization of the colon after rectal resection in case of low tie. However whether this better vascularization has clinical consequences, e.g. less anastomotic leakage (AL), has not been examined. Despite the fact that there are several studies that have investigated the vascularization in case of high or low tie rectal resection there still is no clear answer. Several aspects participate to this unclearness. First of all measurement of vascularization is difficult. Several devices exist; all have their liabilities which have been well described by Karliczek[10]. Laser Doppler flowmetry, used in our study, requires good tissue contact without disturbing local blood flow; pulsatile blood flow is required, as well as repeated measurements making it time consuming. Secondly good prospective research is necessary, with precise documentation of which artery was ligated. Retrospective research in this field has a strong risk of bias, as exact description of the anatomy and its possible variations is not performed, therefore not documenting the real situation in the operative record. Ideally a randomized prospective study should be performed between high and low tie in case of rectal resection, documenting rate of AL, number of lymph nodes harvested, survival, and rate of nerve dysfunction. Unfortunately such a study would need a very high number of inclusions for these outcome measures, needing multicentric participation and important funding.

To compensate for the lack of randomized studies, prospective databases of all colorectal resections should be obligatory, with extent of resection (including resected vascularization), quantity of lymph nodes harvested and their location, survival, and postoperative complications documented. This is important to increase knowledge on quantity and location of metastatic lymph nodes per tumor location and size, extent of resection, and (potential ischemic) anastomotic complications.

COLORECTAL ANASTOMOSIS: TECHNIQUE AND HEALING

As the first paragraph of this chapter well describes, the creation of an anastomosis can have important consequences, and should not be taken extremely serious. The small bowel has a more

extensive vascularization and much lower leakage rate than colon and rectum anastomoses[11]. For many elements of surgery residents can refer to key note publications with evidence based conclusions and to internationally adopted guidelines. However, a wide variety of techniques of colorectal anastomosis exists and is taught. Preferences of individual surgeons are handed down from teacher to student without documentation of its exact properties and its incidence of AL. The systematic review of **Chapter 4** results in a conclusion based on experimental studies combined with clinical studies for a number of aspects: single layer continuous sutures by an inverting technique with slowly absorbable monofilament material seems preferable based on level 1b evidence. However for the other aspects of the suture technique, such as how far to place the suture from the anastomotical edge, the intersuture distance in relation to the distance to the edge, what layers to include in the bite, how high the tension on the suture should be, and through what configuration the anastomosis should be made, surgeons probably rely on their teachers and gut-feeling rather than on scientific evidence. There is no difference in leakage rate between handsewn and stapled anastomoses except in a meta-analysis selecting ileocolic anastomosis after colic cancer resection where a lower incidence of AL was found for stapled anastomosis[12]. Regarding microvascularisation of the anastomosis, in the hand-sewn anastomosis many surgeons would take great care not to tie sutures too tight in order to prevent local ischaemia and subsequent necrosis. Others are of contrary opinion and technique. Staples are thought to more induce local necrosis due to the small interstaple distance, however without clinical relevance as illustrated in studies comparing stapled to hand-sewn anastomoses[13]. The murine-experiment by Daams *et al*. shows no differences in AL nor histopathologic results between colon anastomoses with 5, 12 stitches, or an extreme quantity of stitches (>30 stitches) representing disturbance of microcirculation[14]. This might indicate that local ischaemia does not negatively influence colonic wound healing, as long as tight apposition is present.
We feel routine education regarding different existing techniques for the creation of colorectal anastomosis is obligatory during surgical residency, both handsewn and stapled, with the available information on outcome. Therefore detailed technique-related registration of anastomosis of all colorectal operations should be performed, to provide for clear information to residents regarding the quality of the different techniques they encounter during their career, to make the gesture of creation of an anastomosis prepared at best and of excellent familiarity.

A validated and effective adhesion barrier is a potentially ‘golden product’, as it would prevent many intestinal occlusions, infertility, and difficult reoperations with iatrogenic lesions. However, if an adhesions barrier is capable to adequately diminish fibrin deposition and thus the formation of adhesions, it is essential to investigate whether wound healing, also relying on fibrin deposition followed by collagen formation, is not impaired. A clinical study has emphasized this fragile balance

through results showing more AL in patients receiving an anti-adhesive film[15]. Therefore we feel all new adhesion barriers should be tested for potential impairment of colorectal healing before being used. The adhesion barrier tested in **Chapter 5** showed a trend towards more AL in the study group with a p-value of 0.08, therefore it needs additional studying, with larger groups of animals, before being used.

COLORECTAL ANASTOMOSIS: POSTOPERATIVE CARE

The large Rotterdam prospective APPEAL study, described in **Chapters 6, 7 and 9** showed 7.3% AL after colorectal resection (19 out of 259 patients). In two patients abscesses were diagnosed, 7 patients had peritonitis, and 9 patients were in sepsis. In 8 patients it was diagnosed by CT scanning, in 7 patients during laparotomy, and in 4 the diagnosis was made after faecal discharge from the drain. In two patients therapy consisted of placing a drain, in 3 antibiotics were given, 4 had a stoma for faecal diversion, 2 patients had re-anastomosis, and in 8 patients surgeons proceeded to an end-colostomy or Hartmann's intervention.

With current diagnostic methods the interval between construction of a colorectal anastomosis and diagnosis of leakage varies between 6 and 13 days in literature[16-18]. Since delay of diagnosis of AL is associated with higher mortality rates[19, 20], the most rapid detection of AL is needed. Wound fluid obtained at the anastomotic site is likely to contain bacteria and they are therefore a potential indicator for AL. Gram-negative Escherichia coli (E. coli) and gram-positive Enterococcus faecalis (E. faecalis) belong to the most common species of the colon[21, 22]. Using a culture to identify these bacteria is of little use, as the incubation period is 48h. Polymerase chain reaction (PCR) is another technique to identify these bacterial species that is much faster, allowing detection of both viable and non-viable bacteria, and less susceptible to contamination. We have shown in **Chapter 6** that measuring the presence of E. Coli in drain fluid by PCR the first 3 days is a valuable tool when searching for AL. Negative predicting value is excellent; positive predicting value however is lower due to many false positive tests in relation to the low number of positives (7.3% AL).

What might be practical consequences to these results? Positive screening PCR results should certainly lead to a higher suspicion of AL in daily follow up. Often in case of failure to thrive of a patient alertness is raised but without consequences. With a positive outcome of this PCR test immediate action should be undertaken (CT-scan with transanal contrast, explorative laparoscopy/-tomy) since a shorter interval between clinical suspicion and treatment of AL has been shown to be beneficial in terms of morbidity and mortality[20].

However the results of the study described above are based on drain fluid analysis, and the drain tube in colorectal surgery has now been largely abandoned. A Cochrane review concluded that routine drainage does not prevent complications as AL, wound infection and reintervention[23]. Only

in the Dutch TME trial (level IB evidence) the lack of a pelvic drain was an independent risk factor for anastomotic dehiscence, and reduced the need for surgical reintervention in patients with an anastomotic leak[24]. However, on reviewing the published work, most authors agree to use a pelvic drain only selectively in patients where there have been technical difficulties during surgery, or peritonitis due to perforation in emergency settings[25]. The purpose of this drainage can be prevention of accumulation of fluids in the pelvic or peritoneal cavity and permit early detection of anastomotic dehiscence by faecal or purulent discharge from the drain as proven in the APPEAL study in **Chapter 6**.

Once AL has occurred, what to do? Many possibilities exist: drainage of abscess/lavage of peritoneal cavity, repair of the anastomosis or contruction of a new anastomosis, adding a diverting ileostomy, breaking down the anastomosis and making an end-colostomy. Fraccalvieri *et al.* showed interesting results of an observational study of salvage versus breakdown of the anastomosis after AL, in favor of salvage regarding mortality, stoma reversal, and morbidity[26]. It is clear that non-randomization is a strong limitation of this study. Watson *et al.* showed good results for salvage of the anastomosis in case of a minor leak. In case of a major leak anastomoses were broken down, but none of the end-colostomies were restored[27]. Rickert *et al.* showed salvage of the anastomosis without a protective ileostomy frequently results in failure of the procedure, compared to with an ileostomy[28].

The theoretical cases of patients with AL that were presented to Dutch surgeons, asking for their treatment decisions (**Chapter 7**), show that more efforts are being made in young people to preserve the anastomosis, compared to >80 years ASA3 patients. Elderly people are an interesting patient category regarding this subject. It is known that older patients experience many problems taking care of a stoma at risk of losing their independence at home. Therefore anastomosis-sparing strategy can be even most beneficial in this patient-category considering the risk of never restoring continuity in case of end-colostomy. Randomized-controlled trials do not exist.

COLORECTAL ANASTOMOSIS: RISK FACTORS FOR LEAKAGE AND PREVENTION

An extensive list of publications regarding risk factors for AL exists, aiming to identify patients in whom extra care is necessary and zero risk should be taken. We know a defunctioning stoma results in a reduction of rate and mortality of AL[29, 30], largely proven in patients with a low anastomosis after rectum resection. However, there are important negative aspects associated with defunctioning stomas. Complications such a dehydration, parastomal skin irritation, difficulties in stoma-care, retraction or stenosis, granulomas, and parastomal hernia can diminish quality of life, especially in elderly patients. David *et al.* reviewed 6581 patients undergoing low anterior resection[31]. In 14.6% a temporary defunctioning stoma was created; in 25% of patients it was never reversed. The mean age in this group of non-reversal was 69 years, with significant more comorbidities. In the group of

patients in whom the stoma was temporary, mean duration to closure of the stoma was 207 days. Chow *et al.* conducted a review on morbidity after closure of defunctioning stomas[32]. They found 7.2% of mechanical ileus (2.5% reoperation rate), 1.4% AL, 5% wound infection, and 1.5% stoma site hernia. Den Dulk *et al.* conducted a prospective study on 927 low anterior resections[33]. In 57% of patients a defunctioning stoma was constructed, 19% of stomas were not reversed. Mean time to closure of the stoma was 4.1 months. The risk factor for not closing the stoma was the occurring of postoperative complications.

A balance must be found between the benefit of a defunctioning stoma in terms of reduction of morbidity and mortality of AL, and the diminished quality of life in case of complications or non-reversal of the stoma. Therefore it is important to identify major risk factors for AL, giving the possibility to make risk calculations per patient. Surgeons are bad at predicting anastomotic leakage[34], therefore we have to go towards a risk calculation per patient, not leaving the construction of a protective stoma to intra-operative gut feeling of the surgeon.

Chapters 8 and **9** contribute to the identification of two new risk factors for AL.

The first risk factor is represented by corticosteroids, whose influence on intestinal wound healing remained unclear with 4 studies showing a negative influence on septic complications after colorectal surgery[35-38], and 9 studies finding no influence[39-47]. The prospective study presented in **Chapter 8** demonstrates an increased risk for AL in patients taking corticosteroids, even for short-term duration of corticosteroids peri-operatively. Corticosteroids given peri-operatively, as during the APPEAL study according to the Dutch guideline for prevention of postoperative pulmonary complications in COPD patients, should be reduced to minimal use in case of absolute necessity. This is especially valid since in international literature no guideline recommends the use of corticosteroids preoperatively to diminish postoperative pulmonary complications.

The second risk factor for AL we identified, is represented by the degree of atherosclerosis in the aorto-iliac trajectory. For this retrospective study described in **Chapter 9**, preoperative CT scans were used and analyzed with a program permitting calculation of intra-luminal calcium score and mass in the aorto-iliac trajectory. This tool offers the possibility to give exact degree of state of mesenteric vascularization instead of the usual broad knowledge that “it is a patient with vascular comorbidity”. With an aging population this becomes of increasing importance: in patients with fragile balance of arterial flow towards the colon and rectum a high risk of anastomotic leakage is suspected. Since almost all patients have had a preoperative CT scan, it is a very easy tool of preoperative risk calculation for impaired anastomotic healing. However any new scientific finding should always be confirmed in a prospective study. This will be easier when calcium score calculation will be specially developed for visceral vascularization and when different brands of CT scanners will be comparable,

this not being the case yet. A prospective validation needs to be done, and the degree of aorto-iliac atherosclerosis should be put in a database together with patient characteristics, anastomotic characteristics, harvested lymph nodes, extent of resection, and postoperative complications and survival, to further define its prognostic value.

Prevention of complications is something every surgeon wishes for his patients. A tool for prevention of leakage of bowel content into the abdominal cavity, therefore significantly lowering the morbidity of AL, would be a reassurance for surgeon and patient, significantly lowering hospital costs and mortality. In other fields of surgery sealants have been tested clinically, such as for (cardio)vascular anastomoses with positive results[48-50], in pancreatic surgery where sealants have not shown benefit on pancreatic leaks[51, 52], in thoracic surgery where both positive and negative results have been published regarding diminishing air leaks after pulmonary resection[53-57], and one level 1b study in bariatric surgery where fibrin sealing of staple lines has not shown superior[58]. The study **in Chapter 10** shows the results of 6 sealants applied in a mouse model for anastomotic leakage. This study shows grim results: none of the sealants were able to reduce rates of AL. Furthermore, use of the majority of sealants resulted in failure to thrive, increased rates of ileus, and higher death rates.
Prevention of AL is a worthy research-topic in colorectal surgery considering the potential benefits in morbidity and mortality. The negative results of this study emphasize the need of systemic research, investigating histologic tissue reaction of the bowel to different sealants, the capacity of sealants to form a watertight barrier, their time of degradation, and their results in large animal models for AL, before being used clinically.

OPTIMIZING COLORECTAL LAPAROSCOPY

Nowadays an increasing percentage of all colorectal resections is performed through laparoscopic surgery[59, 60]. Vision of the surgical field changes with laparoscopy, and correct recognition of anatomy such as in laparotomy needs training. Combining cognitive and motor skills with anatomical recognition is challenging for the resident, but nonetheless essential for a successful procedure. Anatomy courses during residency are gaining more importance, as it is crucial for young residents to have an excellent knowledge of 3D anatomy of the surgical field[61]. Since a large part of interventions are performed by laparoscopy nowadays, we realized that open anatomy-teaching in human anatomical specimen is clearly no longer sufficient. We feel training ‘before the job’ of laparoscopic anatomical skills permits more time-consuming and detailed anatomic exploration. The training model presented in **Chapter 11**, developed on a human specimen with a new embalming technique, makes it possible to practice laparoscopic skills as well as laparoscopic surgical anatomy for

laparoscopic colorectal surgery. We feel this training is essential and obligatory for young residents in colorectal surgery.

As addressed in the introduction of this thesis, mechanical bowel preparation (MBP) has been abandoned in open colorectal surgery, since it does not results in less AL or wound infections[62], but questions have been raised on the effect of MBP on the volume of the bowel, and thus on exposure, during laparoscopic interventions. To evaluate the current practice among Dutch laparoscopic gastrointestinal surgeons we performed a questionnaire survey in **Chapter 12**. The results of this questionnaire show that bowel preparation is still frequently used in laparoscopic colorectal procedures in the Netherlands, mostly in rectal resection. Sixteen per cent of respondents prescribe MBP prior to surgery in order to improve surgical field exposure. Almost a third of the respondents felt MBP might influence the diameter of the small bowel and exposure; this can be placed in either a positive or a negative perspective since some feel MBP results in an emptied bowel and some in a bowel filled with liquid or gas bowel contents[63]. The effect of MBP on the volume of the bowel and its competition with the insufflated CO^2 influencing exposure might play an important role in the course of the laparoscopic intervention itself, therefore we conducted the pig study described in **Chapter 13**. Amount of pneumoperitoneum was compared between pigs having received MBP, and pigs without MBP. Pneumoperitoneum was calculated at different intra-abdominal pressures through images made by CT scanning. Results show a significant increase in pneumoperitoneum volume in the group receiving MBP pre-operatively. This gain in pneumoperitoneum volume of 500ml CO_2 is independent of the pressure of pneumoperitoneum, and represents a relative increase of 43% at 5 mmHg, 21% at 10 mmHg, and 18% at 15 mmHg. Consequently, with pre-operative MBP the same volume of pneumoperitoneum can be obtained at lower intra-abdominal pressures.
However, it is largely accepted that MBP is patient unfriendly. In a blinded, randomized controlled trial in gynaecologic laparoscopic surgery for benign disease, a 7-day low fiber diet gave as good exposure as MBP (scored by the surgeon) but was far better tolerated [64]. This raises the question of the necessity of *mechanical* bowel preparation, however the increased volume of pneumoperitoneum observed in this study after MBP could represent an important benefit in technically challenging intestinal and non-intestinal laparoscopic surgery.

CONCLUSION

Several factors remain an issue in the field of colorectal surgery, including extent of resection, anastomotic healing, risk factors for anastomotic leakage, postoperative detection and treatment of anastomotic leakage, and amelioration of laparoscopic surgery. These factors have been addressed in

this thesis, aiming for critical revision of dogmas and for amelioration of current management of colorectal disease.

To improve knowledge in colorectal surgery we urgently need standardization of techniques, especially with regard to anastomosis, structured postoperative monitoring, large databases, combining patient-factors with technique, complications, and outcome (histopathological results and survival in case of malignancy). Increasing our knowledge with these results will continue improving quality in colorectal surgery.

REFERENCES

1. Nelson H, Petrelli N, Carlin A, et al. Guidelines 2000 for colon and rectal cancer surgery. J Natl Cancer Inst 2001; 93(8):583-96.
2. Sternberg A. Carcinoma of the colon: margins of resection. J Surg Oncol 2008; 98(8):603-6.
3. Cahill RA, Leroy J, Marescaux J. Could lymphatic mapping and sentinel node biopsy provide oncological providence for local resectional techniques for colon cancer? A review of the literature. BMC Surg 2008; 8:17.
4. Park IJ, Choi GS, Kang BM, et al. Lymph node metastasis patterns in right-sided colon cancers: is segmental resection of these tumors oncologically safe? Ann Surg Oncol 2009; 16(6):1501-6.
5. Rouffet F, Hay JM, Vacher B, et al. Curative resection for left colonic carcinoma: hemicolectomy vs. segmental colectomy. A prospective, controlled, multicenter trial. French Association for Surgical Research. Dis Colon Rectum 1994; 37(7):651-9.
6. Miles WE. A method of performing abdomino-perineal excision for carcinoma of the rectum and of the terminal portion of the pelvic colon (1908). CA Cancer J Clin 1971; 21(6):361-4.
7. Moynihan BG. The surgical treatment of cancer of the sigmoid flexure and rectum. Surg Gynecol Obstet 1908:463.
8. Lange MM, Buunen M, van de Velde CJ, Lange JF. Level of arterial ligation in rectal cancer surgery: low tie preferred over high tie. A review. Dis Colon Rectum 2008; 51(7):1139-45.
9. Corder AP, Karanjia ND, Williams JD, Heald RJ. Flush aortic tie versus selective preservation of the ascending left colic artery in low anterior resection for rectal carcinoma. Br J Surg 1992; 79(7):680-2.
10. Karliczek A, Benaron DA, Baas PC, et al. Intraoperative assessment of microperfusion with visible light spectroscopy in esophageal and colorectal anastomoses. Eur Surg Res 2008; 41(3):303-11.
11. Schiesser M, Guber J, Wildi S, et al. Utility of routine versus selective upper gastrointestinal series to detect anastomotic leaks after laparoscopic gastric bypass. Obes Surg 2011; 21(8):1238-42.
12. Choy PY, Bissett IP, Docherty JG, et al. Stapled versus handsewn methods for ileocolic anastomoses. Cochrane Database Syst Rev 2011(9):CD004320.
13. Lustosa SA, Matos D, Atallah AN, Castro AA. Stapled versus handsewn methods for colorectal anastomosis surgery. Cochrane Database Syst Rev 2001(3):CD003144.
14. Daams F, Monkhorst K, van den Broek J, et al. Local ischaemia does not influence anastomotic healing: an experimental study. Eur Surg Res 2013; 50(1):24-31.
15. Beck DE, Cohen Z, Fleshman JW, et al. A prospective, randomized, multicenter, controlled study of the safety of Seprafilm adhesion barrier in abdominopelvic surgery of the intestine. Dis Colon Rectum 2003; 46(10):1310-9.
16. Buchs NC, Gervaz P, Secic M, et al. Incidence, consequences, and risk factors for anastomotic dehiscence after colorectal surgery: a prospective monocentric study. Int J Colorectal Dis 2008; 23(3):265-70.
17. Hyman N, Manchester TL, Osler T, et al. Anastomotic leaks after intestinal anastomosis: it's later than you think. Ann Surg 2007; 245(2):254-8.
18. Bellows CF, Webber LS, Albo D, et al. Early predictors of anastomotic leaks after colectomy. Tech Coloproctol 2009; 13(1):41-7.
19. Alves A, Panis Y, Pocard M, et al. Management of anastomotic leakage after nondiverted large bowel resection. J Am Coll Surg 1999; 189(6):554-9.
20. den Dulk M, Noter SL, Hendriks ER, et al. Improved diagnosis and treatment of anastomotic leakage after colorectal surgery. Eur J Surg Oncol 2009; 35(4):420-6.
21. Marteau P, Pochart P, Dore J, et al. Comparative study of bacterial groups within the human cecal and fecal microbiota. Appl Environ Microbiol 2001; 67(10):4939-42.
22. Balamurugan R, Rajendiran E, George S, et al. Real-time polymerase chain reaction quantification of specific butyrate-producing bacteria, Desulfovibrio and Enterococcus faecalis in the feces of patients with colorectal cancer. J Gastroenterol Hepatol 2008; 23(8 Pt 1):1298-303.

23. Jesus EC, Karliczek A, Matos D, et al. Prophylactic anastomotic drainage for colorectal surgery. Cochrane Database Syst Rev 2004(4):CD002100.
24. Peeters KC, Tollenaar RA, Marijnen CA, et al. Risk factors for anastomotic failure after total mesorectal excision of rectal cancer. Br J Surg 2005; 92(2):211-6.
25. Tsujinaka S, Kawamura YJ, Konishi F, et al. Pelvic drainage for anterior resection revisited: use of drains in anastomotic leaks. ANZ J Surg 2008; 78(6):461-5.
26. Fraccalvieri D, Biondo S, Saez J, et al. Management of colorectal anastomotic leakage: differences between salvage and anastomotic takedown. Am J Surg 2012; 204(5):671-6.
27. Watson AJ, Krukowski ZH, Munro A. Salvage of large bowel anastomotic leaks. Br J Surg 1999; 86(4):499-500.
28. Rickert A, Willeke F, Kienle P, Post S. Management and outcome of anastomotic leakage after colonic surgery. Colorectal Dis 2010; 12(10 Online):e216-23.
29. Montedori A, Cirocchi R, Farinella E, et al. Covering ileo- or colostomy in anterior resection for rectal carcinoma. Cochrane Database Syst Rev 2010(5):CD006878.
30. Matthiessen P, Hallbook O, Rutegard J, et al. Defunctioning stoma reduces symptomatic anastomotic leakage after low anterior resection of the rectum for cancer: a randomized multicenter trial. Ann Surg 2007; 246(2):207-14.
31. David GG, Slavin JP, Willmott S, et al. Loop ileostomy following anterior resection: is it really temporary? Colorectal Dis 2010; 12(5):428-32.
32. Chow A, Tilney HS, Paraskeva P, et al. The morbidity surrounding reversal of defunctioning ileostomies: a systematic review of 48 studies including 6,107 cases. Int J Colorectal Dis 2009; 24(6):711-23.
33. den Dulk M, Smit M, Peeters KC, 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.
34. Karliczek A, Harlaar NJ, Zeebregts CJ, et al. Surgeons lack predictive accuracy for anastomotic leakage in gastrointestinal surgery. Int J Colorectal Dis 2009; 24(5):569-76.
35. Golub R, Golub RW, Cantu R, Jr., Stein HD. A multivariate analysis of factors contributing to leakage of intestinal anastomoses. J Am Coll Surg 1997; 184(4):364-72.
36. Konishi T, Watanabe T, Kishimoto J, Nagawa H. Risk factors for anastomotic leakage after surgery for colorectal cancer: results of prospective surveillance. J Am Coll Surg 2006; 202(3):439-44.
37. Post S, Betzler M, von Ditfurth B, et al. Risks of intestinal anastomoses in Crohn's disease. Ann Surg 1991; 213(1):37-42.
38. Yamamoto T, Allan RN, Keighley MR. Risk factors for intra-abdominal sepsis after surgery in Crohn's disease. Dis Colon Rectum 2000; 43(8):1141-5.
39. Allsop JR, Lee EC. Factors which influenced postoperative complications in patients with ulcerative colitis or Crohn's disease of the colon on corticosteroids. Gut 1978; 19(8):729-34.
40. Bruewer M, Utech M, Rijcken EJ, et al. Preoperative steroid administration: effect on morbidity among patients undergoing intestinal bowel resection for Crohns disease. World J Surg 2003; 27(12):1306-10.
41. Colombel JF, Loftus EV, Jr., Tremaine WJ, et al. Early postoperative complications are not increased in patients with Crohn's disease treated perioperatively with infliximab or immunosuppressive therapy. Am J Gastroenterol 2004; 99(5):878-83.
42. Heimann TM, Greenstein AJ, Mechanic L, Aufses AH, Jr. Early complications following surgical treatment for Crohn's disease. Ann Surg 1985; 201(4):494-8.
43. Jex RK, van Heerden JA, Wolff BG, et al. Gastrointestinal anastomoses. Factors affecting early complications. Ann Surg 1987; 206(2):138-41.
44. Knudsen L, Christiansen L, Jarnum S. Early complications in patients previously treated with corticosteroids. Scand J Gastroenterol Suppl 1976; 37:123-8.
45. Lipska MA, Bissett IP, Parry BR, Merrie AE. Anastomotic leakage after lower gastrointestinal anastomosis: men are at a higher risk. ANZ J Surg 2006; 76(7):579-85.

46. Tresallet C, Royer B, Godiris-Petit G, Menegaux F. Effect of systemic corticosteroids on elective left-sided colorectal resection with colorectal anastomosis. Am J Surg 2008; 195(4):447-51.
47. Vignali A, Fazio VW, Lavery IC, et al. Factors associated with the occurrence of leaks in stapled rectal anastomoses: a review of 1,014 patients. J Am Coll Surg 1997; 185(2):105-13.
48. DeAnda A, Jr., Elefteriades JA, Hasaniya NW, et al. Improving outcomes through the use of surgical sealants for anastomotic sealing during cardiovascular surgery. J Card Surg 2009; 24(3):325-33.
49. Schenk WG, 3rd, Burks SG, Gagne PJ, et al. Fibrin sealant improves hemostasis in peripheral vascular surgery: a randomized prospective trial. Ann Surg 2003; 237(6):871-6; discussion 876.
50. Shireman PK, Greisler HP. Fibrin sealant in vascular surgery: a review. J Long Term Eff Med Implants 1998; 8(2):117-32.
51. Fingerhut A, Veyrie N, Ata T, et al. Use of sealants in pancreatic surgery: critical appraisal of the literature. Dig Surg 2009; 26(1):7-14.
52. Schulick RD, Yoshimura K. Stents, glue, etc.: is anything proven to help prevent pancreatic leaks/fistulae? J Gastrointest Surg 2009; 13(7):1184-6.
53. D'Andrilli A, Andreetti C, Ibrahim M, et al. A prospective randomized study to assess the efficacy of a surgical sealant to treat air leaks in lung surgery. Eur J Cardiothorac Surg 2009; 35(5):817-20; discussion 820-1.
54. De Leyn P, Muller MR, Oosterhuis JW, et al. Prospective European multicenter randomized trial of PleuraSeal for control of air leaks after elective pulmonary resection. J Thorac Cardiovasc Surg 2011; 141(4):881-7.
55. Gonfiotti A, Santini PF, Jaus M, et al. Safety and effectiveness of a new fibrin pleural air leak sealant: a multicenter, controlled, prospective, parallel-group, randomized clinical trial. Ann Thorac Surg 2011; 92(4):1217-24; discussion 1224-5.
56. Malapert G, Hanna HA, Pages PB, Bernard A. Surgical sealant for the prevention of prolonged air leak after lung resection: meta-analysis. Ann Thorac Surg 2010; 90(6):1779-85.
57. Tan C, Utley M, Paschalides C, et al. A prospective randomized controlled study to assess the effectiveness of CoSeal(R) to seal air leaks in lung surgery. Eur J Cardiothorac Surg 2011; 40(2):304-8.
58. Silecchia G, Boru CE, Mouiel J, et al. The use of fibrin sealant to prevent major complications following laparoscopic gastric bypass: results of a multicenter, randomized trial. Surg Endosc 2008; 22(11):2492-7.
59. Buchanan GN, Malik A, Parvaiz A, et al. Laparoscopic resection for colorectal cancer. Br J Surg 2008; 95(7):893-902.
60. Lim SB, Choi HS, Jeong SY, Park JG. Feasibility of laparoscopic techniques as the surgical approach of choice for primary colorectal cancer: an analysis of 570 consecutive cases. Surg Endosc 2008; 22(12):2588-95.
61. Mattingly MW, Dean RE, Carrow R, Kareti R. Problem-based anatomy for surgical residents. Curr Surg 2000; 57(4):377-380.
62. Guenaga KK, Matos D, Wille-Jorgensen P. Mechanical bowel preparation for elective colorectal surgery. Cochrane Database Syst Rev 2009(1):CD001544.
63. Mahajna A, Krausz M, Rosin D, et al. Bowel preparation is associated with spillage of bowel contents in colorectal surgery. Dis Colon Rectum 2005; 48(8):1626-31.
64. Lijoi D, Ferrero S, Mistrangelo E, et al. Bowel preparation before laparoscopic gynaecological surgery in benign conditions using a 1-week low fibre diet: a surgeon blind, randomized and controlled trial. Arch Gynecol Obstet 2009; 280(5):713-8.

Chapter 15

Nederlandse samenvatting

Colorectale anatomie en type colorectale resectie

Hoofdstuk 2 geeft een overzicht in tekst en beeld van de anatomie van colon en rectum, met aandacht voor de chirurgische relevantie van de anatomische structuren. **Hoofdstuk 3** beschrijft de resultaten van een klinische studie waarin de perfusie van het colon descendens is gemeten na resectie voor rectumcarcinoom. Twee technieken zijn met elkaar vergeleken: peroperatieve ligatie van de a. colica sinistra (high tie) versus ligatie van de a. rectalis superior (low tie). Resultaten laten zien dat de perfusie van het resterende deel colon descendens beter is na low tie. Of dit klinisch vermindering geeft van postoperatieve complicaties is in deze studie niet onderzocht.

Colorectale anastomose: techniek en naadgenezing

Hoofdstuk 4 geeft een systematisch overzicht van de verschillende technieken voor het aanleggen van een colorectale naad, aangevuld met de beschikbare klinische en experimentele resultaten met betrekking tot lekkage. Dit overzicht laat zien dat een eenlagige voortlopende hechting, inverterend met langzaam-absorberend hechtmateriaal, de voorkeur heeft met niveau 1b evidence. Andere aspecten van de techniek, zoals de afstand tussen hechting en wondrand van de naad, afstand tussen de hechtingen, welke lagen van de darm mee te nemen in de hechting, hoe hoog de spanning op de hechtdraad, en welke configuratie de naad moet hebben, zijn daarentegen onderbelicht in de wetenschappelijke literatuur. Er is geen verschil tussen handgelegde en gestapelde naden met betrekking tot naadlekkage, behalve in een meta-analyse geselecteerd op ileocolische naden na resectie voor coloncarcinoom, waarbij een lagere incidence naadlekkage gevonden werd voor gestapelde naden.

Klinische studies naar adhesiebarrières hebben laten zien dat het gevaar bestaat van een gestoorde naadgenezing. In een gerandomiseerde studie naar Seprafilm® ontstond meer naadlekkage in de patiëntengroep bij wie de adhesie-remmer gebruikt werd in in vergelijking met controlegroep. Om die reden vermeldt **Hoofdstuk 5** de resultaten zien van een nieuwe adhesie-remmer, in een model voor naadgenezing in de dikke darm van ratten. Er was geen significant verschil in naadlekkage tussen de controlegroep en de anti-adhesiegroep, weliswaar met een p-waarde van 0.08, hetgeen het belang toont van meer onderzoek voordat klinische toepassing aan de orde kan zijn.

Colorectale anastomose: postoperatieve zorg

De gemiddelde tijdsduur tussen het aanleggen van een colorectale naad, en het diagnosticeren van naadlekkage is 6 tot 13 dagen. Deze lange tijdsduur gaat gepaard met een al ernstig zieke patiënt ten tijde van de diagnose, en hoge morbiditeit en mortaliteit. **Hoofdstuk 6** laat een nieuwe techniek zien om sneller naadlekkage aan te tonen. Deze techniek is gebaseerd op het met de PCR-techniek aantonen van Escherichia Coli of Enterococcus Faecalis in wondvocht, afgenomen via een tijdens de

operatie intra-abdominaal geplaatste drain. De PCR techniek toont de aanwezigheid van bacteriën binnen enkele uren aan, en niet na pas enkele dagen zoals het geval bij de klassieke kweekmethode die tot nu toe gebruikt wordt. De prospectieve klinische studie in **Hoofdstuk 6** toont aan dat de aanwezigheid van E. Coli in drainvocht gedurende de 3 eerste opeenvolgende dagen na de operatie een verhoogd risico op naadlekkage aangeeft. Deze PCR-methode biedt de kans naadlekkage in een vroegere fase op te sporen, zodat patiënten in minder zieke toestand voor naadlekkage behandeld kunnen worden.

Hoofdstuk 7 beschrijft voor welke behandelplannen voor naadlekkage door Nederlandse chirurgen gekozen wordt. Een enquête gebaseerd op verschillende casus van naadlekkage laat zien dat een aantal chirurgen meent dat een anastomose-sparende behandeling in geval van naadlekkage succesvol kan zijn, vaker in het geval van naden gelegen onder het promontorium (50%) dan er boven (27%). Met betrekking tot patiënten boven de 80 jaar met ASA3 comorbiditeit is het percentage chirurgen dat gelooft in een anastomose-sparende techniek veel kleiner.

<u>Colorectale anastomose: risicofactoren naadlekkage en preventie</u>

Hoofdstuk 8 en 9 beschrijven twee risicofactoren voor naadlekkage. **Hoofdstuk 8** vermeldt de analyse van 259 patiënten die een colorectale resectie ondergaan hebben. In deze analyse kwam naar voren dat bij patiënten die corticosteroïden gebruiken vaker naadlekkage optreedt. Gedurende deze studie kregen patiënten met instabiele COPD een corticosteroïden-schema peroperatief, ter voorkomen van postoperatieve pulmonale complicaties; ook deze patiëntengroep had meer risico op naadlekkage.

Hoofdstuk 9 laat zien dat de mate van calcificaties in het aorto-iliacale arteriële traject het risico op naadlekkage verhoogt. In deze retrospectieve studie zijn de calcificaties gemeten met behulp van pre-operatief gemaakt CT scans. Deze risicofactor zou dus gemakkelijk te bepalen zijn bij alle patiënten die een abdominale CT-scan ondergaan hebben voorafgaand aan een colorectale resectie.

In het kader van preventie zijn 6 verschillende sealants getest in de studie weergegeven in **Hoofdstuk 10**. Deze zijn rondom de naad aangebracht in een muismodel voor naadlekkage. Geen van de sealants verminderde het risico op naadlekkage, daarentegen werden andere complicaties zoals ileus wel vaak waargenomen. Het klinisch toepassen van sealants ter preventie van naadlekkage is dus niet geschikt; meer experimenteel onderzoek naar een adequate sealant moet uitgevoerd worden.

Optimaliseren van colorectale laparoscopie

Met behulp van de nieuwe balsemingmethode Anubifix^{TM} is een trainingsmodel gemaakt waarin laparoscopie uitgevoerd kan worden, waarbij de anatomie relevant voor colorectale operaties aangekleurd is (**Hoofdstuk 11**). In **Hoofdstuk 12** wordt op basis van een Nederlandse enquête beschreven hoe vaak en waarom mechanische darmvoorbereiding gebruikt wordt binnen de laparoscopische colorectale chirurgie. In **Hoofdstuk 13** wordt de hypothese getoetst dat mechanische darmvoorbereiding het volumen darminhoud vermindert, en hierdoor de werkruimte tijdens laparoscopie verhoogt. Deze hypothese wordt bevestigd door middel van een studie waarbij de helft van de varkens darmvoorbereiding kreeg. Na het aanleggen van een pneumoperitoneum werd met behulp van een CT-scan de inhoud van het pneumoperitoneum bepaald, waarbij deze significant hoger (500ml CO_2meer) was in de groep met mechanische darmvoorbereiding.

Chapter 16

List of publications

Acknowledgements

PhD portfolio

Curriculum Vitae

LIST OF PUBLICATIONS

1. **Acute phase proteins in drain fluid: a new screening tool for colorectal anastomotic leakage?**
   Komen NA, Slieker JC, Willemsen P, Mannaerts G, Pattyn P, de Wilt H, van der Harst E, de Rijke Y, Murawska M, Jeekel H, Lange JF
   The American Journal of Surgery, in press

2. **Chain Reaction for Enterococcus faecalis in drain fluid: the first screening test for symptomatic colorectal anastomotic leakage.**
   Komen NA, Slieker JC, Willemsen P, Mannaerts G, Pattyn P, Karsten T, de Wilt H, van der Harst E, van Leeuwen W, Decaestecker C, Jeekel H, Lange JF
   International Journal of Colorectal Disease, in press

3. **Prevention of leakage by sealing colon anastomosis: experimental study in a mouse model**
   Slieker JC, Vakalopoulos KA, Komen NA, Jeekel J, Lange JF
   Journal of Surgical Research. 2013 Oct; 184 (2): 819-824

4. **Local ischemia does not influence anastomotic healing: an experimental study**
   Daams F, Monkhorst K, van den Broek J, Slieker JC, Jeekel J, Lange JF
   European Surgical Reseach. 2013; 50(1): 24-31

5. **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
   Dig Surg. 2012; 29(6): 516-521

6. **Systematic review of the technique of colorectal anastomosis**
   Slieker JC, Daams F, Mulder IM, Jeekel J, Lange JF
   JAMA Surgery. 2013 Feb; 148(2): 190-201

7. **Optimizing working space in laparoscopy: measuring the effect of mechanical bowel preparation in a porcine model**
   Slieker JC, Vlot J, Wijnen R, Lange JF, Bax KN
   Surgical Endoscopy. 2013 Jun; 27(6): 1980-1985

8. E**ffects of a new anti-adhesion polyvinyl alcohol gel on healing of colon anastomoses in rats**
   Slieker JC, Ditzel M, Harlaar JJ, Mulder IM, Deerenberg EB, Bastiaansen-Jenniskens YM, Kleinrensink GJ, Jeekel J, Lange JF
   Surgical Infections. 2012 Dec; 13(6): 396-400

9. **Polyvinyl alcohol hydrogel decreases formation of adhesions in a rat model of peritonitis**
   Deerenberg EB, Mulder IM, Ditzel M, Slieker JC, Bemelman WA, Jeekel J, Lange JF
   Surgical Infections. 2012 Oct; 13(5); 321-325

10. **The influence of mechanical bowel preparation in elective colorectal surgery for diverticulitis**
    Van't Sant HP, Slieker JC, Hop WC, Weidema WF, Lange JF, Vermeulen J, Contant CM
    Techniques in Coloproctology. 2012 Aug; 16(4): 309-314

11. **Significant contribution of the portal vein to blood flow through the common bile duct**
Slieker JC, Farid WR, van Eijck CH, Lange JF, van Bommel J, Metselaar HJ, de Jonge J, Kazemier G
Annals of Surgery. 2012 Mar; 255(3): 523-527

12. **Training in laparoscopic colorectal surgery: a new educational model using specially embalmed human anatomical specimen**
Slieker JC, Theeuwes HP, van Rooijen GL, Lange JF, Kleinrensink GJ
Surgical Endoscopy. 2012 Aug; 26(8): 2189-2194

13. **Long-term and perioperative corticosteroids in anastomotic leakage: a prospective study of 259 left-sided colorectal anastomoses**
Slieker JC, Komen N, Mannaerts GH, Kartsen TM, Willemsen P, Murawska M, Jeekel J, Lange JF
Archives of Surgery. 2012 May; 147(5): 447-452

14. **Bowel preparation prior to laparoscopic colorectal resection: what is the current practice?**
Slieker JC, Van't Sant HP, Vlot J, Daams F, Jansen FW, Lange JF
Journal of Laparoendoscopic & Advanced Surgical Techniques. 2011 Dec; 21(10): 899-903

15. **High tie versus low tie in rectal surgery: comparison of anastomotic perfusion**
Komen N, Slieker JC, de Kort P, de Wilt JH, van der Harst E, Coene PP, Gosselink MP, Tetteroo G, de Graaf E, van Beek T, den Toom R, van Bockel W, Verhoef C, Lange JF
International Journal of Colorectal Disease. 2011 Aug; 26(8): 1075-1078

16. **The importance of portal veinous blood flow in ischemic-type biliairy lesions after liver transplantation**
Farid WR, de Jonge J, Slieker JC, Zondervan PE, Thomeer MG, Metselaar HJ, de Bruin RW, Kazemier G
American Journal of Transplantation. 2011 Apr; 11(4): 857-862

17. **Calcium score: a new risk factor for colorectal anastomotic leakage**
Komen N, Klitsie P, Dijk J, Slieker JC, Hermans J, Havenga K, Oudkerk M, Weyler J, Kleinrensink GJ, Lange JF
American Journal of Surgery. 2011 Jun; 201(6): 759-765

18. **The ability of a novel algorithm for automatic estimation of the respiratory variations in arterial pulse pressure to monitor fluid responsiveness in the operating room**
Cannesson M, Slieker JC, Desebbe O, Bauer C, Chiari P, Hénaine R, Lehot JJ
Anesthesia and Analgesia. 2008 Apr; 106(4): 1195-1200

19. **Predicition of fluid responsiveness using respiratory variations in left ventricular stroke area by transoesophageal echocardiographic automated border detection in mechanically ventilated patients**
Cannesson M, Slieker JC, Desebbe O, Farhat F, Bastien O, Lehot JJ
Critical Care. 2006; 10(6): R171

PHD PORTFOLIO

Summary PhD training and teaching

PhD period: November 2008 – September 2010

Promotor: prof. Dr J.F. Lange

1. PhD training	Year	Workload (ECTS)
General courses		
Animal Experimental Research	2008	5.7
Classical Methods for Data-analysis	2009	5.7
Good Clinical Practice	2008	1.5
Presentations and conferences		
Chirurgendagen NVVH, Veldhoven, the Netherlands	2009 + 2010	
Najaarsvergadeing NVVH, the Netherlands	2009	
Voorjaarsdagen NVGE/NVGIC, the Netherlands	2009	
SEOHS, the Netherlands	2009 + 2010	
RICH congress, the Netherlands	2008-2010	
Hernia congress EHS/AHS, Germany	2009	
ESSR, Switzerland	2010	
2. Teaching		
Supervision		
Master Thesis Delft University of Technology	2009/2010	5.0
4th year research thesis Erasmus University Medical Center Rdam	2008	5.0
4th year research thesis (Erasmus University Medical Center Rdam	2010	2.0
Lectures		
4th-year students Delft University of Technology	2009	
4th-year students Erasmus University Medical Center Rotterdam	2009+2010	
First Aid Examinations	2008+2009	

CURRICULUM VITAE

Juliette Caroline Slieker was born in Sèvres, France, on January 21st 1985. In 2002 she finished secondary school (Nehalennia Stedelijke Scholengemeenschap Middelburg) and started her medical training at the Erasmus University Medical Center Rotterdam. Clinical rotations were conducted in Lyon (France), Zomba (Malawi), and Lausanne (Switzerland). Her medical degree was obtained cum laude in 2008, after which she joined the REPAIR research group at the Department of Surgery of the Erasmus Medical Centre Rotterdam, supervised by professors J.F. Lange, J. Jeekel, and G.J. Kleinrensink. She performed clinical and experimental research during two years, which has resulted in this thesis.

In October 2010 she started her surgical training at the Centre Hospitalier Universitaire Vaudois in Lausanne, Switzerland.