Functional outcome after pouch surgery in patients with ulcerative colitis or rectal cancer

Functioneel resultaat na pouch chirurgie bij patiënten met colitis ulcerosa of een rectumcarcinoom

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Voor Manon, Belya en Frits

Functional outcome after pouch surgery in patients with ulcerative colitis or rectal cancer

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CHAPTER 1

General introduction and outline of the thesis

INTRODUCTION

Loss of normal bowel control has a devastating effect on quality of life. Psychological implications and social restrictions with impaired continence have been extensively documented. Therefore restoration of intestinal continuity after rectal resection with acceptable postoperative morbidity is a challenge to surgeons. This thesis will focus on the functional outcome after sphincter-preserving procedures in the treatment of ulcerative colitis and rectal cancer. Especially, continence mechanisms after colonic pouch construction and the role of gut flora in the etiology of pouchitis after ileal pouch surgery have been investigated.

ILEAL POUCH–ANAL ANASTOMOSIS AND POUCHITIS

Ulcerative colitis (UC) is common in The Netherlands, affecting at least 25.000 inhabitants. The incidence of UC appears to be increasing. Approximately 30% of patients with UC require surgical treatment because of medically refractory disease, dysplasia or cancer. In the past, the prospect of a permanent stoma remained unpalatable to many patients. In 1947, Ravitch and Sabiston, were the first to describe the straight ileoanal anastomosis after proctocolectomy.[1] However, functional results were poor. Later, Parks and Nicholls developed the ileal pouch-anal anastomosis (IPAA) following transanal mucosectomy (Figure 1).[2] The ileal reservoir was anastomosed to the dentate line using a transanal suturing technique. Long-term functional results were generally gratifying since an acceptable defecation frequency and degree of incontinence could be obtained in most patients. Nowadays, this technique is considered the preferred surgical option for the treatment of UC. The advent of stapling instruments enabled the construction of a double-stapled IPAA, without transanal mucosectomy. Despite technical developments and evolution over time, the IPAA procedure is still associated with quite a number of postoperative complications and significant functional disturbances, due to pouchitis and impaired continence. A recent meta-analysis of 43 observational studies comprising 9317 patients by Hueting *et al.* shows the incidence of the different complications and functional disturbances after a median follow-up period of 37 months (Table 1).[3]

In this meta-analysis, pouchitis is the most common complication with a pooled incidence of 18.8%. The cumulative risk of developing pouchitis after construction of an IPAA tends to increase with prolonged follow-up, between 36 and 51% at 5 years.[4-7] Approximately two-third of these patients experience only a few episodes, whereas the others encounter multiple recurrent episodes of pouchitis, with approximately 5% of patients developing chronic pouchitis.[8]

Clinical symptoms of pouchitis are increased stool frequency, urgency, abdominal cramping, and pelvic discomfort.[9,10] A clinical diagnosis of pouchitis should be confirmed by endoscopy and mucosal biopsy of the pouch.[11-13] Endoscopic

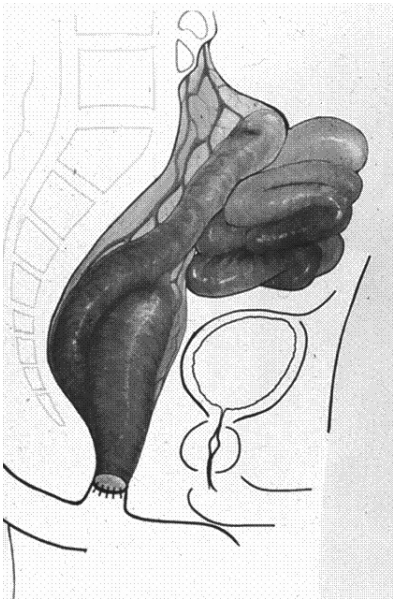

Figure 1.
The ileal pouch-anal anastomosis.

examination shows inflammatory changes, which may include mucosal edema, granularity, contact bleeding, loss of vascular pattern, haemorrhage, and ulceration. Endoscopic examination of the ileum above the pouch should be normal. Histological examination shows acute inflammation, including neutrophil infiltration and mucosal ulceration, superimposed on a background of chronic inflammation, including atrophy, crypt hyperplasia, and chronic inflammatory cell infiltration.

Table 1.
Pooled incidences of pouch related complications and functional disturbances after IPAA of 43 studies (printed with the permission from Hueting WE).

Complication	Number of Patients	Incidence (%)
Pouchitis	7289	18.8
Small bowel obstruction	5853	13.1
Pelvic sepsis	9082	9.5
Stricture	5185	9.2
Urgency	2165	7.3
Fistula	5129	5.5
Severe incontinence	3914	3.7
Sexual dysfunction	5112	3.6

To provide a standardized definition of this diagnostic triad, Sandborn introduced in 1994, the 18-point "Pouchitis Disease Activity Index" (PDAI) (Table 2). This 18-point index is based on clinical symptoms and endoscopic appearance, as well as histological findings of acute inflammation, and represents an objective and reproducible scoring system for pouchitis. Active pouchitis is defined as a score ≥7 and remission is defined as a score <7.[14] It is important to distinguish pouchitis from Crohn's disease of the pouch and cuffitis, since treatment and prognoses differ.[15]

Several studies have been conducted to identify the factors that contribute to the development of pouchitis. It has been shown that extraintestinal manifestations of UC and primary sclerosing cholangitis are associated with an increased risk of pouchitis.[6,10] Other purported risk factors for pouchitis include the presence of perinuclear antineutrophil cytoplastic antibodies and interleukin-1 receptor antagonist gene polymorphisms.[16] Smoking appears to protect against the development of pouchitis.[17] The impact of other factors such as extent of disease, backwash ileitis, and male gender are still controversial.

Although there are several theories on the pathophysiology, the cause of pouchitis is still unknown. The fact that pouchitis occurs almost exclusively in patients with UC and not in patients with familial adenomatous polyposis suggests an underlying genetic predisposition. It has been reported that in patients with a diverting ileostomy, the characteristic signs of pouchitis do not occur until the ileostomy is closed.[9,11] This finding and the observation that pouchitis generally responds to antibiotic therapy supports the hypothesis that bacterial antigens are important in driving the inflammatory process. Several flora related parameters, such as bacterial metabolism of bile acids and shortage of short chain volatile acids, have been associated with pouch inflammation and pouchitis.[18,19]

During the first two decades of pouchitis research, the prevailing theory suggested that fecal stasis in the reservoir, with a subsequent increase in particularly anaerobic bacterial numbers, compared to the normal ileum, resulted in pouchitis.[20-22] However, bacterial overgrowth is probably not sufficient to explain pouchitis, since bacterial overgrowth is present in virtually all pouches. Moreover, quantitative cultures of pouch effluents did not show higher bacterial counts in patients with pouchitis compared to those without pouchitis. In 1994, Ruseler-van Embden *et al.* investigated the composition of the ileal reservoir microflora in patients with and without pouchitis.[23] An abnormal flora was found in patients with pouchitis; an increase of aerobic bacteria, a decrease of anaerobes and lactobacilli, and the presence of the pathogenic bacterium *Clostridium perfringens*. The total number of bacteria was found to be lower in patients with pouchitis. This finding was in contrast with the prevailing opinion that pouchitis is caused by bacterial overgrowth. This study indicated that pouchitis is associated with an instable flora in the pouch. Hereby, the concept of dysbiosis as a cause of developing pouchitis was introduced.

Table 2.
Pouchitis Disease Activity Index (reprinted with the permission from Sandborn WJ).

Pouchitis Disease Activity Index		
Criteria		Score
Clinical		
Stool frequency	Usual postoperative stool frequency	0
	1-2 stool/day > postoperative usual	1
	3 or more stool / day > postoperative usual	2
Rectal bleeding	None or rare	0
	Present daily	1
Faecal urgency and cramps	None	0
	Occasional	1
	Usual	2
Fever (temperature > 37.8° C)	Absent	0
	Present	1
Endoscopic inflammation		
	Oedema	1
	Granularity	1
	Friability	1
	Loss of vascular pattern	1
	Mucous exudates	1
	Ulceration	1
Histological inflammation		
Polymorphonuclear leukocyte infiltration	Mild	1
	Moderate with crypt abscess	2
	Severe with crypt abscess	3
Ulceration per low-power field	<25%	1
	25-50%	2
	>50%	3

SPHINCTER PRESERVATION IN RECTAL CANCER SURGERY

Rectal cancer is a common malignancy in the Western world, and has an incidence of 18 / 100.000. Surgical resection remains the only treatment modality offering a chance of cure. Over the last 150 years, rectal cancer surgery has changed enormously. In 1826, Jacques Lisfranc from Paris was the first to perform a successful rectal

excision for cancer by a perineal approach.[24] Almost sixty years later Vincenz Czerny from Heidelberg stated that removal of a rectal tumour by the perineal approach was inappropriate, because in his opinion complete rectal excision from below was not possible. He therefore proposed a combined abdominal and perineal procedure for removing rectal cancer.[25] Despite this approach, the local recurrence rate remained nearly 100%.

After noting the modes of spread of rectal tumours in autopsies of patients who died for rectal cancer, Ernest Miles proposed that Czerny's operation failed to eradicate the "zone of upward spread". Therefore, he advocated in 1908 a more radical abdominal perineal resection (APR), in order to remove the mesorectum and to eradicate the "zone of upward spread" up to the origin of the inferior mesenteric artery.[26] Although Miles' procedure contained most of the requisite elements of a radical oncologic resection, widespread acceptance was delayed because the procedure related mortality was 36%.[27] In the 1930s improvements in anaesthetic management, allowing prolonged operating time, reduced operative mortality of the Miles procedure to acceptable low levels, and the APR became the gold standard for the treatment of rectal cancer.

In 1923, Hartmann from Paris was the first who excised only the intraperitoneal part of the rectum in patients with a tumour located in the upper third of the rectum, whereas the distal part of the rectum and the anal canal were left in situ.[28] The move towards sphincter-preserving surgery was initiated by the reports of Harry Bacon and Claude Dixon. In 1945, Bacon described his pull-through technique, whereby the descending colon is anastomosed to the everted anus.[29] He later reported that patients with cancer in the middle part of the rectum treated with this sphincter-saving pull-through operation had a survival rate equivalent to those undergoing abdominal perineal resection. However, continence was grossly impaired in most of his patients. Dixon was the first who performed an anterior resection with primary handsewn anastomosis in patients with cancer in the upper third of the rectum. In 1948 he reported a 5 years survival rate of 64% among 512 patients.[30] The major drawback of Dixon's technique was the considerable risk of anastomotic leakage. In the 1950's, anastomotic stapler devices were developed and modified in the former Sovjet Union. The feasibility of clinical application of these instruments was established in the late 1970's.[31] These devices allowed the creation of colo-rectal anastomosis at significantly lower levels than could be achieved with conventional hand-sewn techniques, which resulted in more sphincter preservation in rectal cancer surgery. Nowadays, the majority of colo-rectal anastomoses are constructed in a side-to-end double-stapled fashion by transannally placing an intraluminal circular stapler.[32]

In 1966, Sir Alan Parks from the St Marks Hospital in London was the first to perform a straight colo-anal anastomosis for patients with cancer in the middle and lower third of the rectum.[33] This handsewn anastomosis was constructed after complete rectal excision by an abdominal approach and transanal mucosectomy. According to Parks, this approach was associated with an acceptable morbidity, a low rate of pelvic sepsis, and recurrence and survival figures equivalent to those obtained with APR. Although,

this straight coloanal anastomosis extended the feasibility of sphincter preservation to more distal tumours, less than perfect functional outcomes were realized. This was manifested by significant symptoms of fecal urgency, frequency, and incontinence.[34-37] Although, some improvement in symptoms was noted in time by increase of neorectal capacity, this impaired continence, especially in the early postoperative period, is still a major drawback of this procedure. To attenuate this problem, Lazorthes *et al.* and Parc *et al.* simultaneously described a modification by formation of a colonic J-pouch anal anastomosis in 1986 (Figure 2).[38,39] In the initial studies, the colonic J-pouch-anal anastomosis was handsewn. In subsequent reports the colonic J-pouch-anal anastomosis was handsewn or stapled, according to the preference of the operating surgeon. Significant functional improvement, particularly in the first 24 months after surgery, can be achieved by adding a colonic J-pouch to the colo-anal anastomosis.[40] Despite this advantage, the colonic J-pouch has not achieved universal acceptance.

The next issue was to clarify how radical the resection should be in order to obtain an acceptable survival. Until the early 1980's a distal margin of at least 5 cm was still deemed necessary. In 1983, Williams *et al.* reported that distal spread over a distance greater than 2 cm below the inferior border of the tumour was found in less than 2.5% of the cases.[41] Other studies confirmed that a two cm margin of distal resection did not result in a decreased survival or an increase of local recurrence rate.[42,43] In the same time period, it was recognized that lateral spread of the tumour also contributed to local recurrence. Therefore pathologists began to examine the circumferential resection margin.[44] In 1979 Heald introduced the concept of total mesorectal excision (TME).[45] By using sharp dissection under direct vision, a relatively bloodless plane is followed along the lipoma-like outer surface of the mesorectum. According to several

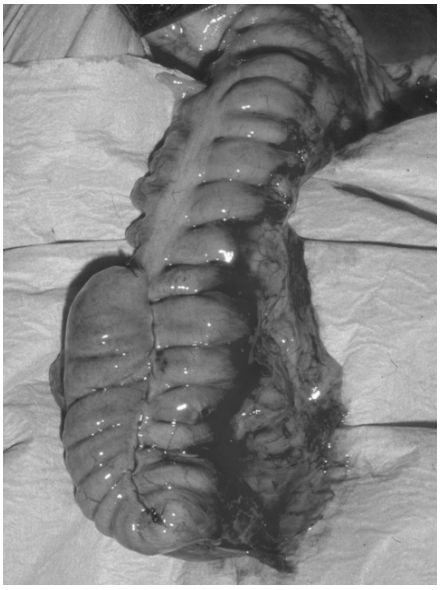

Figure 2.
The colonic J-pouch.

independent groups, TME results in lower recurrence rates and probably a better five-year survival.[46-50]

Since, TME has become the gold standard for the treatment of cancer of the middle and lower third of the rectum. Recently, neoadjuvant treatment for rectal cancer has gained more attention. The efficacy of preoperative radiotherapy has been established in recent years. Both the Swedish and Dutch radiotherapy trials have shown that preoperative radiotherapy reduces the locoregional recurrence rate.[32,51] In the context of sphincter preservation, preoperative radiotherapy or chemoradiotherapy could be used to decrease the volume of the primary tumour. This allows a tumour that previously would have required an APR to be excised by low anterior resection.[52] As sphincter preservation in rectal surgery gained acceptance, the goal of rectal surgeons became the achievement of both good oncological and functional results.

OUTLINE OF THE THESIS

For patients with distal rectal cancer, the colonic J-pouch anal anastomosis provides an alternative to a double stapled low colorectal anastomosis. In patients with ulcerative colitis, the ileal pouch-anal anastomosis avoids the necessity of a permanent stoma. This procedure is an alternative to an ileo-rectal anastomosis in patients with familial adenomatous polyposis. The aim of this thesis is to study the functional outcome after both procedures.

Pouchitis has a detrimental effect on the functional outcome after IPAA and is significantly correlated with impairment of quality of life. In order to enhance the functional outcome after IPAA, we were interested in the treatment and prevention of pouchitis. It is likely that the pouch flora plays an important role in the etiology of pouchitis. However, little is known about the effect of antibiotics on this flora.

Chapter 2 evaluates the pouch flora in patients with UC during episodes of pouchitis, during subsequent treatment with metronidazole or ciprofloxacin and during pouchitis-free periods. In addition, the effects of both antibiotics were determined using the PDAI. In **Chapter 3**, an assessment is made of the influence of probiotics on the prevention of pouchitis. Therefore a single strain, *Lactobacillus rhamnosus* GG, was chosen. Patients with UC operated during the time period between 1997 and 2001 started immediately after the procedure with the daily intake of *Lactobacillus rhamnosus* GG. The control group existed of patients operated during the time period between 1986 and 1996 who never used *Lactobacillus rhamnosus* GG. Fecal samples were studied for microbiological enumeration of *Lactobacillus rhamnosus* GG and other lactobacilli.

Most patients with cancer in the middle or lower third of the rectum are potential candidates for a sphincter saving procedure, such as double-stapled low colo-rectal anastomsis, a straight colo-anal anastomosis or a colonic J-pouch anal anastomosis. The question is whether these procedures are offered to all eligible patients with rectal cancer in the lower two-third of the rectum, in this era of TME and preoperative radiotherapy. Therefore, we examined the different types of surgical procedures

performed in 521 patients with rectal cancer, between 2001 and 2003, in the region of the comprehensive cancer centre Rotterdam with 2.3 million inhabitants. The results of this study are summarized in **Chapter 4**. We found that only half of the patients with distal rectal cancer underwent a sphincter saving procedure, mainly a transanal double-stapled low colo-rectal anastomosis. We were interested in the quality of life after such a double-stapled anastomosis, as compared to colonic J-pouch anal anastomosis and abdominoperineal resection. Therefore, the quality of life was assessed in 204 disease-free survivors, who underwent one of these three procedures between 1997 and 2001 in three different hospitals. The results are described in **Chapter 5**.

Although the functional outcome after pouch surgery is good in most cases, some patients experience a less favorable outcome, characterized by either obstructed defaecation or impaired continence. Because there were no data available regarding the potential role of retrograde bowel irrigation (RBI) in the treatment of these disturbances after pouch surgery, we studied the long-term feasibility and outcome of RBI in patients with defecation disturbances after pouch surgery. The results of this study are reported in **Chapter 6**.

It is well known that anal sphincter function is impaired after pouch surgery. Until recently, surgeons used Park anal retractor during pouch surgery to gain access to the anal canal and to perform a handsewn anastomosis. In recent years, it has been suggested that the use of a Scott retractor, a ring retractor with multiple skin hooks on elastic bands, results in less sphincter damage. In **Chapter 7**, the results of a randomized controlled trial are presented, comparing the effect of the Parks's anal retractor and the Scott retractor on the anal sphincter complex. The results of this trial indicate that the Scott retractor causes less sphincter damage. Based on this conclusion we decided to use this type of retractor to facilitate a handsewn pouch-anal anastomosis.

The functional outcome after pouch surgery depends on adequate reservoir function as well as sphincter integrity. The question is whether transanal mucosectomy followed by handsewn pouch-anal anastomosis at the level of the dentate line damages the anal sphincters. We have studied the integrity and the morphology of both sphincters before and after pouch surgery, using three-dimensional endoanal ultrasonography. The results are presented in **Chapter 8**. Although the overall functional outcome as well as the quality of life are good after colonic J-pouch anal anastomosis, we observed some patients with impaired continence despite adequate sphincter function. Therefore, we investigated whether compliance and sensory perception are altered after a handsewn colonic J-pouch anastomosis, using a Scott retractor. In addition, these changes were prospectively evaluated in relation to the functional outcome in order to gain more insight in the underlying pathophysiological mechanisms. The results of this study are reported in **Chapter 9.**

The results of the studies, described in this thesis, are summarized and discussed in **Chapter 10**.

REFERENCES

1. Ravitch MM, Sabiston DC. Anal ileostomy with preservation of the sphincter. A proposed operation in patients requiring total colectomy for benign lesions. Surg Gynecol Obstet 1947;84:1095-109.
2. Parks AG, Nicholls RJ. Proctocolectomy without ileostomy for ulcerative colitis. Br Med J 1978;2:85-8.
3. Hueting WE, Buskens E, van der Tweel I, Gooszen HG, van Laarhoven CJ. Results and complications after ileal pouch anal anastomosis: a meta-analysis of 43 observational studies comprising 9317 patients. Dig Surg 2005;22:69-79.
4. Stahlberg D, Gullberg K, Liljeqvist L, Hellers G, Lofberg R. Pouchitis following pelvic pouch operation for ulcerative colitis. Incidence, cumulative risk, and risk factors. Dis Colon Rectum 1996;39:1012-8.
5. Hurst RD, Molinari M, Chung TP, Rubin M, Michelassi F. Prospective study of the incidence, timing and treatment of pouchitis in 104 consecutive patients after restorative proctocolectomy. Arch Surg 1996;131:497-500; discussion 501-2.
6. Penna C, Dozois R, Tremaine W, Sandborn W, LaRusso N, Schleck C, Ilstrup D. Pouchitis after ileal pouch-anal anastomosis for ulcerative colitis occurs with increased frequency in patients with associated primary sclerosing cholangitis. Gut 1996;38:234-9.
7. Meagher AP, Farouk R, Dozois RR, Kelly KA, Pemberton JH. J ileal pouch-anal anastomosis for chronic ulcerative colitis: complications and long-term outcome in 1310 patients. Br J Surg 1998;85:800-3.
8. Cheifetz A, Itzkowitz S. The diagnosis and treatment of pouchitis in inflammatory bowel disease. J Clin Gastroenterol 2004;38:S44-50.
9. Madden MV, Farthing MJ, Nicholls RJ. Inflammation in ileal reservoirs: 'pouchitis'. Gut 1990;31:247-9.
10. Lohmuller JL, Pemberton JH, Dozois RR, Ilstrup D, van Heerden J. Pouchitis and extraintestinal manifestations of inflammatory bowel disease after ileal pouch-anal anastomosis. Ann Surg 1990;211:622-7.
11. Moskowitz RL, Shepherd NA, Nicholls RJ. An assessment of inflammation in the reservoir after restorative proctocolectomy with ileoanal ileal reservoir. Int J Colorectal Dis 1986;1:167-74.
12. Shepherd NA, Hulten L, Tytgat GN, Nicholls RJ, Nasmyth DG, Hill MJ, Fernandez F, Gertner DJ, Rampton DS, et al. Pouchitis. Int J Colorectal Dis 1989;4:205-29.
13. Shen B, Achkar JP, Lashner BA, Ormsby AH, Remzi FH, Bevins CL, Brzezinski A, Petras RE, Fazio VW. Endoscopic and histologic evaluation together with symptom assessment are required to diagnose pouchitis. Gastroenterology 2001;121:261-7.
14. Sandborn WJ, Tremaine WJ, Batts KP, Pemberton JH, Phillips SF. Pouchitis after ileal pouch-anal anastomosis: a Pouchitis Disease Activity Index. Mayo Clin Proc 1994;69:409-15.
15. Shen B, Fazio VW, Remzi FH, Delaney CP, Bennett AE, Achkar JP, Brzezinski A, Khandwala F, Liu W, Bambrick ML, Bast J, Lashner B. Comprehensive evaluation of inflammatory and noninflammatory sequelae of ileal pouch-anal anastomoses. Am J Gastroenterol 2005;100:93-101.
16. Carter MJ, Di Giovine FS, Cox A, Goodfellow P, Jones S, Shorthouse AJ, Duff GW, Lobo AJ. The interleukin 1 receptor antagonist gene allele 2 as a predictor of pouchitis following colectomy and IPAA in ulcerative colitis. Gastroenterology 2001;121:805-11.
17. Merrett MN, Mortensen N, Kettlewell M, Jewell DO. Smoking may prevent pouchitis in patients with restorative proctocolectomy for ulcerative colitis. Gut 1996;38:362-4.
18. De Silva HJ. Short-chain fatty acid irrigation in severe pouchitis. N Engl J Med 1989; 16;321:1416-7.
19. Kuisma J, Mentula S, Luukkonen P, Jarvinen H, Kahri A, Farkkila M. Factors associated with ileal mucosal morphology and inflammation in patients with ileal pouch-anal anastomosis for ulcerative colitis. Dis Colon Rectum 2003; 46:1476-83.
20. Kelly, DG, Phillips, SF, Kelly, KA, Weinstein, WM, Gilchrist, MJ. Dysfunction of the continent ileostomy: clinical features and bacteriology. Gut 1983;24:193-201.
21. O Connell, PR, Rankin, DR, Weiland, LH, Kelly, KA. Enteric bacteriology, absorption, morphology and emptying after ileal pouch-anal anastomosis. Br J Surg 1986;73:909-14.
22. Luukkonen, P, Valtonen, V, Sivonen, A, Sipponen, P, Jarvinen, H. Fecal bacteriology and reservoir ileitis in patients operated on for ulcerative colitis. Dis Colon Rectum 1988;31:864-7.

23. Ruseler-van Embden, JG, Schouten, WR, Lieshout, LM. Pouchitis: result of microbial imbalance?" Gut 1994;35:658-64.
24. Lisfranc J. Memoire sur l'excision de la partie inferieure du rectum devenue carcinomateuse. Memoires de l'Academie Royae de Medecine, Paris 1833;3:810.
25. Czerny V. Casuistische Mittheilugen aus de Chirurg Klinik Heidelberg. Munch Med Wochenschr 1894;11.
26. Miles W. A method of performing abdomino-perineal resection for carcinoma of the rectum and of the terminal portion of the pelvic colon. Lancet 1908;2:1812-13.
27. Miles W. Cancer of the rectum. Harrison, 1926.
28. Hartmann H. Chirurgie du rectum. Masson et cie, 1931.
29. Bacon H. Evolution of sphincter muscle preservation and reestablishment of continuity in the operative treatment of rectal and sigmoid cancer. Surg Gynecol Obstet 1945;181:113.
30. Dixon C. Anterior resection for malignant lesions of the upper third of the rectum and lower part of the sigmoid. Ann Surg 1948;128:425.
31. Bolton RA, Britton DC. Restorative surgery of the rectum with a circumferential stapler. Lancet 1980;1:850-1.
32. Kapiteijn E, Marijnen CA, Nagtegaal ID, Putter H, Steup WH, Wiggers T, Rutten HJ, Pahlman L, Glimelius B, van Krieken JH, Leer JW, van de Velde CJ; Dutch Colorectal Cancer Group. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. N Engl J Med 2001; 30;345:638-46.
33. Parks AG. Transanal technique in low rectal anastomosis. Proc R Soc Med 1972;65:975-6.
34. Pedersen IK, Christiansen J, Hint K, Jensen P, Olsen J, Mortensen PE. Anorectal function after low anterior resection for carcinoma. Ann Surg 1986;204:133-5.
35. McDonald PJ, Heald RJ. A survey of postoperative function after rectal anastomosis with circular stapling devices. Br J Surg 1983;70:727-9.
36. van Duijvendijk P, Slors F, Taat CW, Heisterkamp SH, Obertop H, Boeckxstaens GE. A prospective evaluation of anorectal function after total mesorectal excision in patients with a rectal carcinoma. Surgery 2003;133:56-65.
37. Williamson ME, Lewis WG, Finan PJ, Miller AS, Holdsworth PJ, Johnston D. Recovery of physiologic and clinical function after low anterior resection of the rectum for carcinoma: myth or reality? Dis Colon Rectum 1995;38:411-8.
38. Parc R, Tiret E, Frileux P, Moszkowski E, Loygue J. Resection and colo-anal anastomosis with colonic reservoir for rectal carcinoma. Br J Surg 1986;73:139-41.
39. Lazorthes F, Fages P, Chiotasso P, Lemozy J, Bloom E. Resection of the rectum with construction of a colonic reservoir and colo-anal anastomosis for carcinoma of the rectum. Br J Surg 1986;73:136-8.
40. Heriot AG, Tekkis PP, Constantinides V, Paraskevas P, Nicholls RJ, Darzi A, Fazio VW. Meta-analysis of colonic reservoirs versus straight coloanal anastomosis after anterior resection. Br J Surg 2006;93:19-32.
41. Williams NS, Dixon MF, Johnston D. Reappraisal of the 5 centimetre rule of distal excision for carcinoma of the rectum: a study of distal intramural spread and of patients' survival. Br J Surg 1983;70:150-4.
42. Pollett WG, Nicholls RJ. The relationship between the extent of distal clearance and survival and local recurrence rates after curative anterior resection for carcinoma of the rectum. Ann Surg 1983;198:159-63.
43. Karanjia ND, Schache DJ, North WR, Heald RJ. 'Close shave' in anterior resection. Br J Surg 1990;77:510-2.
44. Quirke P, Durdey P, Dixon MF, Williams NS. Local recurrence of rectal adenocarcinoma due to inadequate surgical resection. Histopathological study of lateral tumour spread and surgical excision. Lancet 1986;2:996-9.
45. Heald RJ. A new approach to rectal cancer. Br J Hosp Med 1979;22:277-81.
46. Enker WE, Thaler HT, Cranor ML, Polyak T. Total mesorectal excision in the operative treatment of carcinoma of the rectum. J Am Coll Surg 1995;181:335-46.
47. Wiggers T, de Vries MR, Veeze-Kuypers B. Surgery for local recurrence of rectal carcinoma. Dis Colon Rectum 1996;39:323-8.
48. MacFarlane JK, Ryall RD, Heald RJ. Mesorectal excision for rectal cancer. Lancet 1993;341:457-60.
49. Zaheer S, Pemberton JH, Farouk R, Dozois RR, Wolff BG, Ilstrup D. Surgical treatment of adenocarcinoma of the rectum. Ann Surg 1998;227:800-11.
50. Heald RJ, Moran BJ, Ryall RD, Sexton R, MacFarlane JK. Rectal cancer: the Basingstoke experience of total mesorectal excision, 1978-1997. Arch Surg 1998;133:894-9.

51. Swedish Rectal Cancer Trial. Improved survival with preoperative radiotherapy in respectable rectal cancer. N Engl J Med.1997;3;336:980-7.
52. Minsky BD. Adjuvant therapy of rectal cancer. Semin Oncol 1999;26:540-4.

CHAPTER 2

Eradication of pathogenic bacteria and restoration of normal pouch flora: comparison of metronidazole and ciprofloxacin in the treatment of pouchitis

Gosselink MP, Schouten WR, van Lieshout LM,
Hop WC, Laman JD and Ruseler-van Embden JG.
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ABSTRACT

Pouchitis is the major long-term complication after ileal pouch-anal anastomosis for ulcerative colitis. Metronidazole and ciprofloxacin are commonly used for treatment; however, nothing is known about the effects on the pouch flora during and after pouchitis episodes. This study was designed to evaluate the effect of both antibiotics on eradication of pathogens and the restoration of normal pouch flora. The fecal flora obtained from 13 patients with ulcerative colitis was examined at the beginning of a pouchitis episode before treatment, during treatment with metronidazole or ciprofloxacin, and during pouchitis-free periods. Some patients experienced more than one pouchitis episode. Therefore, a total of 104 samples was obtained. Each sample was cultured under aerobic and anaerobic conditions and the isolated bacteria were identified. Furthermore, the clinical response to both antibiotics was compared using the Pouchitis Disease Activity Index score. During pouchitis-free periods, the patients had a flora characterized by high numbers of anaerobes and no or low numbers of pathogens. This flora resembles normal colon flora. During pouchitis episodes, we found a significant decrease of anaerobes (P=0.01), a significant increase of aerobic bacteria (P=0.01), and significantly more numbers of pathogens, such as *Clostridium perfringens* (in 95% of the samples; P<0.01) and hemolytic strains of *Escherichia coli* (in 57% of the samples; P=0.05). Treatment with metronidazole resulted in a complete eradication of the anaerobic flora, including *C. perfringens*. However, no changes in the numbers of *E. coli* were found. In contrast, when the patient was treated with ciprofloxacin, not only *C. perfringens*, but also all coliforms including hemolytic strains of *E. coli* disappeared. The larger part of the anaerobic flora was left undisturbed during the administration of ciprofloxacin. Patients treated with ciprofloxacin experienced significant larger reductions in Pouchitis Disease Activity Index score compared with patients treated with metronidazole (P=0.04). This study strongly suggests a role of pathogenic bacteria (*C. perfringens* and/or hemolytic strains of *E. coli*) in pouchitis. From a microbiologic and a clinical point of view, ciprofloxacin is preferable to metronidazole, because treatment with ciprofloxacin eradicates both pathogens and results in an optimal restoration of normal pouch flora.

INTRODUCTION

For many years proctocolectomy with ileal pouch-anal anastomosis (IPAA) has been the elective procedure of choice for patients with refractory ulcerative colitis.[1,2] The most significant sequel of IPAA in patients with ulcerative colitis is pouchitis.[3-7] This is an acute, nonspecific inflammatory condition of the ileal pouch, which can mimic ulcerative colitis (UC). An unequivocal diagnosis should be based on a diagnostic triad, consisting of the following components: clinical symptoms, endoscopic features of acute inflammation, and histologic evidence of a prominent polymorphonuclear

leukocyte infiltration.[8-10] To standardize these diagnostic criteria, an 18-point Pouchitis Disease Activity Index (PDAI) has been developed.[11]

The exact etiology of pouchitis is still not clear and medical treatment is largely empirical.[12] The antibiotic metronidazole is most commonly used in the treatment of pouchitis and most patients obtain prompt relief after administration.[13,14] Metronidazole has been proven to be effective in a placebo-controlled, randomized, clinical trial.[14] Based on the side-effects of metronidazole and because some patients recurrent episodes of pouchitis are refractory to metronidazole, some physicians prescribed other antibiotics such as tetracycline, amoxicillin/clavulanic acid, erythromycin, and ciprofloxacin. Ciprofloxacin has been shown to be the most effective with no or only few side effects.[13] Recently Shen et al.compared the effectiveness and side-effects of ciprofloxacin and metronidazole for treating acute pouchitis in a small, randomized, clinical trial.[15] Ciprofloxacin led to a greater degree of reduction in total PDAI score and was better tolerated. The quick response to metronidazole or ciprofloxacin is still an enigma. However, it is obvious that treatment with these antibiotics induces alterations in the composition of the flora that have beneficial effects on the inflammation process in the pouch mucosa. In a previous study, we found that patients after IPAA without pouchitis have a stable flora in their ileoanal reservoir, resembling normal colon flora.[16] During pouchitis, an abnormal flora was cultured including a significant increase of pathogens such as *Clostridium perfringens*.

This study was designed to investigate the effect of metronidazole and ciprofloxacin on eradication of pathogens and the restoration of normal pouch flora. Furthermore, the clinical response to both antibiotics was compared using the PDAI score.

PATIENTS AND METHODS

The fecal flora from 13 patients with UC, who underwent an IPAA at the Erasmus Medical Center in Rotterdam (6 males; median age, 37 (range, 21-47) years) was examined at the beginning of a pouchitis episode before treatment, during treatment with metronidazole or ciprofloxacin, and during pouchitis-free periods. In these 13 patients, 18 episodes of pouchitis were encountered (1 to 3 per individual). We collected at least one sample of each pouchitis period before treatment, two to three samples during antibiotic treatment, and two samples during the disease-free period after treatment. Thus, a total of 104 samples was obtained. Until 1996, each episode of pouchitis was treated with metronidazole (daily, 3 × 500 mg for 2 weeks), according to the international standard at that moment (3 males; median age, 39 (range, 21-47) years). Since 1996, patients with pouchitis were treated with ciprofloxacin (daily, 2 × 500 mg for 2 weeks) based on new microbiologic insights (3 males; median age, 32 (range, 21-42) years). The median follow-up of this historic cohort study was five years.

The diagnosis of pouchitis was based on symptomatic, endoscopic, and histologic

criteria. Symptoms associated with pouchitis are abdominal cramping, bloody diarrhea, increased stool frequency, urgency, malaise, and fever. Endoscopic signs of inflammation included mucosal hyperemia with loss of vascular pattern with or without ulceration. Histologic criteria for pouchitis were characterized by signs of acute inflammation, significant neutrophil infiltration, and ulceration. The severity of pouchitis was calculated according to the 18 point Pouchitis Disease Activity Index (PDAI) [11]. Active pouchitis is defined as a PDAI ≥ 7, and remission is defined as PDAI < 7 in a patient with a history of pouchitis. Symptoms assessment, endoscopic, and histologic evaluations were performed again after 15 days. This study had the approval of the medical ethical committee of the Erasmus Medical Center.

Microbiology

A total of 104 fecal samples were cultured under aerobic and anaerobic conditions, and the isolated bacteria were identified. No enemas were given at least two weeks before stool collection. Within one or two hours after collection, the stools were processed. The samples were thoroughly mixed and tenfold dilutions were prepared in anaerobic dilution solution.[17] Samples of appropriate dilutions were plated aerobically on MacConkey (Oxoid), Sabouraud (Oxoid), Rogosa (Oxoid), azide blood (Oxoid), and blood agar plates. Anaerobes were cultured in anaerobic flasks, filled with a 90% N_2 and 10% CO_2 mixture as described before, on Schaedler Broth (Oxoid) supplemented with 2% agar (Difco), 0.0002% resazurin (BDH), and 0.025% dithiothreitol (Sigma), and azide blood agar.[18] After two days of incubation at 37°C, colonies on the various media were counted. All colonies grown on the anaerobic flasks were tested for aerobic growth on blood agar plates. The aerobes were identified by conventional methods. Gram stain, morphology, carbohydrate fermentation, and gas chromatographically estimated end products of glucose fermentation were used to identify the isolates to genus or species level. Anaerobic bacteria were classified according to Holderman *et al.*[19] Numbers of fecal bacteria are given per gram wet weight.

Clostridium perfringens Enterotoxin and Alpha Toxin

The role of two *C. perfringens* toxins (enterotoxin and α-toxin) in pouchitis was studied. The presence of *C. perfringens* enterotoxin was estimated by means of ELISA techniques; with polymerase chain reaction (PCR) procedure, the presence of *C. perfringens* enterotoxin gene was identified in fecal samples positive for *C. perfringens*.[20] *C. perfringens* strains were grown overnight anaerobically in thioglycollate broth (BBL) at 37°C. *C. perfringens* NCTC 8239 was used as a positive control. From the base sequence of *C. perfringens* enterotoxin gene 2 oligonucleotides were synthesized as primers: primer 1: HLWL95:5'-GGA GAT GGT TGG ATA TTA GG-3' and primer 2: HLWL96: 5'-CCA TCA CCT AAG GAC TGT TC-3', which generate a DNA fragment of 664 base pairs in the PCR. After amplification DNA products were subjected to agarose-gelelectrophoresis. Detection of a 664 bp DNA fragment was regarded as enterotoxin positive.

Presence of *C. perfringens* phospholipase C (lecithinase, alpha-toxin) was determined growing the isolated organisms on egg-yolk agar (Oxoid); neutralization tests were made by use of anti-alpha toxin serum (Pro-lab Diagnostics).[21] The activity of *C. perfringens* phospholipase C was estimated by spectrophotometric measurement of hemoglobin release from rabbit erythrocytes.[22]

Fecal pH

The pH was determined by inserting the electrode (GK2402C, Radiometer, Copenhagen, Denmark) in freshly collected, undiluted, fecal samples of at least 25 g.

Statistical Analysis

We used the average of all the samples for a patient as his or her individual data. Wilcoxon's signed-rank test was used to compare PDAI scores and microbial flora of patients with pouchitis before, during and after antibiotic treatment. Comparison of these changes between treatment with ciprofloxacin or metronidazole groups was conducted using the Mann-Whitney *U* test. $P<0.05$ (two-tailed) was considered the limit of significance.

RESULTS

Patients who were free of pouchitis had a flora characterized by high numbers of anaerobes and no, or low, numbers of pathogens (Figures 1 and 2). During pouchitis episodes, we found a significant decrease of anaerobes ($P=0.01$), a significant increase of aerobic bacteria ($P=0.01$), and significantly more numbers of pathogens, such as *Clostridium perfringens* (in 95% of the samples) and hemolytic strains of *Escherichia coli* (in 57% of the samples). The total numbers of these pathogens were significantly higher than found in pouchitis-free periods ($P<0.05$). Other (potential) pathogenic bacteria were seldom found.

Treatment with metronidazole resulted in a complete eradication of the anaerobic flora (*vs.* pouchitis $P<0.01$), including *C. perfringens* (*vs.* pouchitis $P<0.01$; Figures 1 and 2). No changes in the numbers of *E. coli* were found. When patients were treated with ciprofloxacin, not only *C. perfringens*, all coliforms including hemolytic strains of *E. coli* disappeared (both *vs.* pouchitis $P<0.01$). The larger part of the anaerobic flora was undisturbed. The pH of the feces of patients treated with ciprofloxacin was lowered toward values found in patients who were free of pouchitis (Figure 3).

C. perfringens enterotoxin could not be determined in any of the fecal samples by ELISA techniques, and none of the isolated *C. perfringens* strains was found to be enterotoxin-positive using PCR procedure. Phospholipase C (alpha-toxin) was produced by each isolated strain.

No differences in numbers of fecal streptococci were found between the groups. Only in feces of patients who were free of pouchitis, lactobacilli were present (median

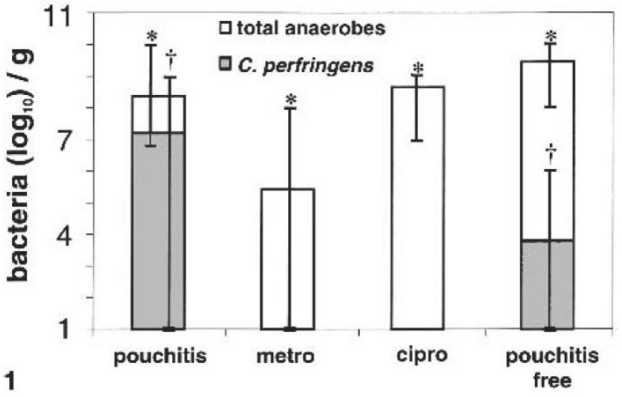

Figure 1.
Anaerobic flora of patients with pouchitis, during antibiotic treatment and in pouchitis-free periods. Values are medians and ranges calculated from mean individual data if a patient had more than one sample. *Range number of anaerobes. Range number of Clostridium perfringens (as part of the anaerobic flora). Numbers of bacteria (log10) are given per gram wet feces. Metro = metronidazole; cipro = ciprofloxacin.

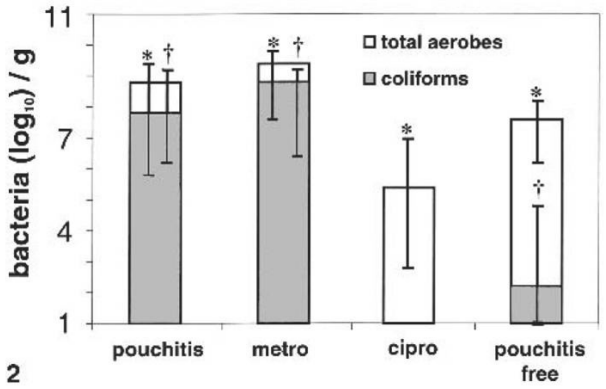

Figure 2.
Aerobic flora of patients with pouchitis, during antibiotic treatment and in pouchitis-free periods. Values are medians and ranges calculated from mean individual data if a patient had more than one sample. *Range number of aerobes. Range number of coliforms (as part of the aerobic flora). Numbers of bacteria (log 10) are given per gram wet feces. Metro = metronidazole; cipro = ciprofloxacin.

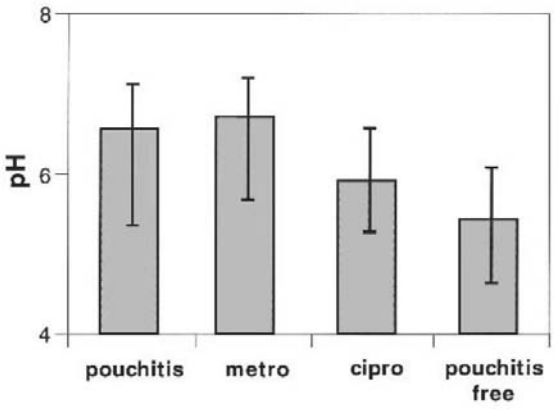

Figure 3.
Fecal pH of patients with pouchitis, during antibiotic treatment and in pouchitis-free periods. Values are medians and ranges calculated from mean individual data if a patient had more than one sample. Metro = metronidazole; cipro = ciprofloxacin.

value, 3.4×10^4 bacteria per gram). Significantly lower numbers of lactobacilli were cultured in feces of patients with pouchitis and during treatment with antibiotics.

During pouchitis episodes, before treatment with antibiotics, the PDAI noted in the patients treated with metronidazole were similar to the indices observed in patients treated with ciprofloxacin (median values, 11 and 10 respectively, P=0.72; Figure 4). PDAI dropped significantly in each group (median values, 5 (P<0.01) and 2.5 (P<0.01) respectively), depicting remission in all patients. The PDAI drop was the result of a significant decrease in the score of each component of the PDAI (clinical symptoms, sigmoidoscopy, and histology). When comparing the change from baseline of PDAI between patients treated with metronidazole and ciprofloxacin, a significant difference was observed (P=0.04) with median changes respectively 6 and 7.5.

Recurrence rates were similar in both groups (metronidazole 3/7; ciprofloxacin 2/6). Recurrence of symptoms was encountered within three weeks after interruption of metronidazole treatment in two of three patients. In two patients treated with ciprofloxacin, a relapse occurred after a median interval of 13 months. Recurrences were treated with respectively metronidazole and ciprofloxacin.

DISCUSSION

This is the first study comparing the effect of ciprofloxacin and metronidazole on the microbial flora of patients with pouchitis. Based on the results of the present study, it seems likely that pathogens play an important role in pouchitis. Nearly every

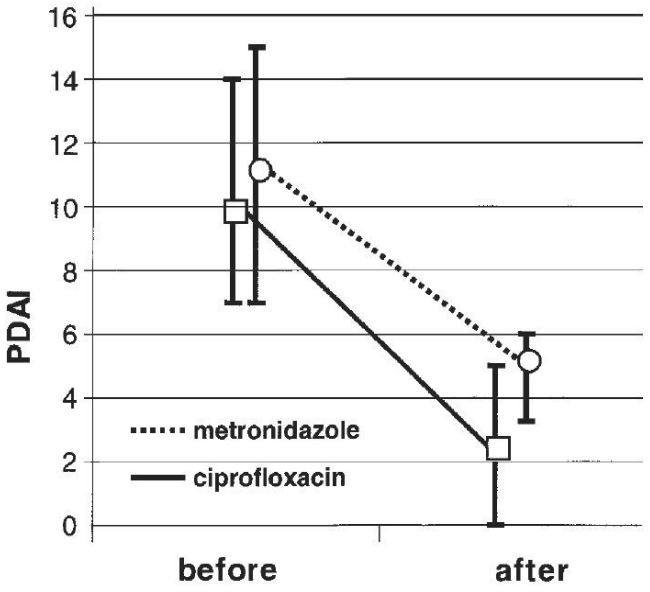

Figure 4.
Pouchitis Disease Activity Index (PDAI) before and after treatment with metronidazole and ciprofloxacin.

patient with pouchitis was contaminated with large numbers of *C. perfringens* and more than one-half of our patients were contaminated with hemolytic *E. coli* as well. It is obvious that treatment with ciprofloxacin, an antibiotic that eradicates both pathogens, is preferable to metronidazole, which is only effective when no hemolytic *E. coli* is present.

Ciprofloxacin is a quinolone that is mainly effective on aerobic and facultative anaerobic microorganisms.[23-25] From microbiologic point of view, ciprofloxacin has another important advantage over metronidazole: ciprofloxacin does not disturb the majority of anaerobic bacteria. These bacteria contribute to the stability of the pouch flora and provide resistance against colonization of pathogens. In an earlier study, we established the importance of a stable anaerobic pouch flora for patients with an ileal reservoir.[16] The relative low pH during treatment with ciprofloxacin is a reflection of the active fermentation process of the anaerobic flora, which is responsible for the production of volatile and other fatty acids.[26] It seems likely that a low pH protects against (potential) pathogens and strongly inhibits the degradation of mucus glycoproteins, which protect the epithelial cells in the reservoir.[16]

Our study shows that the clinical results of ciprofloxacin treatment are better than those of metronidazole treatment. These results are comparable to those

reported by Shen *et al.*, who compared the effectiveness and side-effects of both antibiotics for treating acute pouchitis in a small, randomized, clinical trial.[15] In their study, ciprofloxacin resulted in a greater degree of reduction in total PDAI and greater improvement in symptoms and endoscopic scores. Furthermore, 33% of metronidazole-treated patients reported adverse effects compared with none of those treated with ciprofloxacin. Metronidazole has short-term side effects, such as nausea and dysgeusia, and long-term side effects, such as the peripheral neuropathy and poor quality of sperm.[27]

Until now, the exact cause of pouchitis has not been elucidated. Several studies have hypothesized specific bacteriologic changes or functional abnormalities as the cause of pouchitis, but their findings remain inconclusive.[28-30] The present study is the first that shows that in all patients pouchitis is associated with high numbers of pathogens. The exact role of *C. perfringens*, a bacterium associated with food-born infections and antibiotic-associated diarrhea, in the pathogenesis of pouchitis is not yet clear. We could demonstrate that pouchitis is not caused by an enterotoxigenic strain. *C. perfringens* enterotoxin could not be determined in any of the fecal samples. However, all strains produced a hemolysin, called alpha-toxin or phospholipase C. This toxin is involved in tissue damage by activating the arachidonic acid cascade, stimulation of the release of platelet-activating factor (PAF) in intestinal epithelial cells and causing calcium gates that may lead to blood vessel contraction.[31,32] It seems likely that both effects reduce the blood supply to the mucosa and contributes to ischemic conditions and increased production of radicals in the pouch.[33] Kienle and coworkers showed that pouch hypoperfusion is a risk factor in the development of early postoperative pouchitis.[34] Probably hemolysin producing *E. coli*, which were cultured from 57% of fecal samples from our patients with pouchitis, have a similar effect as *C. perfringens* alpha-toxin.

During pouchitis-free periods, *C. perfringens* was found in fecal samples of approximately one-half of patients, but numbers were always low and therefore may be considered as a part of the normal pouch flora. Also in the colon of healthy patients, *C. perfringens* often is present, but kept at low level by the normal flora.[35] Only when the stability of the flora is disturbed, for example by the use of antibiotics eradicating a large part of the indigenous flora, the number of these bacteria may increase to a harmful level. Well known is pseudomembranous colitis caused by *Clostridium difficile.*[36] The pouch flora in general is very susceptible to dietary variations, antibiotics, stress, and travel, which is reflected by changes in flora composition and changes in pH. This may promote the multiplication of potential pathogenic bacteria. Summarizing, low numbers of these pathogens do not damage the host, but when numbers increase, the amount of secreted alpha-toxin reaches a harmful level and might cause pouchitis. Our data emphasize the importance of a stable fecal flora and a low pH in ileal reservoirs. Significantly lower numbers of lactobacilli were cultured in feces of patients with pouchitis, but also during treatment with antibiotics. Probiotic lactobacilli might help to maintain the microbiologic homeostasis in the pouch and increase the resistance

against colonization of pathogens to prevent pouchitis. Gionchetti and coworkers demonstrated in a double-blind, placebo-controlled trial the efficacy of a probiotic preparation in prophylaxis of pouchitis onset during the first year after ileostomy closure and in the prevention of relapses in patients with chronic pouchitis.[37,38] Recently, our group showed that the first onset of pouchitis was significantly delayed by daily consumption of a *Lactobacillus rhamnosus* GG containing fermented product.[39] Therefore, modification of the microflora by antibiotics and probiotics is the rational approach to control pouchitis.

CONCLUSIONS

Our study reveals that when pouchitis is established using clinical, endoscopic, and histologic criteria, high numbers of *C. perfringens* or hemolytic strains of *E. coli* were detected in each patient. Thus, for a proper diagnosis there is no need to check each stool sample for these pathogens. We conclude that ciprofloxacin is preferable to metronidazole, because ciprofloxacin eradicates both pathogenic bacteria, restores the normal pouch flora, and PDAI score is better. Furthermore, this may result in less or later recurrence of disease and may justify the higher costs of ciprofloxacin compared with metronidazole.

REFERENCES

1. Parks AG, Nicholls RJ. Proctocolectomy without ileostomy for ulcerative colitis. Br Med J 1978; 2: 85-8.
2. Utsunomiya J, Iwama T, Imajo M, Matsuo S, Sawai S, Yaegashi K, Hirayama R. Total colectomy, mucosal proctectomy, and ileoanal anastomosis. Dis Colon Rectum 1980; 23: 459-66.
3. Pemberton JH. The problem with pouchitis. Gastroenterology 1993; 104: 1209-11.
4. Keighley MR. Pouchitis. Br J Surg 1994; 81: 1091-2.
5. Fazio VW, Ziv Y, Church JM, Oakley JR, Lavery IC, Milsom JW, Schroeder TK. Ileal pouch-anal anastomoses complications and function in 1005 patients. Ann Surg 1995; 222: 120-7.
6. Meagher AP, Farouk R, Dozois RR, Kelly KA, Pemberton JH. J ileal pouch-anal anastomosis for chronic ulcerative colitis: complications and long-term outcome in 1310 patients. Br J Surg 1998; 85: 800-3.
7. Lohmuller JL, Pemberton JH, Dozois RR, Ilstrup D, van Heerden J. Pouchitis and extraintestinal manifestations of inflammatory bowel disease after ileal pouch-anal anastomosis. Ann Surg 1990; 211: 622-7.
8. Moskowitz RL, Shepherd NA, Nicholls RJ. An assessment of inflammation in the reservoir after restorative proctocolectomy with ileoanal ileal reservoir. Int J Colorectal Dis 1986; 1: 167-74.
9. Shepherd NA, Hulten L, Tytgat GN, Nicholls RJ, Nasmyth DG, Hill MJ, Fernandez F, Gertner DJ, Rampton DS, et al. Pouchitis. Int J Colorectal Dis 1989; 4: 205-29.
10. Shen B, Achkar JP, Lashner BA, Ormsby AH, Remzi FH, Bevins CL, Brzezinski A, Petras RE, Fazio VW. Endoscopic and histologic evaluation together with symptom assessment are required to diagnose pouchitis. Gastroenterology 2001; 121: 261-7.
11. Sandborn WJ, Tremaine WJ, Batts KP, Pemberton JH, Phillips SF. Pouchitis after ileal pouch-anal anastomosis: a Pouchitis Disease Activity Index. Mayo Clin Proc 1994; 69: 409-15.
12. Sandborn W, McLeod R, Jewell D. Pharmacotherapy for inducing and maintaining remission in pouchitis. Cochrane Database Syst Rev 2000: CD001176.

13. Hurst RD, Molinari M, Chung TP, Rubin M, Michelassi F. Prospective study of the incidence, timing and treatment of pouchitis in 104 consecutive patients after restorative proctocolectomy. Arch Surg 1996; 131: 497-500.
14. Madden MV, McIntyre AS, Nicholls RJ. Double-blind crossover trial of metronidazole versus placebo in chronic unremitting pouchitis. Dig Dis Sci 1994; 39: 1193-6.
15. Shen B, Achkar JP, Lashner BA, Ormsby AH, Remzi FH, Brzezinski A, Bevins CL, Bambrick ML, Seidner DL, Fazio VW. A randomized clinical trial of ciprofloxacin and metronidazole to treat acute pouchitis. Inflamm Bowel Dis 2001; 7: 301-5.
16. Ruseler-van Embden JG, Schouten WR, van Lieshout LM. Pouchitis: result of microbial imbalance? Gut 1994; 35: 658-64.
17. Ruseler-van Embden JG, Both-Patoir HC. Anaerobic gram-negative faecal flora in patients with Crohn's disease and healthy subjects. Antonie Van Leeuwenhoek 1983; 49: 125-32.
18. Ruseler-Van Embden JG, van Lieshout LM. Isolation and characterisation of anaerobic intestinal bacteria. In: Lefkovits I, ed. Immunology methods manual. London: Academic Press Ltd., 1997: 1570-7.
19. Holderman LV CE, Moore WEC. Anaerobe Laboratory manual. Virginia polytechnic Institute and State University, 1977.
20. Damme-Jongsten van M, Wernars K, Notermans S. Cloning and sequencing of the Clostridium perfringens enterotoxin gene. Antonie Van Leeuwenhoek 1989; 56: 181-90.
21. Lyerly DM, Barroso LA, Wilkins TD. Identification of the latex test-reactive protein of Clostridium difficile as glutamate dehydrogenase. J Clin Microbiol 1991; 29: 2639-42.
22. Jolivet-Reynaud C, Moreau H, Alouf JE. Assay methods for alpha toxin from Clostridium perfringens: phospholipase C. Methods Enzymol 1988; 165: 293-7.
23. Schaumann R, Ackermann G, Pless B, Claros MC, Goldstein EJ, Rodloff AC. In vitro activities of fourteen antimicrobial agents against obligately anaerobic bacteria. Int J Antimicrob Agents 2000; 16: 225-32.
24. Edlund C, Nord CE. Effect of quinolones on intestinal ecology. Drugs 1999; 58: 65-70.
25. Appelbaum PC. Quinolone activity against anaerobes. Drugs 1999; 58: 60-4.
26. Royall D, Wolever TM, Jeejeebhoy KN. Clinical significance of colonic fermentation. Am J Gastroenterol 1990; 85: 1307-12.
27. Rubinstein MC, Fisher RL. Pouchitis: pathogenesis, diagnosis, and management. Gastroenterologist 1996; 4: 129-33.
28. Kelly DG, Phillips SF, Kelly KA, Weinstein WM, Gilchrist MJ. Dysfunction of the continent ileostomy: clinical features and bacteriology. Gut 1983; 24: 193-201.
29. O'Connell PR, Rankin DR, Weiland LH, Kelly KA. Enteric bacteriology, absorption, morphology and emptying after ileal pouch-anal anastomosis. Br J Surg 1986; 73: 909-14.
30. Luukkonen P, Valtonen V, Sivonen A, Sipponen P, Jarvinen H. Fecal bacteriology and reservoir ileitis in patients operated on for ulcerative colitis. Dis Colon Rectum 1988; 31: 864-7.
31. Gustafson C, Kald B, Sjodahl R, Tagesson C. Phospholipase C from Clostridium perfringens stimulates formation and release of platelet-activating factor (PAF-acether) in cultured intestinal epithelial cells (INT 407). Scand J Gastroenterol 1991; 26: 1000-6.
32. Gustafson C, Tagesson C. Phospholipase C from Clostridium perfringens stimulates phospholipase A2-mediated arachidonic acid release in cultured intestinal epithelial cells (INT 407). Scand J Gastroenterol 1990; 25: 363-71.
33. Titball RW. Bacterial phospholipases C. Microbiol Rev 1993;57:347-66.
34. Kienle P, Weitz J, Reinshagen S, Magener A, Autschbach F, Benner A, Stern J, Herfarth C. Association of decreased perfusion of the ileoanal pouch mucosa with early postoperative pouchitis and local septic complications. Arch Surg 2001; 136: 1124-30.
35. Guarner F, Malagelada JR. Gut flora in health and disease. Lancet 2003; 361: 512-9.
36. George RH, Symonds JM, Dimock F, Brown JD, Arabi Y, Shinagawa N, Keighley MR, Alexander-Williams J, Burdon DW. Identification of Clostridium difficile as a cause of pseudomembranous colitis. Br Med J 1978; 1: 695.
37. Gionchetti P, Rizzello F, Venturi A, Helwig U, Amadini C, Lammers KM, Ugolini F, Poggioli G, Campieri M. Prophylaxis of pouchitis onset with probiotic therapy: a double-blind, placebo controlled trial. gastroenterology 2000; 118: A190.

38. Gionchetti P, Rizzello F, Venturi A, Brigidi P, Matteuzzi D, Bazzocchi G, Poggioli G, Miglioli M, Campieri M. Oral bacteriotherapy as maintenance treatment in patients with chronic pouchitis: a double-blind, placebo-controlled trial. Gastroenterology 2000; 119: 305-9.
39. Gosselink MP, Schouten WR, van Lieshout LM, Hop WC, Laman JD, Ruseler-van Embden JG. Delay of the first onset of pouchitis by oral intake of the probiotic strain *Lactobacillus rhamnosus* GG. Dis Colon Rectum 2004; 47: 676-84.

CHAPTER 3

Delay of the first onset of pouchitis by oral intake of the probiotic strain *Lactobacillus rhamnosus* GG

Gosselink MP, Schouten WR, van Lieshout LM, Hop WCJ,
Laman JD and Ruseler-van Embden JGH.
Dis Colon Rectum 2004; 47: 876-84

ABSTRACT

Proctocolectomy with ileal pouch-anal anastomosis is the operation of choice for patients with refractory or fulminant ulcerative colitis. The most common long-term complication in these patients is pouchitis. This study was designed to investigate the efficacy of probiotic *Lactobacillus rhamnosus* GG in long-term delaying the first onset of pouchitis. Between 1989 and 2001, a consecutive series of 127 patients presenting with ulcerative colitis underwent an ileal pouch-anal anastomosis at the Erasmus Medical Center in Rotterdam. Histopathologic investigation of the resected specimens revealed unsuspected Crohn's disease in five patients. Postoperative complications resulted in pouch excision in five patients. The remaining 117 patients were included in this study. All episodes of pouchitis occurring in this group were analyzed. Pouchitis was diagnosed on the basis of clinical symptoms and endoscopic and histologic features. The 39 patients, who underwent an ileal pouch-anal anastomosis between 1996 and 2001, started immediately after the operation with the daily intake of *L. rhamnosus* GG in a fermented product. The 78 patients, in whom an ileal pouch-anal anastomosis was performed between 1989 and 1996, received no *L. rhamnosus* GG. Except for the duration of follow-up, the patient characteristics, indications for proctocolectomy, number of postoperative complications, and functional outcome were similar in both groups. First episodes of pouchitis were observed less frequently in patients with a daily intake of *L. rhamnosus* GG (cumulative risk at 3 years: 7 *vs.* 29%; P=0.011). Daily intake of fermented products containing *L. rhamnosus* GG provides significant clinical benefit, without side effects. Based on the results of this study, we recommend a daily intake of *Lactobacillus rhamnosus* GG (dose 1–2 × 10^{10} bacteria) to delay the first onset of pouchitis.

INTRODUCTION

Proctocolectomy with ileal pouch-anal anastomosis (IPAA) is the operation of choice for patients with refractory or fulminant ulcerative colitis (UC).[1,2] This procedure has the advantage of removing all diseased mucosa with preservation of continence, thereby avoiding a permanent ileostomy. Although this procedure is associated with low mortality, the postoperative morbidity caused by functional problems and complications is high.[3-5] In patients with UC, the most common long-term complication after IPAA is pouchitis.[4,6-9] This acute, nonspecific, inflammatory condition of the ileal pouch can mimic inflammatory bowel disease. Clinically, pouchitis is characterized by increased stool frequency, bleeding, abdominal pain, and systemic symptoms, such as fever, fatigue, weight loss, arthralgia, and dermatitis.[9,10] For an unequivocal diagnosis, endoscopic examination and histologic investigation are mandatory.[11-13] The incidence of pouchitis in UC patients varies widely, with a ten-year cumulative incidence ranging from 24 to 46%.[4,8,14-17] Approximately one-third

of these patients have only one episode, whereas the others go on to develop at least one recurrence.[9,18] In 8 to 32% of patients with one or more episodes of pouchitis, a syndrome of chronic pouchitis might develop with frequent exacerbations requiring constant maintenance therapy.[4,8,19-21] This chronic pouchitis finally results in pouch excision in 10% of these patients.[4,20-23]

The etiology of pouchitis is still not clear. The rapid response to antibiotic treatment suggests a pivotal role of the microbial flora in pouchitis. Additionally, high levels of serum antineutrophil cytoplasmic antibodies with perinuclear staining (pANCAs), a marker for the immune response to antigens from enteric bacteria, are shown to be significantly associated with the development of chronic pouchitis after IPAA.[24] A previous study, conducted at our institution,[25] revealed that the pouch flora in UC patients without a history of pouchitis resembles the normal colon flora and is characterized by high numbers of anaerobes, low numbers of pathogens, and the presence of lactobacilli. Furthermore, the pH of the luminal content of their pouch output is low (pH = 5.4), most probably because of fatty acids produced by the anaerobic flora during active fermentation of carbohydrates. A low pH can be considered as a protective mechanism; we showed that a low pH strongly inhibits the degradation of the protective mucus layer of the reservoir by bacterial and endogenous enzymes. Furthermore, it is likely that this low pH protects against colonization of pathogens. The pouch flora in patients with pouchitis was found to be greatly disturbed, with decreased numbers of anaerobes, increased numbers of aerobes, and a high pH (pH = 6.5). High numbers of *Clostridium perfringens,* a pathogen, were noted. Significantly lower numbers of lactobacilli were cultured in feces of patients with pouchitis. Based on these findings, we hypothesized that the intake of probiotic lactobacilli might help to maintain the microbiologic homeostasis in the pouch and increase the resistance against colonization of pathogens to prevent pouchitis. Probiotics are defined as living organisms with health-promoting properties.[26]

Until now only one study has been conducted to evaluate the effectiveness of probiotics in the prevention of the onset of acute pouchitis. Recently, Gionchetti *et al.*[27] demonstrated in a double-blind, placebo-controlled trial the efficacy of a probiotic preparation in delaying the first onset of acute pouchitis during the first year after ileostomy closure. This probiotic preparation, VSL#3® (VSL Pharmaceuticals, Ft. Lauderdale, FL), contains lyophilized bacteria consisting of four strains of *Lactobacillus*, three strains of *Bifidobacterium,* and one *Streptococcus.*[28] For our study, we chose a single strain, *Lactobacillus rhamnosus* GG. This strain was first isolated for its probiotic properties by Gorbach and Goldin[29] in 1985, and at present *L. rhamnosus* GG is the most frequently used and most successful probiotic in gastrointestinal disease.[31-36] Because we know that bacterial enzymes are involved in the breakdown of the mucus that protects the epithelial cells of the pouch, we first established that *L. rhamnosus* GG did not degrade human intestinal glycoproteins and thus far *L. rhamnosus* GG is safe to use for therapy.[37]

The purpose of this study was to investigate the efficacy of probiotic *L. rhamnosus* GG in delaying the first onset of pouchitis during a long time period.

PATIENTS AND METHODS

In the time period between March 1989 and March 2001, a consecutive series of 127 patients with UC underwent an IPAA at the Erasmus Medical Center in Rotterdam. All operations were performed by one surgeon (W.R.S.). Patients operated on during the time period between March 1996 and March 2001 started immediately after IPAA with the daily intake of a probiotic, *L. rhamnosus* GG (Group II). Patients operated on during the time period between October 1986 and March 1996 never used *L. rhamnosus* GG (Group I) and served as a control group. The clinical characteristics within the two groups and indication for surgery are listed in Table 1.

Ninety-three of 127 patients had undergone a subtotal colectomy previously with closure of the rectum stump (Group I = 76%; Group II = 67%). In the remaining 34 patients, a proctocolectomy with subsequent IPAA was performed during one single operation. In all patients in whom an IPAA was performed, a handsewn anastomosis was constructed at the level of the dentate line, after transanal mucosectomy. In 27 of 127 patients, a temporary ileostomy was constructed (Group I = 26%; Group II = 12%). The mean duration of the time interval between IPAA and ileostomy closure was 6.8 (Group I = 6.6; Group II = 7.2) months. In 113 of 127 patients, an "S" reservoir was constructed, in 4 a J-pouch, and in 10 patients a W-pouch (Group I: S = 86%, J = 2%, W = 12%; Group II: S = 95%, J = 5%, W = 0%). All resected specimens were examined by pathologists who were skilled in the evaluation of inflammatory bowel diseases. In five patients, pouch excision was necessary because of early postoperative complications. Another five patients, who were initially diagnosed as having chronic refractory pouchitis, were found to have undetected Crohn's disease by histopathologic investigation of the pouch material. These 10 patients were excluded; the remaining 117 patients were included in the study. The patients in Group I (n=78) never used *L. rhamnosus* GG, and patients in Group II (n=39) were treated with a daily dose of *L. rhamnosus* GG in a fermented product (daily dose of 350 ml of Vifit®, $1.4.10^{10}$ live bacteria, Mona, Woerden, The Netherlands).

Between 1989 and 1996, each episode of pouchitis was treated with metronidazole (daily 3 × 500 mg for 2 weeks), according to the international standard at that time. Since 1996, patients with pouchitis were treated with ciprofloxacin (daily 2 × 500 mg for 2 weeks), based on new microbiologic insights. In a substudy, we evaluated the lactobacilli-flora of 13 patients at the beginning of a pouchitis episode before treatment, during treatment with metronidazole or ciprofloxacin, and during pouchitis-free periods. All patients responded to the antibiotics. During pouchitis-free periods of the same 13 patients, we compared the colonization of freeze-dried *L. rhamnosus* GG in the pouch with a commercial fermented product with *L. rhamnosus* GG. These patients were treated for one year with the freeze-dried bacteria (daily dose of 300 mg *L. rhamnosus* GG: $3.0.10^{11}$ live bacteria, Valio, Helsinki, Finland), followed by one year of treatment with the commercial product (daily dose of 350 ml of Vifit®: $1.4.10^{10}$ live bacteria). The carrier for *L. rhamnosus* GG in the commercial product was fermented

Table 1.
Characteristics of the two groups.

	Group I: Control (1989-1996)	**Group II: Treated with *L*GG (1997-2001)**
Total number	85	42
Males	46 (55)	27 (60)
Median age in years (range)	35 (14-67)	38 (16-63)
Median follow-up after ileostomy closure in months (range)*	68 (11-163)	32 (22-61)
Duration of UC prior to surgical treatment in months (range)	71 (4-223)	54 (10-168)
Primary sclerosing cholangitis	6 (7)	3 (7)
Pancolitis/left-sided colitis	58/27 (68/32)	30/12 (71/29)
Crohn's disease	4 (5)	1 (2)
Indications for surgery		
Acute colitis	50 (59)	28 (67)
Chronic colitis	33 (39)	13 (31)
Dysplasia	2 (2)	1 (2)
Postoperative complications		
Small-bowel obstruction	6 (7)	3 (7)
Pelvic/anastomotic sepsis	6 (7)	3 (7)
Fistulas	3 (4)	1 (2)
Stricture	3 (4)	1 (2)
Pouch excision	6 (6)	2 (4)
Functional results		
Median stool frequency per 24 hours	5 (1-10)	5 (1.5-9)
Incontinence	9 (12)	5 (13)
Daytime or night soiling	23 (29)	10 (26)

Figures in parentheses are percentages or ranges. * P Value < 0,05.

milk. The recommended carrier for the freeze-dried *L. rhamnosus* GG was milk. Each month, fecal samples were collected for microbiologic enumeration of *L. rhamnosus* GG and other lactobacilli. This substudy was conducted before we started to treat all our patients immediately after IPAA with *L. rhamnosus* GG in a fermented product.

This study had the approval of the medical ethical committee of the Erasmus Medical Center and was performed without any interference or financial sponsoring from outside the center.

Assessment of Clinical Results

Hospital records from the time of the operation and outpatient clinic charts were analyzed, and follow-up information was obtained from a prospective database and from personal telephone communication when data were missing. Intervals of the standard follow-up program after IPAA are 3, 6, and 12 months during the first year and then once every year. Independently of these intervals, patients were requested to attend the outpatient clinic of our hospital as soon as they noticed changes in their bowel habit, regarding frequency, urgency, or bleeding.

Immediate postoperative data included mortality and morbidity requiring reoperation within 30 days after IPAA and ileostomy closure. Follow-up data, including stool frequency and degree of incontinence were recorded 12 months after ileostomy closure. Incontinence was defined as involuntary loss of stool requiring a perineal pad. Pouch excision rate was calculated.

All episodes of pouchitis were analyzed. Patients had all undergone continual follow-up with endoscopic analysis of the pouch mucosa at least annually. If symptoms of pouchitis were present or if there was endoscopic abnormality, a pouch biopsy was performed. The diagnosis of pouchitis was based on symptomatic, endoscopic, and histologic criteria. Symptoms associated with pouchitis are abdominal cramping, bloody diarrhea, increased stool frequency, urgency, malaise, and fever. Endoscopic signs of inflammation included mucosal hyperemia with loss of vascular pattern with or without ulceration. Histologic criteria for pouchitis were characterized by signs of acute inflammation, significant neutrophil infiltration, and ulceration. Histologic signs of acute inflammation was an essential requirement for the diagnosis.

The first episode of pouchitis was the primary end point. Secondary end points were total number of episodes of pouchitis and frequency of chronic pouchitis. Chronic pouchitis was defined as continuous symptoms for more than one month and the continued need for drugs to control symptoms.

Microbiology

Feces was collected and cultured more than 200 times to determine the presence of lactobacilli. Within one or two hours after collection, the stools were processed. The samples were thoroughly mixed and tenfold dilutions were prepared in anaerobic dilution fluid.[25] Samples of appropriate dilutions were plated aerobically and anaerobically on Bacto Lactobacilli MRS agar (Difco, Detroit, MI) for *L. rhamnosus* GG and on Rogosa agar (Oxoid Ltd., Basingstoke, England) for other lactobacilli than *L. rhamnosus* GG. After five days of incubation at 37°C, colonies were counted and identified with conventional methods. On MRS agar, colonies of *L. rhamnosus* GG can be easily and exactly discriminated from other colonies of lactobacilli by their colony shape, texture, color, and size, which was confirmed by further identification. The limit of detection for *L. rhamnosus* GG and the other lactobacilli was 2.10^2 bacteria per gram feces.

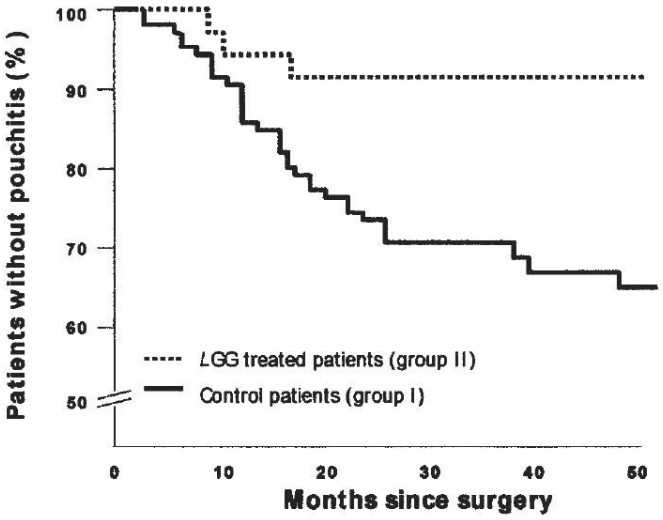

Figure 1.
Kaplan-Meier life-table analysis showing the first episode of pouchitis in patients with and without daily intake of *Lactobacillus rhamnosus* GG.

Statistical Analysis

Proportions were analyzed by chi-squared test or Fisher's exact test when appropriate. Wilcoxon's signed-rank test was used to compare numbers of lactobacilli and *L. rhamnosus* GG in feces, during treatment with the freeze-dried bacteria, and treatment with the commercial product. Wilcoxon's signed-rank test also was used to compare numbers of lactobacilli obtained from patients with pouchitis before, during, and after antibiotic treatment. The risk of pouchitis was estimated using the Kaplan-Meier life table analysis and compared using the log-rank test. $P<0.05$ (two-tailed) was considered the limit of significance.

RESULTS

Clinical Results

Except for the duration of follow-up, patient characteristics, number of postoperative complications, and functional outcome were similar in both groups (Table 1). One hundred seventeen patients had a functional ileoanal anastomotic stricture at the time of evaluation. Median duration of follow-up in Group I was 68 (range, 11–163) months and 32 (range, 22–65) months in Group II. In Group I, with a total follow-up of 442 patient-years, 27 patients developed pouchitis at least once. In

Group II, three patients encountered pouchitis during a total follow-up of 104 patient-years. The occurrence of pouchitis was not affected by age or gender. Figure 1 shows life-table analysis of risk of pouchitis in both groups. First episodes of pouchitis were observed less frequently in patients treated with *L. rhamnosus* GG (Group II) than in the control group (Group I; 7 *vs.* 29% at 3 years; P=0.011).

Eight patients in Group I and two patients in Group II encountered only a single pouchitis episode (Table 2). Twelve patients in Group I experienced recurrent episodes of pouchitis *vs.* one patient in Group II. Seven patients in Group I developed chronic pouchitis that responded poorly to medical treatment. In four of these patients, the pouch had to be excised because of refractory pouchitis or poor functional result. Histologic examination of the removed pouches showed no signs of Crohn's disease.

Table 2.
Frequency of pouchitis.

	Study Group	Control Group	P Value
Cases with single episode	3 (7)	27 (29)	0.011
Cases with recurrent episodes	1 (33)	12 (44)	NS
Cases with chronic pouchitis	0 (0)	7 (26)	NS

NS = not significant.
Data are numbers with percentages in parentheses.

Microbiologic Results

Feces from patients in the substudy, collected at the beginning of a pouchitis episode before treatment and during treatment with metronidazole or ciprofloxacin, contained significantly less lactobacilli than feces from the same patients in a pouchitis-free period (P<0.01; Table 3). No differences in numbers of *L. rhamnosus* GG were found between patients treated with the lyophilized bacteria and those treated with the fermented product (Table 4). *L. rhamnosus* GG was detected in all fecal samples from each patient treated with *L. rhamnosus* GG. Numbers of *L. rhamnosus* GG exceeded the count of resident lactobacilli more than 100 times. When intake of *L. rhamnosus* GG was finished, *L. rhamnosus* GG disappeared from the feces within two days. The total number of other lactobacilli was similar to that found in patients not treated with *L. rhamnosus* GG, during pouchitis-free periods.

DISCUSSION

This study showed that the first onset of pouchitis can be delayed more than three years by a daily dose of the probiotic *L. rhamnosus* GG in a fermented product. We prescribed a fermented product, based on our finding that freeze-dried bacteria and bacteria in a fermented product survived the pouch in equal numbers, although

Table 3.
Lactobacilli in feces of patients in the substudy.

	No. of Patients	No. of Samples	No. of Lactobacilli	P Value*
Patients with pouchitis	13	40	ND (ND-7)	—
Metronidazole treatment	7	34	ND (ND-7)	NS
Ciprofloxacin treatment	6	31	ND (ND-6)	NS
Pouchitis-free periods	13	30	4.53 (ND-7)	0.01

NS = not significant; ND = not detected.
Data are calculated from mean individual data if a patient had more than one sample. No. of bacteria (log 10) are per gram wet feces.
*P values denote differences with the first row (Wilcoxon test).

Table 4.
Lactobacillus rhamnosus GG and other lactobacilli in feces of patients in the substudy.

	No. of Patients	No. of Samples	No. of Lactobacilli*	P Value*	No. of *Lactobacillus rhamnosus* GG	P Value**
Treatment with freeze-dried bacteria	13	46	4.45 (ND-7)	NS	6.50 (5-8)	NS
Treatment with fermented product	13	40	4.43 (ND-7)		6.83 (5-8)	

NS = not significant; ND = not detected.
Data are medians with ranges in parentheses calculated from mean individual data if a patient had more than one sample. No. of bacteria (log 10) are per gram wet feces.
*Other than L. rhamnosus GG.
**P values denote differences between treatment with freeze-dried *L. rhamnosus* GG vs. treatment with fermented product.

the numbers of *L. rhamnosus* GG in the fermented product were 100 times lower than in the freeze-dried application. Probably the survival of *L. rhamnosus* GG, during passage of the intestinal tract, is better when administered in a fermented milk product. Patients with pouchitis, have no or only few lactobacilli in their feces, not only during their pouchitis episode, but also during treatment with antibiotics. Although lactobacilli return in the pouch after successful treatment, their numbers are still lower than those detected in the colon of healthy subjects in whom approximately 10^7 lactobacilli per gram feces are found.[38] By oral intake of *L. rhamnosus* GG, the total numbers of lactobacilli in the pouch, including *L. rhamnosus* GG, increased to levels

comparable to those observed in the colon of healthy subjects. In our opinion, this phenomenon can be considered as restoration of homeostasis in the pouch, which may protect against rapid colonization by pathogens. Therefore, oral administration of *L. rhamnosus* GG seems to be effective in prevention of the first onset of pouchitis as well as the prevention of recurrence after antibiotic treatment. Although we did not analyze side effects, none of the patients had complaints that were possibly connected with the intake of *L. rhamnosus* GG or the fermented product.

Friedman and George[36] reported that administration of *L. rhamnosus* GG in combination with fructo-oligosaccharide, a prebiotic, for one month induced remission in ten patients with chronic pouchitis. In our patients, who received daily *L. rhamnosus* GG, no such chronic pouchitis was seen, which is important because chronic pouchitis implies both the risk of pouch failure caused by fibrotic changes and malignant transformation of the pouch mucosa.

This is the first study that shows that the first onset of pouchitis can be delayed for a long period of time by oral administration of a single strain of the probiotic bacteria *L. rhamnosus* GG. *L. rhamnosus* GG will be most clearly perceived under conditions in which the normal physiologic balance in the intestinal tract has been or will be disturbed. *L. rhamnosus* GG has been proved to be effective in several studies in the field of gastroenterology but also in atopic disease.[39] It has been shown, for example, that *L. rhamnosus* GG prevents antibiotic-associated diarrhea.[32] In addition, it has been demonstrated that relapsing *Clostridium difficile* colitis can be successfully treated with *L. rhamnosus* GG.[33] *L. rhamnosus* GG also plays a role in the prevention of diarrhea among travelers.[35] Shibolet and coworkers[40] showed that *L. rhamnosus* GG significantly declines the severity of colitis in a rat model. This effect was similar to that obtained with a probiotic mixture used by Gionchetti and coworkers.[28] Both probiotic preparations decreased prostaglandin E_2 generation and nitric oxide synthetase (NOS) activity in a similar way.

Recently, Gionchetti *et al.*[27] demonstrated in a double-blind, placebo-controlled trial the efficacy of a probiotic preparation (VSL#3®, VSL Pharmaceuticals, Ft. Lauderdale, FL) in prophylaxis of pouchitis onset during the first year after ileostomy closure. This preparation did contain lyophilized bacteria consisting of four strains of *Lactobacillus* (no *L. rhamnosus* GG), three strains of *Bifidobacterium,* and one *Streptococcus*. Oral administration of VSL#3® also was effective in the prevention of relapses in patients with chronic pouchitis.[28] The use of a mixture of different bacterial species makes it difficult to evaluate which strain is the most active one. Strains may differ significantly in metabolic activity and their effect on the host. Crucial for the efficacy of probiotics is the viability, stability, and biochemical qualities of the strains used. Another prerequisite is that the strains are harmless to the host; patients with pouch strains must be unable to degrade intestinal mucus glycoproteins that protect the epithelial cells of the reservoir. In an earlier study, we showed that *L. rhamnosus* GG satisfies this requirement.[37]

Our present study and the study conducted by Gionchetti and coworkers provides

evidence for the efficacy of a probiotic in the prevention of the first onset of pouchitis. At present, acute pouchitis can only be treated successfully with antibiotics. Recently, Kuisma and coworkers[41] tried to treat patients with an attack of acute pouchitis with *L. rhamnosus* GG alone. No clinical improvement of pouch inflammation was observed. Based on this study, it seems unlikely that *L. rhamnosus* GG is effective in the treatment of pouchitis itself, indicating that antibiotics are still the therapy of choice.

Ulisse *et al.*[42] showed that antibiotic treatment in patients with pouchitis, although able to induce clinical remission, is not able to completely restore normal levels of the cytokine-inducible nitric oxide synthetase (iNOS), and metalloproteinase enzymes activity as observed in patients without pouchitis. *L. rhamnosus* GG induces expression of iNOS gene and enhance the production of the proinflammatory cytokine tumor necrosis factor-α, which in turn may be responsible for the downregulation of iNOS and metalloproteinase activity.[43,44] These findings may help to explain the mechanism of action by which *L. rhamnosus* GG is beneficial in preventing pouchitis. Other possible mechanisms by which *L. rhamnosus* GG exerts its effects on the host might be antagonizing pathogens directly through release of antimicrobial compounds, reducing the gut pH by lactic acid production,[45] competing for binding and receptor sites with potential pathogens,[46,47] and competing with pathogens for available nutrients and other growth factors.[48] Furthermore, it has been shown that *L. rhamnosus* GG improves immune function and stimulates immunomodulatory cells.[40,48-50]

In our study, the incidence of pouchitis at three years was significantly lower in the patients who received daily *L. rhamnosus* GG. The sample size was relatively small, with a historic group as control group, but can be overcome by the large therapeutic effects. A crossover study is warranted to assess whether cessation of *L. rhamnosus* GG intake results in new pouchitis episodes. The incidence of pouchitis, as reported in the literature, shows a wide variability, probably because of a lack of accepted diagnostic criteria, the inclusion of IPAA patients without UC, and the different length of follow-up. In our opinion, a combination of clinical, endoscopic, and histopathologic criteria together define pouchitis. The incidence of pouchitis observed in our control group (24%) is comparable to incidence reported by other investigators who used similar diagnostic criteria and follow-up.[15,16,18,24] Although the first onset of pouchitis can be encountered many years after the IPAA, 80% of all cases of pouchitis occur during the first four years after construction of the IPAA.[14,51] Large, multicenter, placebo-controlled, double-blind, clinical trials are needed to establish the precise role of probiotics in the prevention of the first onset of pouchitis. Furthermore, under the influence of the increasing expenditure in health care, it has become more and more regular to evaluate new treatments before they become general practice. Pouchitis leads to increased patient discomfort and sick leave and thus may result in a considerable economic burden. This has to be included when the costs of daily oral intake of a probiotic are compared with the costs of incidental antibiotic treatment.

CONCLUSIONS

Based on the results of the present study, we recommend daily intake of *L. rhamnosus* GG immediately after the construction of an ileal pouch-anal anastomosis in patients with UC: first, because *L. rhamnosus* GG has shown to be effective; second, because this single strain as a part of a fermented product is less expensive than the lyophilized mixture, VSL#3®. It is worthwhile to investigate if other inexpensive and over-the-counter products, which are enriched with other probiotic strains, can prevent the onset of acute pouchitis.

REFERENCES

1. Parks AG, Nicholls RJ. Proctocolectomy without ileostomy for ulcerative colitis. Br Med J 1978; 2: 85-8.
2. Utsunomiya J, Iwama T, Imajo M, Matsuo S, Sawai S, Yaegashi K, Hirayama R. Total colectomy, mucosal proctectomy, and ileoanal anastomosis. Dis Colon Rectum 1980; 23: 459-66.
3. Johnson E, Carlsen E, Nazir M, Nygaard K. Morbidity and functional outcome after restorative proctocolectomy for ulcerative colitis. Eur J Surg 2001; 167: 40-5.
4. Fazio VW, Ziv Y, Church JM, Oakley JR, Lavery IC, Milsom JW, Schroeder TK. Ileal pouch-anal anastomoses complications and function in 1005 patients. Ann Surg 1995; 222: 120-7.
5. Karlbom U, Raab Y, Ejerblad S, Graf W, Thorn M, Pahlman L. Factors influencing the functional outcome of restorative proctocolectomy in ulcerative colitis. Br J Surg 2000; 87: 1401-8.
6. Pemberton JH. The problem with pouchitis. Gastroenterology 1993; 104: 1209-11.
7. Keighley MR. Pouchitis. Br J Surg 1994; 81: 1091-2.
8. Meagher AP, Farouk R, Dozois RR, Kelly KA, Pemberton JH. J ileal pouch-anal anastomosis for chronic ulcerative colitis: complications and long-term outcome in 1310 patients. Br J Surg 1998; 85: 800-3.
9. Lohmuller JL, Pemberton JH, Dozois RR, Ilstrup D, van Heerden J. Pouchitis and extraintestinal manifestations of inflammatory bowel disease after ileal pouch-anal anastomosis. Ann Surg 1990; 211: 622-9.
10. Madden MV, Farthing MJ, Nicholls RJ. Inflammation in ileal reservoirs: 'pouchitis'. Gut 1990; 31: 247-9.
11. Sandborn WJ. Pouchitis following ileal pouch-anal anastomosis: definition, pathogenesis, and treatment. Gastroenterology 1994; 107: 1856-60.
12. Shepherd NA, Hulten L, Tytgat GN, Nicholls RJ, Nasmyth DG, Hill MJ, Fernandez F, Gertner DJ, Rampton DS, et al. Pouchitis. Int J Colorectal Dis 1989; 4: 205-29.
13. Shen B, Achkar JP, Lashner BA, Ormsby AH, Remzi FH, Bevins CL, Brzezinski A, Petras RE, Fazio VW. Endoscopic and histologic evaluation together with symptom assessment are required to diagnose pouchitis. Gastroenterology 2001; 121: 261-7.
14. Penna C, Dozois R, Tremaine W, Sandborn W, LaRusso N, Schleck C, Ilstrup D. Pouchitis after ileal pouch-anal anastomosis for ulcerative colitis occurs with increased frequency in patients with associated primary sclerosing cholangitis. Gut 1996; 38: 234-9.
15. Stahlberg D, Gullberg K, Liljeqvist L, Hellers G, Lofberg R. Pouchitis following pelvic pouch operation for ulcerative colitis. Incidence, cumulative risk, and risk factors. Dis Colon Rectum 1996; 39: 1012-8.
16. Svaninger G, Nordgren S, Oresland T, Hulten L. Incidence and characteristics of pouchitis in the Kock continent ileostomy and the pelvic pouch. Scand J Gastroenterol 1993; 28: 695-700.
17. Sandborn WJ, Tremaine WJ, Batts KP, Pemberton JH, Phillips SF. Pouchitis after ileal pouch-anal anastomosis: a Pouchitis Disease Activity Index. Mayo Clin Proc 1994; 69: 409-15.
18. Hurst RD, Molinari M, Chung TP, Rubin M, Michelassi F. Prospective study of the incidence, timing and treatment of pouchitis in 104 consecutive patients after restorative proctocolectomy. Arch Surg 1996; 131: 497-502.

19. Setti Carraro P, Talbot IC, Nicholls RJ. Longterm appraisal of the histological appearances of the ileal reservoir mucosa after restorative proctocolectomy for ulcerative colitis. Gut 1994; 35: 1721-7.
20. Mowschenson PM, Critchlow JF, Peppercorn MA. Ileoanal pouch operation: long-term outcome with or without diverting ileostomy. Arch Surg 2000; 135: 463-6.
21. Hurst RD, Chung TP, Rubin M, Michelassi F. The implications of acute pouchitis on the long-term functional results after restorative proctocolectomy. Inflamm Bowel Dis 1998; 4: 280-4.
22. Korsgen S, Keighley MR. Causes of failure and life expectancy of the ileoanal pouch. Int J Colorectal Dis 1997; 12: 4-8.
23. Lepisto A, Luukkonen P, Jarvinen HJ. Cumulative failure rate of ileal pouch-anal anastomosis and quality of life after failure. Dis Colon Rectum 2002; 45: 1289-94.
24. Fleshner PR, Vasiliauskas EA, Kam LY, Fleshner NE, Gaiennie J, Abreu-Martin MT, Targan SR. High level perinuclear antineutrophil cytoplasmic antibody (pANCA) in ulcerative colitis patients before colectomy predicts the development of chronic pouchitis after ileal pouch-anal anastomosis. Gut 2001; 49: 671-7.
25. Ruseler-van Embden JG, Schouten WR, van Lieshout LM. Pouchitis: result of microbial imbalance? Gut 1994; 35: 658-64.
26. Ouwehand AC, Salminen S, Isolauri E. Probiotics: an overview of beneficial effects. Antonie Van Leeuwenhoek 2002; 82: 279-89.
27. Gionchetti P, Rizzello F, Helwig U, Venturi A, Lammers KM, Brigidi P, Vitali B, Poggioli G, Miglioli M, Campieri M. Prophylaxis of pouchitis onset with probiotic therapy: A double-blind, placebo-controlled trial. Gastroenterology 2003; 124: 1202-9.
28. Gionchetti P, Rizzello F, Venturi A, Brigidi P, Matteuzzi D, Bazzocchi G, Poggioli G, Miglioli M, Campieri M. Oral bacteriotherapy as maintenance treatment in patients with chronic pouchitis: a double-blind, placebo-controlled trial. Gastroenterology 2000; 119: 305-9.
29. Gorbach SL, Goldin BR. Lactobacillus strains and methods of isolation. United States, 1989.
30. Schultz M, Sartor RB. Probiotics and inflammatory bowel diseases. Am J Gastroenterol 2000; 95: S19-21.
31. Malin M, Suomalainen H, Saxelin M, Isolauri E. Promotion of IgA immune response in patients with Crohn's disease by oral bacteriotherapy with Lactobacillus GG. Ann Nutr Metab 1996; 40: 137-45.
32. Siitonen S, Vapaatalo H, Salminen S, Gordin A, Saxelin M, Wikberg R, Kirkkola AL. Effect of Lactobacillus GG yoghurt in prevention of antibiotic associated diarrhoea. Ann Med 1990; 22: 57-9.
33. Gorbach SL, Chang TW, Goldin B. Successful treatment of relapsing Clostridium difficile colitis with Lactobacillus GG. Lancet 1987; 2: 1519.
34. Hilton E, Kolakowski P, Singer C, Smith M. Efficacy of Lactobacillus GG as a Diarrheal Preventive in Travelers. J Travel Med 1997; 4: 41-43.
35. Pant AR, Graham SM, Allen SJ, Harikul S, Sabchareon A, Cuevas L, Hart CA. Lactobacillus GG and acute diarrhoea in young children in the tropics. J Trop Pediatr 1996; 42: 162-5.
36. Friedman G, George J. Treatment of refractory "pouchitis" with prebiotic and probiotic therapy. Gastroenterology 2000; 118: A190.
37. Ruseler-van Embden JG, van Lieshout LM, Gosselink MJ, Marteau P. Inability of Lactobacillus casei strain GG, L. acidophilus, and Bifidobacterium bifidum to degrade intestinal mucus glycoproteins. Scand J Gastroenterol 1995; 30: 675-80.
38. Gibson GR, Beatty ER, Wang X, Cummings JH. Selective stimulation of bifidobacteria in the human colon by oligofructose and inulin. Gastroenterology 1995; 108: 975-82.
39. Kalliomaki M, Salminen S, Arvilommi H, Kero P, Koskinen P, Isolauri E. Probiotics in primary prevention of atopic disease: a randomised placebo-controlled trial. Lancet 2001; 357: 1076-9.
40. Kuisma J, Mentula S, Jarvinen H, Kahri A, Saxelin M, Farkkila M. Effect of Lactobacillus rhamnosus GG on ileal pouch inflammation and microbial flora. Aliment Pharmacol Ther 2003; 17: 509-515.
41. Ulisse S, Gionchetti P, D'Alo S, Russo FP, Pesce I, Ricci G, Rizzello F, Helwig U, Cifone MG, Campieri M, De Simone C. Expression of cytokines, inducible nitric oxide synthase, and matrix metalloproteinases in pouchitis: effects of probiotic treatment. Am J Gastroenterol 2001; 96: 2691-9.

42. Korhonen R, Korpela R, Saxelin M, Maki M, Kankaanranta H, Moilanen E. Induction of nitric oxide synthesis by probiotic Lactobacillus rhamnosus GG in J774 macrophages and human T84 intestinal epithelial cells. Inflammation 2001; 25: 223-32.
43. Miettinen M, Vuopio-Varkila J, Varkila K. Production of human tumor necrosis factor alpha, interleukin-6, and interleukin-10 is induced by lactic acid bacteria. Infect Immun 1996; 64: 5403-5.
44. Langhendries JP, Detry J, Van Hees J, Lamboray JM, Darimont J, Mozin MJ, Secretin MC, Senterre J. Effect of a fermented infant formula containing viable bifidobacteria on the fecal flora composition and pH of healthy full-term infants. J Pediatr Gastroenterol Nutr 1995; 21: 177-81.
45. Kailasapathy K, Chin J. Survival and therapeutic potential of probiotic organisms with reference to Lactobacillus acidophilus and Bifidobacterium spp. Immunol Cell Biol 2000; 78: 80-8.
46. Fujiwara S, Hashiba H, Hirota T, Forstner JF. Proteinaceous factor(s) in culture supernatant fluids of bifidobacteria which prevents the binding of enterotoxigenic Escherichia coli to gangliotetraosylceramide. Appl Environ Microbiol 1997; 63: 506-12.
47. Rolfe RD. The role of probiotic cultures in the control of gastrointestinal health. J Nutr 2000; 130: 396S-402S.
48. Isolauri E, Joensuu J, Suomalainen H, Luomala M, Vesikari T. Improved immunogenicity of oral D x RRV reassortant rotavirus vaccine by Lactobacillus casei GG. Vaccine 1995; 13: 310-2.
49. Shibolet O, Karmeli F, Eliakim R, Swennen E, Brigidi P, Gionchetti P, Campieri M, Morgenstern S, Rachmilewitz D. Variable response to probiotics in two models of experimental colitis in rats. Inflamm Bowel Dis 2002; 8: 399-406.
50. Isolauri E, Juntunen M, Rautanen T, Sillanaukee P, Koivula T. A human Lactobacillus strain (Lactobacillus casei sp strain GG) promotes recovery from acute diarrhea in children. Pediatrics 1991; 88: 90-7.
51. Heuschen UA, Autschbach F, Allemeyer EH, Zollinger AM, Heuschen G, Uehlein T, Herfarth C, Stern J. Long-term follow-up after ileoanal pouch procedure: algorithm for diagnosis, classification, and management of pouchitis. Dis Colon Rectum 2001; 44: 487-99.

CHAPTER 4

Introduction of preoperative radiotherapy in the treatment of operable rectal cancer in the Southwest region of The Netherlands

Adapted (in part) from:
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ABSTRACT

After publication of the results of the Dutch TME-trial preoperative radiotherapy followed by TME-surgery was introduced in July 2001 in the region of the comprehensive cancer centre Rotterdam as standard treatment for rectal cancer. The aim of this study is to identify the compliance to a new standardized treatment protocol i.e. the introduction of preoperative radiotherapy and to analyze the results of rectal cancer treatment in the Cancer Centre Rotterdam Region. A total of 521 patients with adenocarcinoma of the rectum were included in the period from 2001 to 2003. All patients were treated with curative intent. There was a significant increase of preoperative radiotherapy for patients with a tumour in the lower two-third of the rectum (21% versus 69%, $p<0.001$). Peri-operative mortality rate was 2.7% and overall anastomotic leakage rate was 10.3%. There was a significant increase in the occurrence of anastomotic leakage in end-to-end anastomoses ($p<0.0001$). Most anastomotic leakages occurred when patients were operated in between 4 and 8 days after the end of radiotherapy. Several aspects such as continence for urine and feces and sexual functions were poorly registered. The total number of lymph nodes registered in pathology reports was low. The rate of reported circumferential margins increased from 37% to 70% after feedback to the regional pathology working group. The regional quality of rectal cancer surgery is conform preset quality-demands. There was a significant increase in the percentage preoperative radiotherapy, but still about 25% of patients who qualified for radiotherapy did not receive radiation. Pathology reports improved during registration, which illustrates the importance of registration to assess and improve quality of rectal cancer treatment.

INTRODUCTION

The average annual incidence of rectal cancer in The Netherlands is 2300 patients and this incidence is rising.[1] The treatment of rectal cancer has evolved into a multidisciplinary treatment with standardized surgical, pathological and radiotherapeutical procedures.[2-5] Total mesorectal excision (TME) leads to a decreased rate of local recurrence.[6] A randomized phase III trial performed by the Dutch Colorectal Cancer Group showed a beneficial effect of preoperative radiotherapy followed by TME-surgery on local control.[2] Based on these results the Dutch national guidelines for the treatment of rectal cancer were changed and all patients were advised to be treated with preoperative radiotherapy. However, a subgroup analysis did not demonstrate the additional effect of short-term preoperative radiotherapy for tumours in the upper third of the rectum.[2] Therefore, in the region of the Comprehensive Cancer Centre Rotterdam only rectal tumours located in the lower two-third of the rectum were treated with 5 × 5 Gray radiotherapy followed by TME-surgery since July 2001.

A registration database was started to analyze the implementation of the new

treatment protocol. There is a rising interest in national and regional registration studies and the analysis of the level of quality of regional and national cancer treatment.[7] In Sweden a national registration database has been used for years to analyze national results of cancer treatment and since 1995 a specialized rectal cancer database has been introduced.[8] In The Netherlands only a few registration studies focus on the quality of national and regional treatment. Most of these projects are retrospective studies that focus on survival and therefore miss information on postoperative complications and functional results (e.g. urinary and fecal continence and sexual functions). The aim of this study is to identify the compliance to a new standardized treatment protocol i.e. the introduction of preoperative radiotherapy; furthermore, to analyze the results of rectal cancer treatment in the Cancer Centre Rotterdam Region and compare these with reference values based on selected patients from randomized trials in the recent literature.

PATIENTS AND METHODS

The region of the Comprehensive Cancer Centre Rotterdam consists of one tertiary referral hospital and 15 general hospitals in the Southwestern part of The Netherlands, which is a region with 2.3 million inhabitants. All oncological colorectal surgeons join in The Regional Network of Surgeons.

All patients who underwent treatment with curative intent for a histologically confirmed adenocarcinoma of the rectum between January 2001 and December 2003 were included in the registry. The rectum was defined as the first 15 cm bowel from the dentate line measured by endoscopy or as the part underlying the virtual line between symphysis pubis and promontory during contrast imaging. National guidelines advise imaging by pelvic CT or MRI of all tumours in case of suspicion of local growth close to and into surrounding structures (T3 and T4). Treatment with curative intent required a patient without evidence of distant metastases and a rectal cancer that allowed for a radical resection based on preoperative imaging studies. A patient was not excluded when radical rectal surgery was combined with the resection of a peroperatively diagnosed distant metastasis. All patient-, tumour- and operative characteristics and postoperative follow-up data were scored according to a preset list including date of diagnosis, previous pelvic surgery, localization and distal margin of tumour, preoperative diagnostics and neoadjuvant treatment. Operative characteristics were as follows: type of surgery, anastomosis, surgeons and the postoperative complications. Tumours were classified according to the UICC TNM-criteria. Follow-up characteristics were as follows: CEA serum levels, local and distant control, loss of continence of urine and feces, and sexual functions. Anastomotic leakage was defined as a clinical observable leakage in which reintervention was necessary. Preset reference values based on literature were as follows: postoperative mortality < 5%, anastomotic leakage < 10%, local recurrence < 10%, loss of urinary

continence < 10% after 3 months, loss of fecal continence < 10% after 3 months and erection disturbances < 35% after 6 months.[2,9,10] Before the start of the prospective registration a retrospective registration study was conducted in the period between January 2001 and June 2002. With the use of PALGA (a nation-wide histopathology database) all patients were selected for the retrospective part of the study. PALGA was also used in the prospective registration to verify if all rectal cancer patients were included in the registration.[11] The retrospective study was conducted by three independent research students who collected data in the participating hospitals and entered this information in a specially designed database.

Treatment

According to regional guidelines all patients treated from the first of July 2001 with a rectal tumour in the lower two-third of the rectum received radiotherapy prior to surgery. The radiotherapy was applied through a posterior-anterior field and two lateral fields with a total dosage of 25 Gray (5 × 5 Gray). The target volume of the radiotherapy consists of the primary tumour and the mesentery with the vascular supply containing the perirectal, presacral and internal iliac nodes. According to the protocol the day of surgery should be between 1 and 7 days after the end of radiotherapy. All operations, except for transanal endoscopic microsurgery (TEM), were performed by TME-technique. This technique implies en-bloc resection of the rectum and perirectal fat and lymphoid tissue.[6] The majority of regional surgeons were previously trained in this technique. Chemotherapy was no standard neoadjuvant or adjuvant treatment in the regional or national guidelines. Pathological examination of the resected specimen was performed by the standardized technique described by Quirke *et al.*[3]

Data collection and statistical analysis

The databases were provided to regional surgeons in Microsoft Access 1997/2000 or Microsoft Excel. One surgeon per hospital was responsible for the registration of all data. The Comprehensive Cancer Centre Rotterdam collected all data bi-annually. A data manager first performed a data-analysis for missing data, inconsistencies and faults, which were then reported to the surgeons. After a second correction all data were integrated in a database and analyzed with SAS statistical software (version 10). During the entire process the privacy of patients was maintained.

RESULTS

All 16 hospitals participated in the retrospective study and 12 hospitals participated in the prospective registration. Four hospitals did not participate because the surgeons reported to have a shortage of time to collect the data. Patient and tumour characteristics did not differ between these hospitals and therefore all data of the retrospective study

were included for further analyses.

The PALGA pathological database indicated 900 patients with a rectal tumour in the period between January 2001 and December 2003. Three hundred and seventy-nine patients were excluded because the tumour-histology other than adenocarcinoma, the tumour was not localized in the rectum or the treatment was with palliative intent. A total of 521 patients were included of which 230 in the retrospective part and 291 in the prospective part of the study. All patient-, tumour- and operation characteristics are summarized in Tables 1 and 2. The number of patients included per hospital varied from 13 to 51 per 2 years. The number of surgeons varied from 1 to 3 per hospital.

Table 1.
Patient and tumour characteristics.

	2001	**2002**	**2003**
Number of patients	155	203	163
Male/female (%)	59/41	62/38	57/43
Age (median)	68 (39-91)	67 (36-90)	65 (31-94)
Prior pelvic surgery (%)	10	10	13
Localization tumour (%)			
Proximal (10-15 cm)	35	27	29
Medial (5-10 cm)	30	35	28
Distal (0-5 cm)	35	37	44
TNM staging (%)			
Tumour			
T1	12	12	10
T2	35	31	36
T3	44	46	44
T4	7	9	4
Tx	2	2	6
Stage (UICC) (%)			
Stage I (T1–T2 N0M0)	39	34	37
Stage II (T3–T4 N0M0)	20	28	20
Stage III (N+)	32	30	29
Stage IV (M+)	8	6	8
Unknown	1	2	6

Table 2.
Operative and pathological characteristics.

	2001	2002	2003	
Operation (%)				
APR	30	27	31	n.s.
(L)AR	52	51	55	
TEM	5	5	0	
HP	10	14	8	
CPAA	3	3	6	
Protective stoma (%)	56	60	55	n.s.
Type of anastomosis (%)				
Hand-sewn	5	6	9	n.s.
Stapled	95	94	91	
Anastomosis (%)				
End to end	10	13	12	n.s.
Side to end	85	81	79	
Coloanal	5	6	9	
Circumferential margin (%)				
≤2 mm	9	9	11	n.s.
>2 mm	28	29	59	
Unknown	64	63	30	
Completeness of resection (%)				
Complete (R0)	91.4	91.5	93.8	n.s.
Microscopically incomplete (R1)	3.3	3.2	3.4	
Macroscopically incomplete (R2)	0.7	1.1	0	
Unknown	4.6	4.2	2.7	

(LAR = (low) anterior resection, APR = abdominoperineal resection, TEM = transanal endoscopic microsurgery, HP = Hartmann procedure, CPAA = colonic J-pouch anal-anastomosis and n.s. = non-significant.

Difference before and after the introduction of a new regional treatment protocol

During the study period a significant increase in the proportion of preoperatively irradiated (5 × 5 Gray) patients with a tumour in the lower two-third of the rectum was observed (21% versus 69%, $p<0.001$; Fig. 1). In the last semester

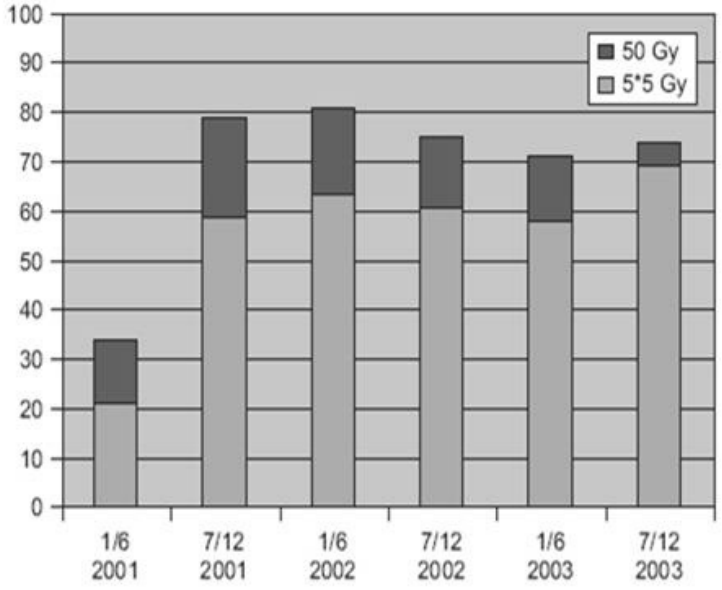

Figure 1.
Percentage preoperative radiotherapy before and after introductionof a new treatment protocol.

of 2003, 74% of the patients with a tumour in the lower two-third of the rectum received preoperative radiotherapy, including 5% undergoing long-term radiation (25 × 2 Gray). The percentage of long-term irradiated patients did not change over the period. There is no significant difference in age between the irradiated and the non-irradiated patients (p=0.37).

The proportion of patients receiving preoperative radiotherapy varied between hospitals from 41% to 100% (p<0.001). The motivation for withholding radiotherapy was not recorded in this study, but was certainly influenced by stage. T1 tumours were treated by preoperative radiotherapy in 47% of the patients, against 75% of T2 tumours and 85% of T3 tumours (p<0.001). The median interval between the last day of radiotherapy and operation was 4 days, 24 patients (10%) had an interval longer than 7 days.

Histopathology reporting

The number of analyzed lymph nodes in pathology specimens remained unchanged during the study period. A median number of 6 nodes (range 0–26) were analyzed without a significant difference between irradiated and non-irradiated patients.

There was also no difference in the number of positive nodes; median 3 positive nodes (range 1–16) in the irradiated group versus 2 (range 1–13) in the non-irradiated group. A substantial part of the pathology reports were not according to regional pathology guidelines. The circumferential resection margin was only reported in 37% of the reports in 2002. After feedback to the regional pathologist network this percentage increased to 70% in 2003.

Surgical management

The proportion of sphincter-sparing surgery did not differ before and after the introduction of the new treatment protocol. The numbers of sphincter-sparing operations were 92%, 81% and 27% for the proximal, middle and distal tumours. 49% of the patients with a tumour located in the lower two third of the rectum underwent a sphincter saving procedure. In most cases transanal double-stapled low colo-rectal anastomosis was performed. In 4% a colonic J-pouch anal anastomosis was constructed. In 58% of patients who underwent an (low) anterior resection a protective ileostomy was constructed. Overall clinical anastomotic leakage was demonstrated in 10.3% of the patients. Although there was no randomization, an analysis of the correlation between certain treatment factors and the occurrence of anastomotic leakage was performed (Table 3). There seemed to be no relation between the occurrence of anastomotic leakage and the construction of a diversion ileostomy or colostomy. There was a significant correlation between the type of anastomosis and the occurrence of anastomotic leakage ($p<0.0001$; Table 3). Postoperative mortality remained low in the entire period (3%). Mortality was significantly higher in patients who experienced anastomotic leakage (2% versus 12.5%, $p=0.02$).

The construction of a protective stoma did not have significant influence on mortality after the occurrence of anastomotic leakage. There were no differences in the completeness of resection in the analyzed period P (Table 2). Patients with an interval of 4–7 days between the end of radiotherapy and the day of surgery had a significantly higher rate of anastomotic leakage compared to patients with a shorter or longer interval ($p=0.04$). The anastomotic leakage rates were 4.1% (1–3 days); 16.7% (4–7 days) and 4.5% if the interval was more than 8 days. Postoperative mortality was not significantly different between the different interval groups ($p=0.84$).

Late morbidity and follow-up

Data on the loss of urinary and fecal continence and changes in sexual functions remained unknown in, respectively, 75%, 37% and 83% of the patients. Considering the high percentage of missing data of functional and sexual outcome no analysis of these data was performed. Pre- and postoperative CEA-values were registered in, respectively, 45% and 30% of the patients.

Table 3.
Correlations between anastomotic leakage and specific treatment factors.

Patient/treatment	Patients with anastomotic leakage		*p*-Value
	N	%	
Preoperative radiotherapy			
No	13	13	
Yes	10	9	n.s.
Protective stoma			
No	10	10.6	
Yes	13	10.3	n.s.
Localization of tumour			
Proximal	8	8	
Middle	10	10	
Distal	6	17	n.s.
Anastomosis			
End to end	6	27.3	
Side to end	18	10.1	
Coloanal	0	0	<0.0001

n.s. = non-significant.

DISCUSSION

Based on the results of the Dutch TME-trial the treatment in the region of the Comprehensive Cancer Centre Rotterdam of patients with a tumour in the lower two-third of the rectum has changed to preoperative radiotherapy (5 × 5 Gray) followed by TME-surgery.[2] This registration study identified a significant increase in the number of preoperatively irradiated patients after the introduction of the new treatment protocol. A significant percentage (25% at the end of the period) of patients, however, did not receive radiation and remained unchanged during the period of intensive registration after the introduction of the new treatment protocol. Identifying the specific reasons for not performing preoperative radiotherapy in a subgroup of patients was not the aim of our study, but reasons could be the lack of additional value of preoperative radiation in small tumours (T1).[2] Although preoperative radiotherapy was introduced in the guidelines for all rectal tumours, the study from Kapiteijn et al. demonstrated that radiotherapy did not reduce the incidence of local recurrences in the subgroup of stage I tumours. Therefore, some surgeons operated on patients with these small tumours without preoperative radiotherapy. This was clearly demonstrated in

this study where the minority of patients with T1 tumours received preoperative radiotherapy versus the majority of patients with higher stage tumours ($p<0.001$). A significant difference in the percentage of patients receiving preoperative radiotherapy per hospital was also identified (range 41–100%). One of the explanations for this difference can be a personal objection of a surgeon against radiotherapy. Other reasons could be a difference in patients with co-morbidity who are sometimes withdrawn from radiotherapy. Logistical reasons could also play a role in not irradiating patients. The current registration offers the possibility to specifically analyze results per hospital or surgeons and to provide feedback in order to optimize and standardize the regional treatment of rectal cancer.

The completeness of resection did not differ over the analyzed years and is comparable with the literature.[12] Mortality and the percentage of anastomotic leakage were in the range of the preset quality reference values. The significantly higher mortality after the occurrence of anastomotic leakage concurs with known literature.[13] The percentage of created protective stomata was comparable with data from the TME-trial.[14] But, in contrast to recently published results describing a protective value of the defunctioning stoma on the occurrence of clinically relevant anastomotic leakage, a lower leakage rate in this group of patients was not experienced.[13] There seemed to be a relation between the type of anastomosis and the rate of anastomotic leakage. In the present study there was no leakage in the small group of patients who received a coloanal anastomosis and colonic pouch. Only few publications describe the type anastomosis as one of the factors influencing anastomotic leakage. Hallböök *et al.*[15] showed a significantly lower anastomotic leakage rate after colon J-pouch compared with straight anastomoses. Other authors have hypothesized that higher leakage rates after straight (end-to-end) anastomosis can be based on impaired microcirculation at the anastomotic site.[15,16] This might be a reason for the higher anastomotic leakage rate found in the straight anastomosis in the present study.

Another interesting difference in anastomotic leakage rate was found between the different interval groups. Patients who were operated on 4–7 days after the last day of radiotherapy experienced a four times higher rate of anastomotic leakage, without an impact on postoperative mortality. In the Dutch TME-trial, however, patients older than 75 who were operated after 9 days had a significantly higher postoperative mortality (personal communication, Marijnen *et al.*). In theory postradiation oedema and inflammation could potentially lead to complications and this might be influenced by the time interval between radiotherapy and surgery. Until now the relevance of the total treatment time is virtually unknown and further studies are needed to fully understand this phenomenon.

The total number of lymph nodes examined by a pathologist is of importance for the accurate staging of a tumour and to accurately define the prognosis of the patient.[17] Instead of the generally accepted minimum of 12 lymph nodes examined for accurate staging only a mean of 6 nodes were examined in our region.[18] There was no analysis of the surgical quality of the resected TME-specimen; therefore, the reason for the

low number of lymph nodes cannot be attributed to poor surgery or poor pathology. In contrast to the TME-trial there was no significant influence of radiotherapy on the number of lymph nodes retrieved in the specimen.[19] The percentage of reported circumferential resection margins, being one of the most important factors for local control, was low in the beginning of the study.[20] However, after feedback to the regional pathology network an increase in the reported margins was noticed.

Because of the low percentage of reported functional and sexual results during follow-up it was not possible to perform reliable analyses on these data. Better and more reliable results on functional outcome can be obtained using anonymous quality of life questionnaires, such as the EORCT QLQ C30 or CR38.[21] The outcomes of randomized studies out of a carefully selected population cannot always be translated to the population in daily practice. The evaluation of the results of treatment of the patient population in daily practice can be of additive value to the results deducted from controlled studies. A prospective cancer-related database can identify regional quality of treatment, but can also identify individual differences between hospitals and surgeons. Compliance to introduced guidelines and new treatment protocols can be identified. A problem, however, is that the high workload of surgeons creates a burden for reliable and complete data-registration. An internal audit halfway the registration identified the lack of time of the surgeon as the only factor for failure to registration.

Participating surgeons

Dr. R.J. Oostenbroek, Dr. W.F. Blom and Dr. P.W. Plaisier, Albert Schweitzer Hospital Dordrecht; Dr. P.D. de Rooij, and Dr. E. van der Harst, Medical Center Rotterdam Zuid; Dr. J.G.F. van Kleef and Dr. O.C.M. Varin, Hospital Zeeuws-Vlaanderen; Drs. J.H. ten Thije and Drs. C.M. Dijkhuis, Oosterschelde Hospital Goes; Dr. H.E. Lont, Vlietland Hospital Schiedam; Dr. R. den Toom, Ruwaard van Putten Hospital Spijkenisse; Dr. W.F. Weidema, Ikazia Hospital Rotterdam; Dr. G.W.M. Tetteroo, IJsselland Hospital Rotterdam; Dr. H.W. P.M. Kemperman, Franciscus Hospital Roosendaal; Dr. R. van der Hul and Drs. M.R. Ketting, Van Weel-Bethesda Hospital Dirksland; Drs. E.J.R. Slingenberg, Lievensberg Hospital Bergen op Zoom; Dr. F. Logeman, Beatrix Hospital Gorinchem; Drs. G. Collet, Havenziekenhuis Rotterdam; Dr. W.R. Schouten, Drs. C. Verhoef, Dr. A.W.K.S. Marinelli and Dr. J.H.W. de Wilt, Erasmus Medical Centre Rotterdam.

Comprehensive Cancer Centre Rotterdam

Drs. E. van den Aardweg, Mw M. Sloover-Dankers, Mw. L.M.A.J. Muller, Drs. R.A.M. Damhuis.

REFERENCES

1. Siesling S, Van Dijck JA, Visser O, Coebergh JW. Trends in incidence of and mortality from cancer in The Netherlands in the period 1989–1998. Eur J Cancer 2003; 39 (17): 2521–30.
2. Kapiteijn E, Marijnen CA, Nagtegaal ID, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. N Engl J Med 2001; 345 (9): 638–46.
3. Quirke P, Durdey P, Dixon MF, Williams NS. Local recurrence of rectal adenocarcinoma due to inadequate surgical resection. Histopathological study of lateral tumour spread and surgical excision. Lancet 1986; 2 (8514): 996–9.
4 Nagtegaal ID, Van Krieken JH. The role of pathologists in the quality control of diagnosis and treatment of rectal cancer-an overview. Eur J Cancer 2002; 38 (7): 964–72.
5 Wiggers T, Van de Velde CJ. The circumferential margin in rectal cancer. Recommendations based on the Dutch Total Mesorectal Excision Study. Eur J Cancer 2002; 38 (7): 973–6.
6 Enker WE, Thaler HT, Cranor ML, Polyak T. Total mesorectal excision in the operative treatment of carcinoma of the rectum. J Am Coll Surg 1995; 181 (4): 335–46.
7. Kuijpens JL, Hoekstra OS, Hamming JF et al. [Surgery and referral for subsequent 131I therapy for patients with differentiated thyroid carcinoma in the south-east of The Netherlands, 1983–1996, compared to the consensus guidelines from 1987]. Ned Tijdschr Geneeskd 2002; 146 (10): 473–7.
8 Gunnarsson U, Seligsohn E, Jestin P, Pahlman L. Registration and validity of surgical complications in colorectal cancer surgery. Br J Surg 2003; 90 (4): 454–9.
9 Nesbakken A, Nygaard K , Bull-Njaa T, Carlsen E, Eri LM. Bladder and sexual dysfunction after mesorectal excision for rectal cancer. Br J Surg 2000; 87 (2): 206–10.
10 Havenga K, Enker WE, McDermott K, et al. Male and female sexual and urinary function after total mesorectal excision with autonomic nerve preservation for carcinoma of the rectum. J Am Coll Surg 1996; 182 (6): 495–502.
11 Bijlsma F, Van der Esch EP. [PALGA, of labor pains of the Pathological Anatomical District Automatized Archives]. Ned Tijdschr Geneeskd 1972; 116 (21): 902–3.
12 Kapiteijn E, Marijnen CA, Colenbrander AC et al. Local recurrence in patients with rectal cancer diagnosed between 1988 and 1992: a population-based study in the West Netherlands. Eur J Surg Oncol 1998; 24 (6): 528–35.
13 Gastinger I, Marusch F, Steinert R, et al. Protective defunctioning stoma in low anterior resection for rectal carcinoma. Br J Surg 2005; 92 (9): 1137–42.
14 Peeters KC, Tollenaar RA, Marijnen CA, et al.. Risk factors for anastomotic failure after total mesorectal excision of rectal cancer. Br J Surg 2004.
15 Hallbook O, Pahlman L, Krog M, Wexner SD, Sjodahl R. Randomized comparison of straight and colonic J pouch anastomosis after low anterior resection. Ann Surg 1996; 224 (1): 58–65.
16 Hallbook O, Johansson K, Sjodahl R. Laser Doppler blood flow measurement in rectal resection for carcinoma–comparison between the straight and colonic J pouch reconstruction. Br J Surg 1996; 83 (3): 389–92.
17 Tepper JE, O'Connell MJ, Niedzwiecki D et al. Impact of number of nodes retrieved on outcome in patients with rectal cancer. J Clin Oncol 2001;19 (1): 157–63.
18. Baxter NN, Virnig DJ, Rothenberger DA et al. Lymph node evaluation in colorectal cancer patients: a population-based study. J Natl Cancer Inst 2005; 97 (3): 219–25.
19 Marijnen CA, Nagtegaal ID, Klein Kranenbarg E et al. No downstaging after short-term preoperative radiotherapy in rectal cancer patients. J Clin Oncol 2001; 19 (7): 1976–84.
20 Nagtegaal ID,. Marijnen CA, Kranenbarg EK,. Van de Velde CJ, Van Krieken JH. Circumferential margin involvement is still an important predictor of local recurrence in rectal carcinoma: not one millimeter but two millimeters is the limit. Am J Surg Pathol 2002; 26 (3): 350–7.
21 Sprangers MA, te Velde A, Aaronson NK. The construction and testing of the EORTC colorectal cancer-specific quality of life questionnaire module (QLQ-CR38). European Organization for Research and Treatment of Cancer Study Group on Quality of Life. Eur J Cancer 1999; 35 (2): 238–47.

CHAPTER 5

Quality of life after total mesorectal excision for rectal cancer

Gosselink MP, Busschbach JJ, Dijkhuis CM,
Stassen LP, Hop WC and Schouten WR.
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ABSTRACT

After total mesorectal excision for rectal cancer, many surgeons try to avoid an abdominoperineal resection (APR) by performing a transanally double stapled low colo-rectal anastomosis (LRA), frequently without a pouch. This policy is mainly based on the assumption that the quality of life after such LRA is higher than after APR. It has been suggested that a better functional outcome and therefore a higher quality of life might be achieved by a colo-anal J-pouch anastomosis (CPAA). The aim of this study was to assess quality of life among disease-free survivors after APR, LRA and CPAA. The charts of 301 consecutive patients who had undergone surgery for cancer in the middle or lower third of the rectum were analysed. Two hundred four patients were eligible for inclusion. The quality of life among these patients was assessed using one generic (EQ-5D) and two disease-specific questionnaires (EORTC QLQ-C30 and EORTC QLQ-CR38). The response rate was 82%. The median follow-up was 31 months. Overall, quality of life was good but CPAA patients had better quality of life scores than APR and LRA patients. This difference was not only due to the better functional outcome but also to the lower incidence of disturbed micturition and sexual problems in the CPAA group. The quality of life after colo-anal J-pouch anastomosis is better than after abdominoperineal resection (APR) and low colo-rectal anastomosis (LRA). The quality of life after APR is similar to that after LRA.

INTRODUCTION

Total mesorectal excision (TME) has become the gold standard for the treatment of cancer in the middle or lower third of the rectum. It has been shown that, world wide, local recurrence rates have declined since the introduction of TME.[1] Good long-term quality of life is therefore becoming increasingly important. Due to its concomitant preservation of the pelvic autonomic nerves, which are essential for sexual function and urinary continence, TME itself might improve quality of life.[2] In addition, it has been shown that, since the introduction of TME, the number of abdominoperineal resections (APR) has dropped.[3] Although it is assumed that patients after APR have a worse quality of life than those without a colostomy, many patients pay the price for avoiding colostomy in terms of poor functional outcome. Following the principles of TME, a very low anastomosis, almost at the level of the pelvic floor, is inevitable if the tumour is located in the middle or lower third of the rectum. The closer the anastomosis is to the anal canal, the worse the surgical and functional outcome.[4] This may underlie the statement by Pachler and Wille-Jørgensen in a recent Cochrane Database Systemic Review that there is no significant evidence that quality of life after reconstructive surgery is superior to that after an APR.[5]

If reconstruction is possible, many surgeons perform a circular transanal double-stapled low colo-rectal or colo-anal anastomosis, frequently without a pouch (LRA).

However, due to impaired neorectal function, the outcome in these patients is often comprised, especially during the phase of adaptation in the postoperative period. Referring to this aspect, some authors introduced the term 'anterior resection syndrome .[6,7] In 1986, Parc *et al.*[8] and Lazorthes *et al.*[9] introduced the colonic J pouch-anal anastomosis (CPAA). In randomised prospective studies, the colonic J-pouch has been reported to give less defecation urgency and reduction in stool frequency than a straight coloanal anastomosis especially in the early postoperative phase.[10-14]

Based on these findings it seems clear that the addition of a J-pouch enhances the functional outcome. The question is whether a better functional outcome results in a better quality of life. Only two of these controlled randomised trials included validated quality of life questionnaires.[13,14] Hallböök *et al.*[13] failed to detect differences between the two groups after one year. More recently, Sailer *et al.*[14] conducted a randomised clinical trial, in which the functional outcome and quality of life were assessed at predefined, regular intervals. Patients with a pouch reconstruction had a significantly better functional score and quality of life, particularly in the early months after surgery.

No studies have been conducted to compare CPAA with APR. Furthermore the precise impact of functional outcome, urinary problems and sexual dysfunction after total mesorectal excision on quality of life in the long term is unclear. This study therefore sets out to provide a comprehensive insight into these factors and at quality of life in a large series of patients with cancer in the middle or lower third of the rectum after an APR, LRA or a CPAA.

PATIENTS AND METHODS

To determine the quality of life after APR, LRA and CPAA, a consecutive series of 301 patients was studied. All these patients underwent total mesorectal excision for cancer in the middle or lower third of the rectum between 1997 and 2001 at a university centre and two district hospitals. Patients with a locally advanced tumour or synchronous distant metastases were excluded. Furthermore CPAA or LRA patients without anorectal function were not included. All participating surgeons were trained in total mesorectal excision under auspices of the Dutch Colorectal Cancer Group (DCRCG).

We recorded the demographics, duration of follow-up since surgery, postoperative complications and functional outcome. The three groups were compared regarding comorbidity, such as diabetes, renal or cardiovascular diseases, chronic obstructive pulmonary disease, low back problems, arthritis, obesity or malignancies other than rectal cancer. A questionnaire was mailed to all patients registered at the three hospitals. This included the Rockwood fecal incontinence severity index system (RFISI), the EuroQol EQ-5D, the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 and the QLQ-CR38.

We evaluated fecal incontinence by means of a detailed questionnaire based on the fecal incontinence severity index system (RFISI).[15] This system, developed by Rockwood, uses two basic components: the type of incontinence and its frequency. We used the validated weighting scores that are based on patients input. To evaluate aspects of sexual dysfunction such as impotence, retrograde ejaculation in men, and dyspareunia in women were recorded. With regard to micturition problems, patients had to report urinary retention or persistently high frequency of voiding.

The EuroQol EQ-5D consisted of a so-called 'index score' representing 'the societal value' of the health state, and a visual analogue scale, the EQ-VAS, representing the patient perspective.[16] The quality of life scores were compared with a sex- and age-matched, community-based sample of healthy persons in The Netherlands without comorbidity (unpublished data, Stolk EA *et al.*).

Disease-specific quality of life was measured according to the official scoring procedures for the EORTC QLQ-C30 and EORTC QLQ-CR38 questionnaires. The EORTC QLQ-C30 was developed to assess the quality of life of cancer patients. It contains 30 items that can be computed in five functional scales (physical, role, emotional, cognitive and social functioning), three symptom scales (fatigue, nausea and vomiting, pain), and six single items (dyspnoea, insomnia, loss of appetite, constipation, diarrhoea and financial difficulties).[17] EORTC QLQ-CR38 was designed especially for the evaluation of colon cancer therapy from a patient perspective.[18] It is subdivided into two functional scales (i.e. body image and sexual functioning), seven symptom scales (micturition problems, gastrointestinal tract symptoms, chemotherapy side-effects, defaecation problems, stoma-related problems and male and female sexual problems), and three single-item measures (sexual enjoyment, weight loss, and future perspective). The validity and reliability of these questionnaires have been established in Dutch patients with colorectal cancer. In both QLQ-C30 and the QLQ-CR38 scores are summed within scales and rescaled from 0 to 100. A higher score indicates better functioning for all functioning scales and for two of the single items, sexual enjoyment and future perspective. A higher score on all symptom scales and the remaining single item (weight loss) indicates a lower level of symptomatology.

When appropriate, patient groups were compared using the chi-square test or Fisher's exact test. Continuous variables were compared using the Mann–Whitney test. Comparisons between groups were also performed using ANOVA, allowing for gender, age and time of follow-up. A P-value ≤ 0.05 was considered statistically significant.

RESULTS

The charts of 301 consecutive patients who had undergone surgery for cancer in the middle or lower third of the rectum were analysed. Ninety-seven were not eligible for inclusion. Fifty-five of these patients had died. Ten died within 30 days after the operation due to procedure related complications. The mortality of 38 patients

was disease related (local recurrence *n*=8; distant metastases *n*=20; both *n*=10). The remaining 7 patients died of causes unrelated to the rectal cancer. Twenty-five patients could not be contacted because of disease progression (local recurrence *n*=4; distant metastasis *n*=18; or both *n*=3). At time of the mailing of the questionnaire, eight LRA patients and one CPAA patient still had a temporary ileostomy. Eight patients could not be traced since they had moved house and their addresses were not available. The questionnaires were send to the remaining 204 patients. The overall response rate was 82% (LRA=76%, CPAA=85%, APR=84%, *P*=NS), resulting in 167 questionnaires returned by 204 operated patients.

Patient characteristics regarding type of procedure and oncological data are listed in Table 1. Regarding their clinical characteristics, the nonresponders did not differ from the responders. Baseline characteristics of the responders were similar in the three groups except for median age and location of tumour. The median duration of time interval between the operation and the mailing was 31 months (range: 9-72 months). APR and LRA patients were significant older at the index operation than the CPAA group (both $P<0.05$). The location of the tumour was lower in the APR group ($P<0.001$). In the patients who underwent an LRA, an end-to-end technique was utilized in 68% of the patients. A side-to-end anastomosis was performed in 32% of these patients. Patient characteristics and oncological data showed no differences between the series from the university centre and from the two district hospitals. Almost all CPAA procedures were performed in the university centre.

Table 1.
Baseline characteristics of the 167 responders operated on.

	LRA	CPAA	APR
Numbers of responders	71	45	51
Median age	66 (51 - 87)	61 (41 - 81) *	71 (52 - 88)
Median Length of follow-up in months	31 (9 - 72)	29 (9 - 69)	31 (10 - 62)
Male (%) / female (%)	62 / 38	61 / 39	63 / 37
Tumour stadium (I/II/III/IV) (%)	4 / 52 / 41 / 3	14 / 43 / 33 /10	3 / 53 / 38 / 6
Location tumour (lower/middle one third) (%)	34 / 64	54 / 46	92 / 8 **
Preoperative radiotherapy (%)	22	18	24
Postoperative chemotherapy (%)	17	19	14
Comorbidity (%)	28	25	32

Data are percentages or numbers with ranges in parentheses. Low colo-rectal anastomosis (LRA), a colo-anal J-pouch anastomosis (CPAA) or an abdominoperineal resection (APR). Median (Range). * P<0.05 versus LRA and APR, ** P<0.01 versus LRA and CPAA

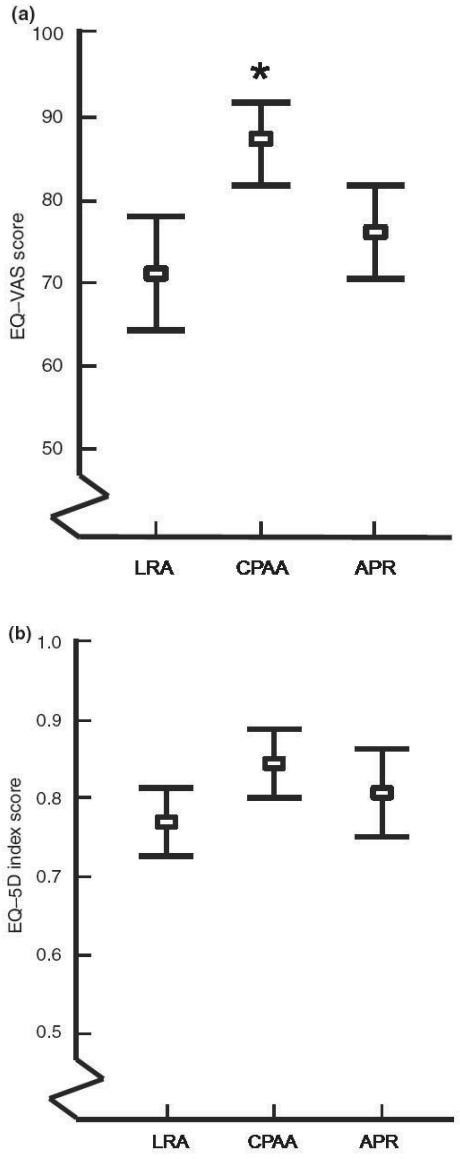

Figure 1.
Mean score of (a) ED-VAS score and (b) EQ-5D score and 95% confidence interval. Low colorectal anastomosis (LRA), a colo-anal J-pouch anastomosis (CPAA) or an abdominoperineal resection (APR). *P<0.05 vs LRA and APR.

The mean scores and 95% confidence intervals of the EQ-5D for the patient groups are presented in Figure 1. From the patient perspective, the mean general quality of life score (EQ-VAS) was higher in the CPAA group ($P<0.01$) compared to the mean EQ-VAS score of the sex and age matched general population. In the LRA and APR group these scores were similar to those of the general population. Univariate analysis showed a significant difference regarding the mean EQ-VAS score between the CPAA group and the LRA group ($P=0.001$) and between the CPAA group and the APR group ($P=0.044$). Adjusted for age, gender and duration of follow-up using ANOVA, these differences both remained significant ($P=0.009$ and $P=0.011$, respectively). Gender was found to be an independent factor related to the quality of life ($P=0.05$), with men having a better quality of life compared to women.

From the social perspective, the mean EQ-5D index score was found to be significantly higher in the CPAA as compared to the sex-age matched general population ($P=0.026$). In the LRA and APR group the EQ-5D index scores were similar to those of the general population. The EQ-5D index score did not differ between the three groups.

Scores of the EORTC QLQ-CR30 and the QLQ-CR38 for the patient groups are presented in Tables 2 and 3. Univariate analysis showed differences between the three groups on 5 scales. CPAA patients had significantly higher scores with regard to global health status and male sexuality than patients with an APR or LRA ($P<0.05$ and $P<0.05$, respectively). CPAA patients had better perception of body image than APR patients ($P<0.01$) and fewer mictirition problems ($P<0.05$). CPAA patients had less defaecation problems than LRA patients ($P<0.05$). LRA patients had a better perception of body image than APR patients ($P<0.05$).

The mean RFISI scores among LRA and CPAA patients were 21 and 14, respectively. Although this difference this is not significant ($P=0.098$), the 95% confidence interval of this difference ranged between −1 to +11. This latter finding indicates a trend to a better functional outcome among CPAA patients. Comparing the side-to-end and the end-to-end anastomosis in the LRA group no significant difference was found regarding the mean RFISI ($P=0.25$). Among all LRA and CPAA patients the RFISI was found to be correlated with the quality of life (EQ-VAS) (Spearman's rho = −0.240, $P=0.04$). However after adjusting for gender, age and duration of follow-up, this correlation was no longer significant ($P=0.073$).

One hundred and four patients were sexually active (62%). Retrograde ejaculation occurred in 10% of men, whereas impotence was reported in 22%. Women reported fewer sexual problems. Dyspareunia after operation was encountered in 12% of the women. Significantly less sexual problems were seen after CPAA (CPAA=16% *vs* LRA=26% and APR=28%, both $P=0.02$). Urinary problems were reported in 21% of the patients. There were significant more micturition problems after APR (APR=29% *vs* LRA=16% and CPAA=11%, both $P<0.01$). Univariate analysis revealed that the quality of life (EQ-VAS) was affected by the presence of micturition ($P=0.011$) and sexual problems ($P=0.014$).

Table 2.
EORTC QLQ-C30 scores of the 167 responders.

	LRA		CPAA		APR	
	Mean	Median (range)	Mean	Median (range)	Mean	Median (range)
Physical function	83	90 (20 - 100)	91	100 (40 - 100)	82	87 (13 100)
Role function	80	83 (0 - 100)	90	83 (33 - 100)	81	83 (0 - 100)
Emotional function	83	92 (17 - 100)	87	92 (44 - 100)	87	92 (33 - 100)
Cognitive function	86	100 (17 - 100)	90	100 (50 - 100)	90	100 (33 - 100)
Social function	69	67 (0 - 100)	62	67 (0 - 100)	73	67 (0 - 100)
Global health status	76	75 (17 - 100)	86	83 (33 -100) *	78	75 (25 - 100)
Fatigue	80	81 (11 - 100)	89	94 (11 - 100)	86	89 (0 - 100)
Nausea/ vomiting	95	100 (17 - 100)	97	100 (0 - 100)	97	100 (67 - 100)
Pain	91	100 (0 -100)	96	100 (67 - 100)	91	100 (0 - 100)
Dyspnoea	87	100 (0 - 100)	93	100 (33 - 100)	87	100 (0 - 100)
Sleep disturbance	82	100 (0 - 100)	87	100 (33 - 100)	89	100 (33 - 100)
Appetite loss	97	100 (33 - 100)	98	100 (0 - 100)	96	100 (0 - 100)
Constipation	85	100 (0 - 100)	90	100 (0 - 100)	97	100 (67 - 100)
Diarrhoea	89	100 (0 - 100)	87	100 (33 - 100)	91	100 (33 - 100)
Financial worries	94	100 (0 - 100)	93	100 (33 - 100)	95	100 (33 - 100)

A high subscale score indicates low distress and good functioning. LRA = low colo-rectal anastomosis, CPAA = colo-anal J-pouch anastomosis, APR = abdominoperineal resection.
* $P<0.05$ versus LRA and APR.

DISCUSSION

The purpose of this inventory study was to provide a comprehensive overview of the functional outcome and quality of life over time in a large series of patients with cancer in the middle or the lower third of the rectum. All these patients underwent total mesorectal excision followed either by an APR, or by an LRA or a CPAA. The quality of life among disease-free survivors was good, with scores that were comparable to or even higher than those of the population-based reference group. Adjusted for age, gender and duration between surgery and questionnaire, this study shows that the

Table 3.
EORTC QLQ-CR38 scores of the 167 responders.

	LRA		CPAA		APR	
	Mean	Median (range)	Mean	Median (range)	Mean	Median (range)
Micturition problems	81	78 (44 - 100)	90	100 (56 - 100)	75	67 (33 - 100) %
Gastrointestinal problems	80	80 (40 - 100)	85	87 (60 - 100)	84	89 (53 - 100)
Weight loss	94	100 (33 - 100)	95	100 (33 - 100)	95	100 (33 - 100)
Body image	85	100 (0 - 100)	88	100 (33 - 100)	78	78 (0 - 100) %
Defecation problems	77	80 (47 - 100)	89	92 (66 - 100) &	-	-
Stoma problems	-	-	-	-	81	90 (19 - 100)
Chemo side-effects	90	89 (22 - 100)	93	100 (33 - 100)	94	100 (33 - 100)
Sexual function	24	17 (0 - 83)	31	33 (0 - 67)	20	17 (0 - 67)
Sexual enjoyment	53	67 (0 - 100)	54	67 (0 - 100)	56	67 (0 - 100)
Male sex problems	46	42 (0 - 100)	70	75 (0 - 100) *	48	33 (0 - 100)
Female sex problems	81	83 (33 - 100)	83	83 (50 - 100)	74	83 (17 - 100)
Future perspective	72	67 (0 - 100)	76	67 (33 - 100)	74	67 (33 - 100)

A high subscale score indicates low distress and good functioning. LRA = low colo-rectal anastomosis, CPAA = colo-anal J-pouch anastomosis, APR = abdominoperineal resection.
* $P<0.05$ versus LRA and APR , ** $P<0.05$ versus LRA, % $P<0.05$ versus LRA and CPAA, % $P<0.05$ versus CPAA.

quality of life was higher in patients with a CPAA than in those with an LRA or an APR.

It is remarkable that most of our patients in all three ranked their quality of life as high or even higher as that in the population-based reference group. This finding might be due to several methodological shortcomings in our study design. The present study is limited by its retrospective nature, the relatively small number of patients and the lack of control measurements before treatment. Nevertheless, good arguments exist for the validity of the expressed values and our finding is consistent with other reports on quality of life in cancer survivors.[19,20] The relatively high quality of life, observed among our patients, might be explained by the fact that the measurement followed their earlier diagnosis of a life-threatening disease, which changed their perceptions of the length of life, thereby shifting their expectations and priorities with regard to life fulfilment. Successful treatment therefore might result in a higher quality of life as reported by the patient. This effect, known as 'rejoice', has been noted from the beginning of quality-of-life research.[21]

An additional contributing factor might be the adaptation of the patients to their morbidity over time, a phenomenon that is also referred to as coping or 'response shift'. Adaptation is defined as a change in the meaning of a respondent's self-evaluation of quality of life that results from changes in his or her internal standards, values or conceptualization of quality of life.[22,23] In other words, to accommodate deteriorating function, patients may lower their internal standards, alter their values and change their ideas about what constitutes a good quality of life. Response shift is related to the subjective value of morbidity. This explains why the morbidity may be only weakly correlated with the more subjective measure of quality of life. To test the use of coping strategies, Boyd and coworkers posted a treatment preference questionnaire to patients with rectal cancer treated by APR or by radiotherapy without colostomy. The questionnaire was also send to physicians and healthy volunteers. All subjects were asked to imagine living the rest of their lives with a colostomy.[24] Healthy volunteers and patients with rectal cancer, treated by radiotherapy, without the need of a colostomy, were the most averse to treatment that involved a colostomy. Physicians and patients who had a colostomy were the most ready to accept living the rest of their life with a colostomy.

Although the overall quality of life among all our patients was good, significant differences were observed between the groups. This study showed that the quality of life was higher in patients with a CPAA than those with an APR or an LRA. The quality of life after APR was similar to that after LRA. Most surgeons try to avoid an APR by performing an LRA, frequently without a pouch. This policy is based mainly on the assumption that the quality of life after such LRA is higher than after APR. This is not confirmed by the present study in which quality of life after LRA was similar to that after APR. Our finding is in agreement with observations reported by others. Camilleri-Brennan *et al.*[25] and Rauch *et al.*[26] found no differences between the quality of life after APR and the quality of life after LRA. In a prospective study, Grumann *et al.*[27] showed that following LRA patients had even a lower quality of life than those who underwent an APR. In contrast, however, Engel *et al.*[28] and Sprangers *et al.*[29] observed that APR patients experienced a poorer quality of life. Four of the eight studies included in a recent Cochrane Database Systemic Review revealed no difference with regard to quality of life between LRA and APR.[5] In one study it was shown that the quality of life in patients with a colostomy was only slightly affected. The three other studies revealed that formation of a stoma significantly affected the patients' quality of life[5] These conflicting results and the data obtained from our own study do not provide substantial evidence for to the assumption that the quality of life after LRA is better than after APR with the formation of a permanent colostomy.

The functional outcome after a LRA without a pouch is not as good as first thought.[30] Moreover, pre-operative radiotherapy has significant adverse effects on anorectal function.[31] A poor functional outcome after LRA without a pouch is characterized by high frequency, urgency and impaired continence, especially during the first two years after the operation. It has been shown that pre-operative radiotherapy

increases urgency, defaecation frequency, usage of pads and rectal blood loss.[32] In case of a disappointing functional outcome, the patient is confronted with a lack of control, which adversely affects quality of life.[33] The experience of lack of bowel control and uncertainty probably explains our observation that the quality of life after LRA was equal to that after APR. It seems likely that patients with a colostomy have a better sense of control, especially compared to LRA patients after pre-operative radiotherapy. When a colostomy becomes necessary, modern stoma appliances are so effective that most patients with a colostomy enjoy normal lives. Engel *et al.*[28] who reported that APR patients have a consistently lower quality of life, stated that 60% of the patients in their sample were poorly informed about stoma irrigation techniques. This underlines the importance of instruction by enterostomal therapists on colostomy care and washout, enabling more bowel control. The quality of life among LRA patients might be improved by a better control of their bowel function. Recently it has been shown that colonic irrigation is beneficial for patients with a low anastomosis in controlling their bowel function.[34] In the present study, we found a lower perception of body-image in APR patients as compared to LRA and CPAA patients, which is in agreement with other studies.[25] However, despite this poorer body image perception, the social and psychological functioning of APR patients were similar to those of CPAA patients and LRA patients.

Although a better functional outcome was found to be correlated with a better quality of life, this finding cannot fully explain the higher quality of life in patients after CPAA. In the present study, other factors such as gender, urinary problems and sexual dysfunction were found to be independently associated with quality of life. Our male patients ranked their quality of life higher than our female patients. This is in accordance with other population based studies revealing a higher quality of life among men.[16] Post-operatively sexual dysfunction and urinary problems were experienced by 24% and 19% of the patients, respectively. These figures are similar to those reported by others after total mesorectal excision.[35,36] In the present study, a higher incidence of sexual dysfunction was observed after APR and LRA than after CPAA. Urinary problems were more frequently encountered after APR than after LRA and CPAA. These differences are difficult to explain, and are probably surgeon dependent.

Our observation, that the quality of life after APR is equal to the quality of life after LRA might have implications for current clinical practice. Most surgeons are convinced that the construction of a double-stapled LRA results in a higher quality of life than an APR followed by the construction of a permanent colostomy. In the treatment of patients with cancer located in the middle or lower third of the rectum, total mesorectal excision, is now being established as the therapeutic golden standard. After this procedure, a transanally double-stapled anastomosis can only be constructed at the level of or just above the pelvic floor. Most surgeons believe that the preservation of a short rectal remnant is beneficial for the patient. However, it has been shown that this does not offer any functional advances.[37,38] Moreover, most

surgeons underestimate the high risk of anastomotic leakage after the construction of such a low anastomosis. Recently a population based study from Sweden revealed that the incidence of this serious complication was 24% when the anastomosis was located within 6 centimetres from the anal verge.[39] Such an anastomotic leakage in this region is associated not only with a high morbidity, but also with a significant mortality.[40] It has been also been reported that an anastomotic leakage adversely effects disease-free survival.[41] The reported incidence of anastomotic leakage after CPAA varies between 0 and 9%, which seems to be much lower than after a double stapled LRA.[42,43] This is in agreement with our own experience. Our findings and those reported by others indicate that a CPAA is associated with a better functional outcome and thereby a better quality of life as compared to a double stapled LRA.[14] Taking into account the high leakage rate, which is another major drawback of such an LRA, we advise the construction of a CPAA instead of an LRA in all patients with cancer located in the middle or the lower third of the rectum.

REFERENCES

1. Heald RJ, Moran BJ, Ryall RD, Sexton R, MacFarlane JK. Rectal cancer: the Basingstoke experience of total mesorectal excision, 1978-1997. Arch Surg 1998;133:894-9.
2. Murty M, Enker WE, Martz J. Current status of total mesorectal excision and autonomic nerve preservation in rectal cancer. Semin Surg Oncol 2000;19:321-8.
3. Martling AL, Holm T, Rutqvist LE, Moran BJ, Heald RJ, Cedemark B. Effect of a surgical training programme on outcome of rectal cancer in the County of Stockholm. Stockholm Colorectal Cancer Study Group, Basingstoke Bowel Cancer Research Project. Lancet 2000;356:93-6.
4. Montesani C, Pronio A, Santella S, Boschetto A, Aguzzi D, Pirozzi R, D'Amato A, Vestri A. Rectal cancer surgery with sphincter preservation: functional results related to the level of anastomosis. Clinical and instrumental study. Hepatogastroenterology. Volume 51, 2004:718-21.
5. Pachler J, Wille-Jorgensen P. Quality of life after rectal resection for cancer, with or without permanent colostomy. Cochrane Database Syst Rev, 2004:CD004323.
6. Pedersen IK, Christiansen J, Hint K, Jensen P, Olsen J, Mortensen PE. Anorectal function after low anterior resection for carcinoma. Ann Surg 1986;204:133-5.
7. Lewis WG, Martin IG, Williamson ME, Stephenson BM, Holdsworth PJ, Finan PJ, Johnston D. Why do some patients experience poor functional results after anterior resection of the rectum for carcinoma? Dis Colon Rectum 1995;38:259-63.
8. Parc R, Tiret E, Frileux P, Moszkowski E, Loygue J. Resection and colo-anal anastomosis with colonic reservoir for rectal carcinoma. Br J Surg 1986;73:139-41.
9. Lazorthes F, Fages P, Chiotasso P, Lemozy J, Bloom E. Resection of the rectum with construction of a colonic reservoir and colo-anal anastomosis for carcinoma of the rectum. Br J Surg 1986;73:136-8.
10. Lazorthes F, Chiotasso P, Gamagami RA, Istvan G, Chevreau P. Late clinical outcome in a randomized prospective comparison of colonic J pouch and straight coloanal anastomosis. Br J Surg 1997;84:1449-51.
11. Hallbook O, Pahlman L, Krog M, Wexner SD, Sjodahl R. Randomized comparison of straight and colonic J pouch anastomosis after low anterior resection. Ann Surg 1996;224:58-65.
12. Seow-Choen F, Goh HS. Prospective randomized trial comparing J colonic pouch-anal anastomosis and straight coloanal reconstruction. Br J Surg 1995;82:608-10.
13. Hallbook O, Hass U, Wanstrom A, Sjodahl R. Quality of life measurement after rectal excision for cancer. Comparison between straight and colonic J-pouch anastomosis. Scand J Gastroenterol 1997;32:490-3.

14. Sailer M, Fuchs KH, Fein M, Thiede A. Randomized clinical trial comparing quality of life after straight and pouch coloanal reconstruction. Br J Surg 2002;89:1108-17.
15. Rockwood TH, Church JM, Fleshman JW, Kane RL, Mavrantonis C, Thorson AG, Wexner SD, Bliss D, Lowry AC. Patient and surgeon ranking of the severity of symptoms associated with fecal incontinence: the fecal incontinence severity index. Dis Colon Rectum 1999;42:1525-32.
16. Kind P, Dolan P, Gudex C, Williams A. Variations in population health status: results from a United Kingdom national questionnaire survey. Bmj 1998;316:736-41.
17. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, Filiberti A, Flechtner H, Fleishman SB, de Haes JC, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993;85:365-76.
18. Sprangers MA, te Velde A, Aaronson NK. The construction and testing of the EORTC colorectal cancer-specific quality of life questionnaire module (QLQ-CR38). European Organization for Research and Treatment of Cancer Study Group on Quality of Life. Eur J Cancer 1999;35:238-47.
19. Gotay CC, Muraoka MY. Quality of life in long-term survivors of adult-onset cancers. J Natl Cancer Inst 1998;90:656-67.
20. Ganz PA, Rowland JH, Desmond K, Meyerowitz BE, Wyatt GE. Life after breast cancer: understanding women's health-related quality of life and sexual functioning. J Clin Oncol 1998;16:501-14.
21. Nord E. The significance of contextual factors in valuing health states. Health Policy 1989;13:189-98.
22. Sprangers MA. Response-shift bias: a challenge to the assessment of patients' quality of life in cancer clinical trials. Cancer Treat Rev 1996;22 Suppl A:55-62.
23. Schwartz CE, Sprangers MA. Methodological approaches for assessing response shift in longitudinal health-related quality-of-life research. Integrating response shift into health-related quality of life research: a theoretical model. Soc Sci Med 1999;48:1531-48.
24. Boyd NF, Sutherland HJ, Heasman KZ, Tritchler DL, Cummings BJ. Whose utilities for decision analysis? Med Decis Making 1990;10:58-67.
25. Camilleri-Brennan J, Steele RJ. Objective assessment of morbidity and quality of life after surgery for low rectal cancer. Colorectal Dis 2002;4:61-66.
26. Rauch P, Miny J, Conroy T, Neyton L, Guillemin F. Quality of life among disease-free survivors of rectal cancer. J Clin Oncol 2004;22:354-60.
27. Grumann MM, Noack EM, Hoffmann IA, Schlag PM. Comparison of quality of life in patients undergoing abdominoperineal extirpation or anterior resection for rectal cancer. Ann Surg 2001;233:149-56.
28. Engel J, Kerr J, Schlesinger-Raab A, Eckel R, Sauer H, Holzel D. Quality of life in rectal cancer patients: a four-year prospective study. Ann Surg 2003;238:203-13.
29. Sprangers MA, Taal BG, Aaronson NK, te Velde A. Quality of life in colorectal cancer. Stoma vs. nonstoma patients. Dis Colon Rectum 1995;38:361-9.
30. Rasmussen OO, Petersen IK, Christiansen J. Anorectal function following low anterior resection. Colorectal Dis 2003;5:258-61.
31. Welsh FK, McFall M, Mitchell G, Miles WF, Woods WG. Pre-operative short-course radiotherapy is associated with faecal incontinence after anterior resection. Colorectal Dis 2003;5:563-8.
32. Dehni N, McNamara DA, Schlegel RD et al. Clinical effects of preoperative radiation therapy on anorectal function after proctectomy and colonic J-pouch-anal anastomosis. Dis Colon Rectum 2002; 45: 1635–40.
33. Amir M, Roziner I, Knoll A, Neufeld MY. Self-efficacy and social support as mediators in the relation between disease severity and quality of life in patients with epilepsy. Epilepsia 1999;40:216-24.
34. Gosselink MP, Darby M, Zimmerman DD, Smits AA, van Kessel I, Hop WC, Briel JW, Schouten WR. Long-term follow-up of retrograde colonic irrigation for defaecation disturbances. Colorectal Dis 2005;7:65-9.
35. Maurer CA, Z'Graggen K, Renzulli P, Schilling MK, Netzer P, Buchler MW. Total mesorectal excision preserves male genital function compared with conventional rectal cancer surgery. Br J Surg 2001;88:1501-5.
36. Nesbakken A, Nygaard K, Bull-Njaa T, Carlsen E, Eri LM. Bladder and sexual dysfunction after mesorectal excision for rectal cancer. Br J Surg 2000;87:206-10.

37. Montesani C, Pronio A, Santella S, Boschetto A, Aguzzi D, Pirozzi R, D'Amato A, Vestri A. Rectal cancer surgery with sphincter preservation: functional results related to the level of anastomosis. Clinical and instrumental study. Hepatogastroenterology 2004;51:718-21.
38. Matzel KE, Stadelmaier U, Muehldorfer S, Hohenberger W. Continence after colorectal reconstruction following resection: impact of level of anastomosis. Int J Colorectal Dis 1997;12:82-7.
39. Matthiessen P, Hallbook O, Andersson M, Rutegard J, Sjodahl R. Risk factors for anastomotic leakage after anterior resection of the rectum. Colorectal Dis 2004;6:462-9.
40. Eriksen MT, Wibe A, Norstein J, Haffner J, Wiig JN. Anastomotic leakage following routine mesorectal excision for rectal cancer in a national cohort of patients. Colorectal Dis 2005;7:51-7.
41. Walker KG, Bell SW, Rickard MJ, Mehanna D, Dent OF, Chapuis PH, Bokey EL. Anastomotic leakage is predictive of diminished survival after potentially curative resection for colorectal cancer. Ann Surg 2004;240:255-9.
42. Dehni N, Parc R, Church JM. Colonic J-pouch-anal anastomosis for rectal cancer. Dis Colon Rectum 2003;46:667-75.
43. Alberts JC, Parvaiz A, Moran BJ. Predicting risk and diminishing the consequences of anastomotic dehiscence following rectal resection. Colorectal Dis 2003;5:478-82.

CHAPTER 6

Long term follow-up of retrograde bowel irrigation for disabling defecation disturbances after pouch surgery

Adapted (in part) from
Gosselink MP, Darby M, Zimmerman DD, Smits AA, Kessel I, Hop WC, Briel JW and Schouten WR.
Colorectal Dis. 2005 Jan;7(1):65-9

ABSTRACT

Although addition of a pouch improves the functional outcome and quality of life compared to straight anastomosis, a number of patients suffer from soiling, frequent bowel movements or evacuation difficulties. In our institution, all patients with disabling defecation disturbances after pouch surgery, not responding to medical treatment and biofeedback therapy, were offered retrograde bowel irrigation (RBI). This study is aimed at evaluating the long-term feasibility and outcome of RBI in patients after pouch surgery as compared with the outcome of RBI for other indications. Between 1989 and 2001, eleven patients experienced disabling defecation disturbances after pouch surgery were offered RBI on an ambulatory basis. In the same time period a large group of 256 patients was offered RBI for other indications. All patients were instructed by one of our enterostomal therapists. All patients with defecation disturbances after pouch surgery were available for follow-up. In the group of patients, who received RBI for other indications, twenty-eight patients were lost to follow-up. A detailed questionnaire was sent by mail to 239 patients. The total response rate was 79% (190 patients). All eleven patients, who received RBI after pouch surgery returned their questionnaires. Thirty-two patients were admitted with soiling, 71 patients with fecal incontinence, 37 patients with obstructed defecation and 29 had defecation disturbances after low anterior resection. According to the returned questionnaires, all patients after pouch surgery considered RBI to be effective and beneficial. None of these patients ceased the RBI, despite 63% of them experienced irrigation related problems. Among patients with soiling and fecal incontinence, RBI was found to be effective in respectively 47 and 41% of the subjects. Despite of the reported effectiveness, ten patients with soiling (67%) and 5 patients with fecal incontinence (17%) decided to stop. Among patients with obstructed defecation and those with defecation disturbances after low anterior resection or pouch surgery the effectiveness of RCI was found to be 65 and 79% respectively. None of these patients ceased their therapy. If creation of a stoma is considered, especially in patients with disabling defecation disturbances after pouch surgery, it might be worthwhile to offer these patients first retrograde bowel irrigation.

INTRODUCTION

During the last two decades sphincter-preserving procedures have been introduced for the treatment of ulcerative colitis, familial adenomatous polyposis, and rectal cancer. Although addition of a pouch improves the functional outcome and quality of life compared to straight anastomosis, a number of patients suffer from soiling, frequent bowel movements or evacuation difficulties.

In 1989, Iwama and co-workers introduced the rectal application of a conventional colostomy irrigation set in order to washout the distal part of the colon in ten patients,

who complained of frequent urge to defecate and impairment of bowel control after low anterior resection.[1] In all these patients, the frequent urge to defecate disappeared. Other authors have confirmed that irrigation of the distal part of the gastrointestinal tract is beneficial for patients with problems such as fecal soiling, fecal incontinence or obstructed defecation.[2-4]

In our institution retrograde bowel irrigation (RBI) has been offered to patients with defecation disturbances, not responding to medical treatment and biofeedback since 1989. Because there are no data available regarding the potential role of RBI in the treatment of disabling disturbances after pouch surgery, it seems worthwhile to report our experience with this treatment modality. Therefore, we studied the long-term feasibility and outcome of RBI in patients after pouch surgery as compared with the outcome of RBI for other indications.

PATIENTS AND METHODS

Between 1989 and 2001, 127 patients underwent ileal pouch-anal anastomosis (IPAA) for either ulcerative colitis or familial adenomatous polyposis in our hospital. In the same time period, complete rectal excision and colonic J-pouch-anal anastomosis (CPAA) were performed in 62 patients. Eleven patients experienced disabling defecation disturbances after pouch surgery, not responding to medical treatment and biofeedback, and were offered retrograde bowel irrigation (RBI) on an ambulatory basis. Eight patients presented with nocturnal incontinence after IPAA and 3 patients presented with obstructed defecation after CPAA. In the same time period a large group of 256 patients was offered RBI for other indications. All patients were instructed by one of our enterostomal therapists. Hospital records and outpatient clinic data were analysed.

All patients with defecation disturbances after pouch surgery were available for follow-up. In the group of patients, who received RBI for other indications, twenty-eight patients were lost to follow-up. Fifteen of them died during follow-up and thirteen patients could not be contacted since they moved abroad and their new address was not available. A detailed questionnaire was sent by mail to 239 patients. The questionnaire included questions about the method of retrograde bowel irrigation, the effectiveness of RBI in releasing the patients from their original complaints, continuation (or discontinuation) of treatment, procedure related problems and patient satisfaction. Procedure related problems were abdominal discomfort, too time consuming, anal pain, loss of instilled water during the day and technical problems. Technical problems included problems with instillation of the water, problems evacuating the instilled water and rapid loss of instilled water before achieving adequate washout. The total response rate was 79% (190 patients). All eleven patients, who received RBI after pouch surgery returned their questionnaires. We compared these patients with 32 patients who received RBI for fecal soiling, 71 patients for fecal incontinence,

37 patients for obstructed defecation and 18 patients for fecal incontinence or high stool frequency after low anterior resection (Table 1).

Table 1.

Patient characteristics.

Indication	Number of Responders	Males	Median Age *(years)*	Range *(years)*
Defecation disturbances after Pouch surgery	11	6	41	25 - 71
Soiling	32	28	47	17 - 65
Incontinence	71	21	57	20 - 87
Obstructed Defecation	37	5	54	20 - 68
Defecation disturbances after LAR	18	9	58	49 - 81
Total	169	68	52	17 - 87

Method of Retrograde Colonic Irrigation

All patients received both verbal and written instructions about colonic irrigation by one of our enterostomal therapists. A conventional colostomy irrigation set was used. The device consisted of an irrigation bag, a tube and a cone-tip (Biotrol Iryflex, B. Braun Medical B.V., Oss, The Netherlands) (Figure 1). Patients were instructed to hang the irrigation bag at shoulder height or one meter above the toilet seat. The advised volume of tap water varied between 500 to 1000 ml. The temperature of the water, used for the washout, had to be approximately 37 degrees centigrade. Cold water had to be avoided since instillation of a volume of cold water might lead to collapse or abdominal cramp. To prevent nausea, the patient was advised to perform the washout at least 2 hours after a meal. The patient was instructed to irrigate the feeding tube prior to introduction of the lubricated cone-tip into the anal canal in order to avoid installation of air in the distal part of the gastrointestinal tract. The patient was instructed to wait until the urge to defecate was experienced before taking out the cone-tip. After removal of the cone-tip, evacuation of the irrigation fluid could take place.

RESULTS

The median duration of the time interval between the start of the RBI and the mailing was 56 months (range: 8-154 months). All patients with a pouch reported RBI to be effective and beneficial (Figure 2). None of these patients ceased the RBI during the time period of follow-up, despite 63% of them experienced irrigation related problems.

Among the group of 158 patients who received RBI for other indications 91

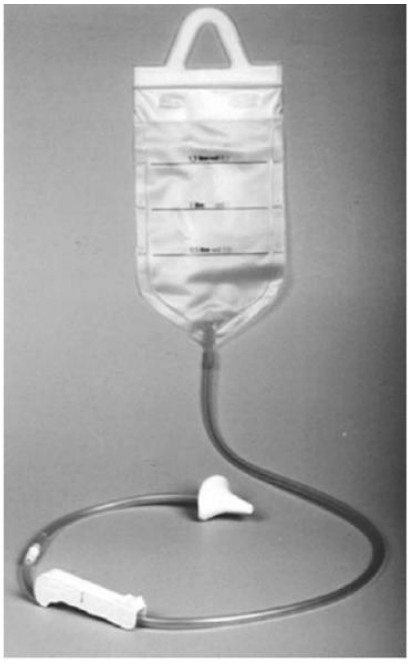

Figure 1.
Irrigation bag with the cone tip at the end of the tube.

(58%) also reported this therapy to be effective and beneficial. Among patients with soiling and fecal incontinence, RBI was found to be effective in, respectively, 47 and 41% of the subjects. Despite of the reported effectiveness, 10 (67%) patients with soiling and 5 (17%) patients with fecal incontinence decided to cease the therapy, despite its effectiveness. Patients with soiling had stopped because of the time consuming aspect of RBI and irrigation related problems. The patients with incontinence had stopped RBI because of irrigation related problems and loss of irrigation fluid during the day. Among patients with obstructed defecation and those with defecation disturbances after low anterior resection the effectiveness of RBI was found to be 65 and 66%, respectively. None of these patients ceased their therapy.

Among all the patients who continued RBI, the irrigation frequency varied between once per four days and five times per day (median frequency one time per day). The median volume of tap water was 1000 cc (range: 500 cc - 3000 cc). The median time duration of the RBI was 30 minutes (range: 10-115). Most of the patients found the morning to be the most appropriate time for irrigation (83%). One out of three patients used medication in order to facilitate their defecation.

74% of all the 76 patients who still performed RBI on a regular basis, experienced

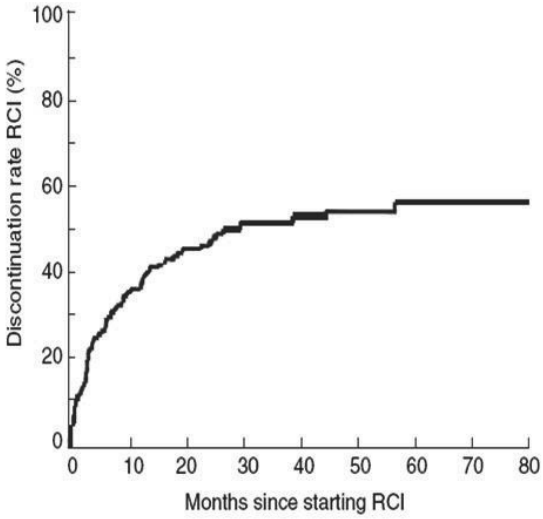

Figure 2.
Cumulative discontinuation rates of retrograde colonic irrigation.

irrigation-related problems. The number of these problems varied from one to three. Technical problems, abdominal cramping and loss of irrigation fluid during the day were most frequently reported as therapy related technical problems (Figure 3). Despite the high number of RBI-related problems mentioned by the patients still performing RBI, 86% of them considered RBI as beneficial improving their quality of their lives.

DISCUSSION

For many patients with disabling defecation disturbances after pouch surgery, the creation of a stoma is the only option left. The present study indicates that RBI is an attractive alternative. All our patients with a pouch reported RBI to be effective and beneficial.

The lack of efficacy was the most important reason for patients, who received RBI for other indications, to cease their therapy. 34% of the patients in whom, soiling and fecal incontinence was treated successful with RBI, stopped this therapy despite its effectiveness. The discontinuation among patients with fecal incontinence in whom RBI was effective might be explained by the fact that they probably prefer surgical therapy rather than life-long irrigation of their colon. Many patients with soiling also stopped with RBI despite its effectiveness. Their decision to stop was mainly based on the time consuming aspect of the irrigation and the loss of irrigation during the day. Coping with these problems must

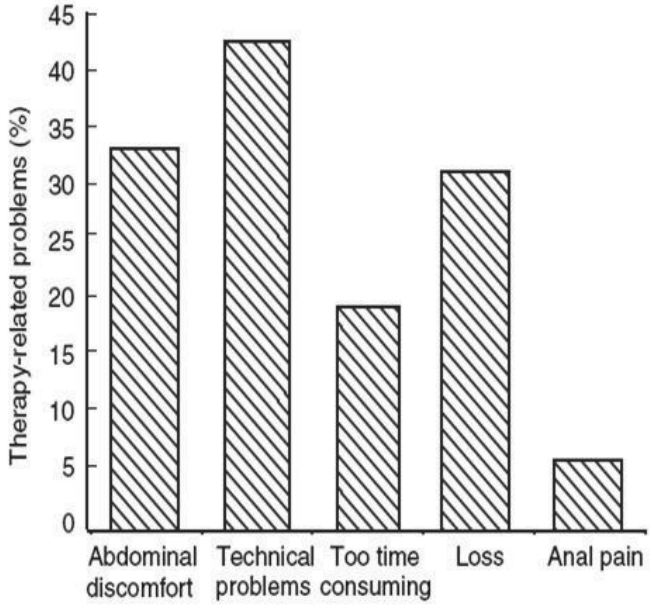

Figure 3.
Problems mentioned in 76 patients who still performed retrograde colonic irrigation.

counterbalance with the consequences of soiling.

None of the patients with obstructed defecation and those with defecation disturbances after low anterior resection or pouch surgery ceased their therapy if they considered RBI effective.

Despite irrigation related problems, they all continued the irrigation. The prospect of a permanent stoma as the only option left might contribute to the high continuation rate in these patients.

Irrigation requires considerable self-motivation and consumes valuable time. Patients are told that complete and predictable bowel control is usually not immediate. During the first month after starting RBI, the irrigation procedure is determined by trial and error with individualised frequencies of administration and volume of water used. During this initial period, instructions from an experienced nurse with a special interest in this field are very important.

If creation of a stoma is considered, especially in patients with disabling defecation disturbances after pouch surgery, it might be worthwhile to offer these patients first retrograde bowel irrigation. In our opinion, this is the first treatment of choice, since it is minimally invasive, easy to learn, safe with only minor side effects.

REFERENCES

1. Iwama T, Imajo M, Yaegashi K, et al. Self washout method for defecational complaints following low anterior rectal resection. Jpn J Surg 1989; 19: 251-3.
2. Christensen P, Kvitzau B, Krogh K, et al. Neurogenic colorectal dysfunction - use of new antegrade and retrograde colonic wash-out methods. Spinal Cord 2000; 38: 255-61.
3. Briel JW, Schouten WR, Vlot EA, et al. Clinical value of colonic irrigation in patients with continence disturbances. Dis Colon Rectum 1997; 40: 802-5.
4. Krogh K, Kvitzau B, Jorgensen TM, et al. Treatment of anal incontinence and constipation with transanal irrigation. Ugeskr Laeger 1999; 161: 253-6.

CHAPTER 7

Impact of two different types of anal retractor on fecal continence: a prospective, randomized, clinical trial

Adapted (in part) from:
Zimmerman DD, Gosselink MP, Hop WCJ,
Darby M, Briel JW, Schouten WR
Dis Colon Rectum 2003; 46: 1674-1679

ABSTRACT

This study was designed to compare two different types of anal retractors (Parks vs. Scott) with regard to their impact on fecal continence. Between November 2000 and November 2001, 30 patients were randomized into two groups. In group A (n=15) a Parks retractor was used during fistula repair, whereas in group B (n=15), the repair was performed with a Scott retractor. Before and three months after surgery, maximum anal resting pressure and maximum anal squeeze pressure were recorded. In addition, continence status was evaluated using both the Rockwood Fecal Incontinence Severity Index and the scoring system according to Parks. In group A, the median anal resting pressure dropped from 76 to 42 mmHg. In group B, no significant difference was observed between the preoperative and postoperative anal resting pressure. The difference in the changes from the baseline between the two groups was statistically significant (P=0.035). No significant changes in anal squeeze pressure were observed. In group A, the median Rockwood fecal incontinence score increased from 0 to 12. In group B, the median Rockwood fecal incontinence score did not change after the operation. The difference between the two groups was statistically significant (P=0.038). The use of a Parks retractor during perianal fistula repair has a deteriorating effect on fecal continence, probably because of damage to the internal anal sphincter. Because this side effect was not observed after the use of a Scott retractor, we advocate the use of this retractor.

INTRODUCTION

It is well known that anal sphincter function is impaired after pouch surgery. Until recently, surgeons used Parks anal retractor during pouch surgery to gain access to the anal canal and to perform a handsewn anastomosis. In recent years, it has been suggested that the use of a Scott retractor, a ring retractor with multiple skin hooks on elastic bands, results in less sphincter damage. Postoperative sphincter function is of key relevance for the long-term outcome after a handsewn pouch-anal anastomosis. This obviates the need for better understanding of the effects of both retractors on the sphincters and on fecal continence.

Several 'sphincter saving techniques' have been introduced to prevent impairment of continence after repair of high transsphincteric fistula. The transanal advancement flap repair (TAFR) is used most often. Several authors did not observe continence disturbances at all after this technique.[1-3] According to other studies however, the incidence of disturbed continence varies between 8 to 15%.[4-6] In a previous study, performed at our institution, an even higher incidence of disturbed continence was observed.[7] These findings have recently been confirmed by other authors.[8]

The exact cause of this high incidence is not clear, because TAFR is designed to minimize damage to the anal sphincters. Recently, it has been suggested, that anal

stretch caused by the use of a Parks retractor is a major contributing factor in the impairment of fecal continence.[9] In our own previous study, all patients were operated on using a Parks anal retractor.[7] Other authors, using Parks (or similar) retractor, found similar results.[8] This study was designed to compare two different types of anal retractor (Parks versus Scott) with regards to their impact on fecal continence after fistula repair.

PATIENTS AND METHODS

Between November 2000 and November 2001, 30 patients with a perianal fistula entered the study. Preoperatively, all patients were randomized into two groups. In group A (n=15) a Parks retractor (Figure 1) was used during fistula repair, whereas in group B (n=15) the repair was performed with a Scott retractor (Lone Star Retractor System, Lone Star Medical Products®, Houston, Texas) (Figure 2). Patient characteristics are depicted in Table 1. Twenty-three patients had a high transsphincteric fistula, passing through the upper two thirds of the external anal sphincter. Seven patients(group A; n=4, group B; n=3) had a low transsphincteric fistula, passing to the lower third of the external anal sphincter, or an intersphincteric fistula. Patients who underwent fistulotomy were not included in the present series.

Surgical Technique

All patients were operated on by one single, experienced, colorectal surgeon (W.R.S.). All patients underwent core-out fistolectomy. Care was taken not to divide

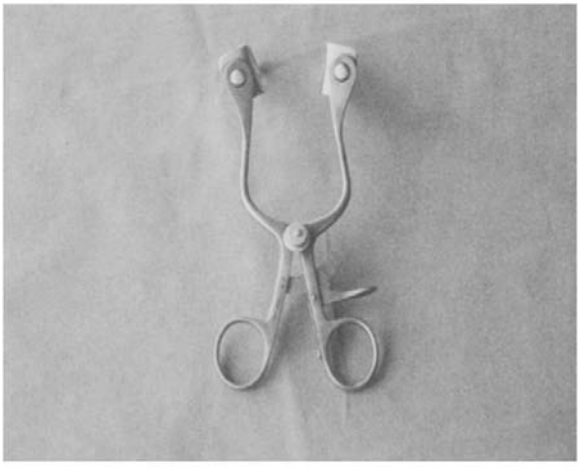

Figure 1.
Parks retractor.

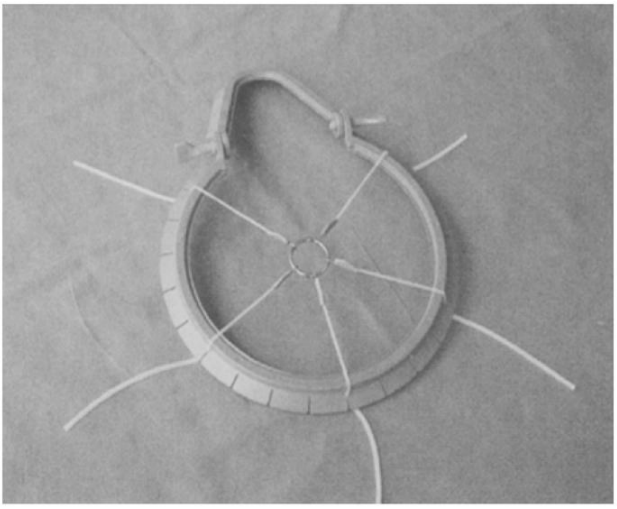

Figure 2.
Scott retractor.

Table 1.
Characteristics of Different Groups before fistula repair.

	Group A (Parks Retractor)	Group B (Scott Retractor)
No Pts	15	15
M:F Ratio	12:3	9:6
Median Age	46 (35-54)	45 (25-72)

any sphincter muscle. Patients with a high transsphincteric fistula (*n*=23) underwent a transanal advancement flap repair. In patients in whom the fistula traversed the lower one-third of the external anal sphincter or in whom the fistulous tract was intersphincteric, the core-out fistulectomy was followed by instillation of fibrin glue (Tissucol®, Baxter Healthcare Corp., Deerfield, Illinois) as described by Cintron *et al.*[10] Fistulotomies were not performed in the present series.

Manometry

Anal manometry was performed prior to the procedure and 12 weeks after the repair. The preoperative and postoperative manometric data were studied and compared between groups. Anal pressures were measured using a microtip pressure transducer (Millar Instruments, Inc., Houston, Texas, U.S.A.) with an outside diameter of 1.7 millimeters. In each subject, the catheter was introduced into the rectum

until rectal pressure was recorded, after which the probe was removed manually. This maneuver was repeated three times. The mean value of the maximum anal resting pressure (MARP) was determined for each subject. After this, a maximum voluntary contraction was performed, and the resultant pressure relative to the baseline pressure was recorded to determine the maximal anal squeeze pressure (MASP).

Fecal continence

Continence status was evaluated using both the classification system according to Parks and the Rockwood Fecal Incontinence Severity Index (RFISI).[11] This scoring system is based on a type x frequency matrix, that was developed using both surgeons and patients input for the specifications of the weighting scores. For the present study, input from patients were used. Continence was evaluated before and twelve weeks after the procedure. The preoperative and postoperative RFISI data were studied and compared between groups.

Statistical analysis

Changes (pre- minus postoperative) within groups were evaluated using Wilcoxon's signed-rank test. Comparison of these changes between groups was conducted using the Mann-Witney U test. For both tests, a p-value smaller than 0.05 was considered to be statistically significant.

RESULTS

The values of Maximum Anal Resting Pressure (MARP), Maximal Anal Squeeze Pressure (MASP) and the Rockwood Fecal Incontinence Severity Indices (RFISI), measured before and twelve weeks after the operation, are depicted in Table 2.

Table 2.

Mean Anal resting pressure, Maximal anal Squeeze pressure and Rockwood Fecal Incontinence Severity Index before and 12 weeks after the operation. †: p=0,035 (paired t-test), ‡: p=0,008 (paired t-test).

	MARP before	MARP after	MASP before	MASP after	RFISI before	RFISI after
Group A	76 †	42†	144	191	0 ‡	12 ‡
(Range)	(38-112)	(16-108)	(73-336)	(79-286)	(0-21)	(0-39)
Group B	79	71	151	121	5	6
(Range)	(26-109)	(40-93)	(35-275)	(57-229)	(0-48)	(0-33)

Manometry

Group A (Parks) and Group B (Scott) had similar values of MARP before the operation (median, 76 mmHg and 79 mmHg, respectively). The same applied for preoperative MASP values (144 versus 151 mmHg).

In group A, the median dropped significantly from 76 mmHg to 42 mmHg ($P<0.035$). In group B, median MARP dropped from 79 mmHg to 71 mmHg. When comparing the change from baseline of MARP between group A and group B, a statistically difference was observed ($P=0.035$) with median changes of 34 mmHg and 8 mmHg, respectively. After the operation, no significant change in median MASP was observed within either group ($P>0.05$, Figure 3). The observed changes did not significantly differ between groups ($P=0.59$).

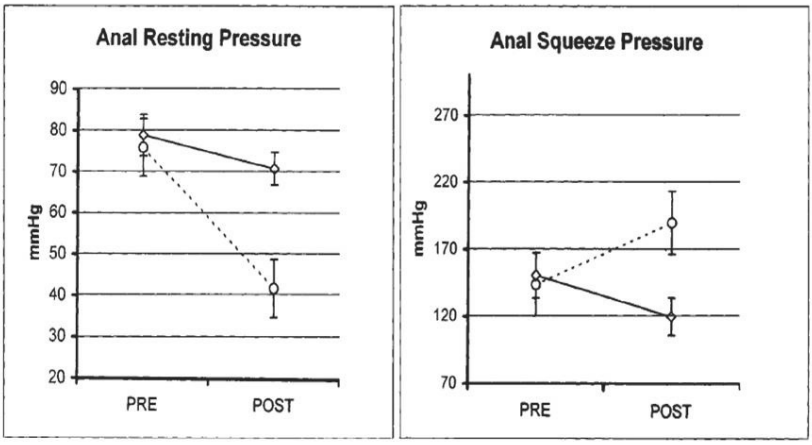

Figure 3.
Anal manometry (median ± standard error of the mean) before and 12 weeks after surgery. Circle = Group A (Parks); diamond = Group B (Scott). * $P=0.035$ (significant).

Fecal continence - RFISI

Before the fistula repair, similar Rockwood Fecal Incontinence Severity Indices (RFISI) were found in both groups ($P=0.47$). Three months after the operation, the Rockwood Fecal Incontinence Index rose (depicting a deterioration of fecal continence) from a median of 0 to 12 in group A ($P<0.01$). In group B, the median RFISI increased from a median of 5 to 6 ($P=0.27$). When comparing the change from baseline in RFISI between Group A and Group B, a statistically significant difference ($P=0.038$) was observed with median changes 6 and 0, respectively.

Fecal Continence - Parks

Prior to the fistula repair, both groups showed a similar continence score according to Parks (p=0.50). Thirteen patients (43%) were fully continent before the operation (Parks I). Four of these patients (31%) encountered soiling and/or incontinence for gas after the procedure (Parks II). None of these patients complained of accidental bowel movements. Continence impairment was only observed in group A.

Thirteen patients (43%) presented with mild continence disturbances at the time of admission to our hospital (incontinence for gas or soiling; Parks II). Three of these patients (23%) encountered incontinence for solid stool after the procedure.

DISCUSSION

Until now only one study, which evaluated the impact of Parks anal retractor on anal sphincter function, has been conducted. Van Tets and coworkers[9] conducted a prospective, randomized study in patients, who underwent a closed hemorrhoidectomy. Forty patients were randomized and underwent the procedure with or without the use of a Parks retractor. Comparing both groups, anal resting pressure was found to decline in 23 and 8% of patients, respectively. Although this difference is not statistically significant, this finding indicates that the use of a Parks retractor adversely affects the integrity of the internal anal sphincter.[9]

Van Tets and coworkers suggested that overstretching of the anal sphincters by a Parks retractor results in rupture of small nerve branches and consequently to denervation of muscle fibres.[9] In animal studies it has been shown that prolonged stretching can lead to local necrosis of external anal sphincter fibres.[12] It seems likely that these factors also contribute to the decreased internal sphincter tone observed in our patients in whom a Parks retractor was used to gain exposure. Willis and coworkers[3] performed a TAFR in 12 patients with a transsphincteric fistula. During this procedure, they used a Parks retractor in all their patients. These authors observed a statistically significant decrease in anal resting pressure and anal squeeze pressure of approximately 20%. Despite these significant pressure drops, they did not observe any postoperative incontinence. It is noteworthy that they assessed postoperative continence only at 6 weeks after the procedure. This very short follow-up might account for the low incidence of incontinence, as reported by these authors.

The Scott retractor is a ring retractor with multiple skin hooks on elastic bands. Using this type of retractor, the distal part of the anal canal is 'everted', thereby providing an excellent exposure, whereas the amount of stretch on the anal sphincters is minimized. Because no blades are inserted into the anal canal, the pressure on the internal anal sphincter is minimized, thereby reducing the risk of local necrosis. Although internal anal sphincter fibers were included to strengthen the flap, no deterioration of continence was observed after the flap repair using a Scott retractor.

Therefore it seems unlikely that inclusion of internal anal sphincter fibers contributes to the impairment of fecal continence after transanal advancement flap repair. In our opinion avoidance of anal stretch during the procedure is far more important in reducing the risk of postoperative continence disturbances.

The present study shows a significant increase in the Rockwood Fecal Incontinence Severity Index after the use of Parks retractor in fistula repair. Such an increase was not found after the use of a Scott retractor. These findings indicate that use of a Parks retractor is a major contributing factor to the impairment of continence after transanal surgical procedures.

CONCLUSION

The use of a Parks retractor during perianal fistula repair has a deteriorating effect on fecal continence, probably caused by damage of the internal anal sphincter. Because this side effect was not observed after the use of a Scott retractor, we advocate this retractor during transanal surgery.

REFERENCES

1. Wedell J, Meier zu Eissen P, Banzhaf G and Kleine L. Sliding flap advancement for the treatment of high level fistulae. Br J Surg 1987; 74: 390-1.
2. Shemesh EI, Kodner IJ, Fry RD and Neufeld DM. Endorectal sliding flap repair of complicated anterior anoperineal fistulas. Dis Colon Rect 1988; 31: 22-4.
3. Willis S, Rau M, et al. Chirurgische therapie hoher anorectaler und rectovaginaler fisteln mittels transanaler endorectaler verschliebelappenplastik. Chirurg 2000; 71: 836-840.
4. Aguilar PS, Plasencia G, Hardy TG, Hartman RF and Stewart WRC. Mucosal advancement in the treatment of anal fistula. Dis Colon Rect 1985; 28: 496-8.
5. Ortiz H, Marzo J. Endorectal flap advancement repair and fistulectomy for high transsphincteric and suprasphincteric fistulas. Br J Surg 2000; 87: 1680-1683.
6. Golub RW, Wise WE, Kerner BA, et al. Endorectal mucosal advancement flap: the preferred method for complex cryptoglandular fistula in ano. J Gastrointest Surg 1997; 1: 487-491.
7. Schouten WR, Zimmerman DD, Briel JW. Transanal advancement flap repair of transsphincteric fistulas. Dis Colon Rectum 1999; 42: 1419-23.
8. Gustafsson U-M, Graf W. Excision of anal fistula with closure of the internal opening: functional and manometric results. Dis Colon Rect 2002; 45: 1672-8.
9. Van Tets WF, Kuijpers JHC, Tran K, Mollen R and van Goor H. Influence of Parks' anal retractor on anal sphincter pressures. Dis Colon Rect 1997; 40: 1042-5.
10. Cintron JR, Park JJ, Orsay CP. Repair of fistulas-in-ano using fibrin adhesive. Dis Colon Rectum 2000; 43: 944-950.
11. Rockwood TH, Church JM, Fleshman JW, et al. Patient and surgeon ranking of the severity of symptoms associated with fecal continence. Dis Colon Rectum 1999; 42:1525-1532.
12. Li L, Zhang JZ, Lu GW, He GR, Lui XH, Damaging effects of anal stretching on the external anal sphincter. Dis Colon Rectum 1996 Nov; 39(11): 1249-54.

CHAPTER 8

Integrity of the anal sphincters after pouch-anal anastomosis: evaluation with three-dimensional endoanal ultrasonography

Gosselink MP, West RL, Kuipers EJ,
Hansen BE and Schouten WR.
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ABSTRACT

The aim of the present study was to assess the integrity of the anal sphincters after handsewn pouch-anal anastomosis performed with the help of a Scott retractor. For this purpose the anal sphincters were visualized with three-dimensional endoanal ultrasonography. Patients undergoing a colonic pouch-anal anastomosis or an ileal pouch-anal anastomosis were included. Before and six months after the procedure, the length and volume of both sphincters were assessed with three-dimensional endoanal ultrasonography, and anal manometry was performed. Continence scores were determined using the Rockwood Fecal Incontinence Severity Index (RFISI). Fifteen patients with a colonic pouch and 13 patients with an ileal pouch were examined. Six months after the procedure, three-dimensional endoanal ultrasonography showed significant alterations of the internal anal sphincter in eight patients with a colonic pouch-anal anastomosis (53%) and in eight patients with an ileal pouch-anal anastomosis (62%). These alterations were characterized by asymmetry or thinning. No defects were seen in the colonic pouch group, but, in two patients with an ileal pouch, a small defect in the internal anal sphincter was found. A decrease in internal anal sphincter volume was seen only in patients with a colonic pouch-anal anastomosis (P=0.009). In both groups the length of the internal anal sphincter and the length, thickness, and volume of the external anal sphincter remained the same. After the procedure a reduction of maximum anal resting pressure was found in both groups (colonic pouch: P<0.001, ileal pouch: P=0.001). Maximum anal squeeze pressure was reduced in only patients with an ileal pouch-anal anastomosis (P=0.006). The observed alterations of the internal anal sphincter and the manometric findings showed no correlation with the postoperative Rockwood Fecal Incontinence Severity Index scores. Handsewn pouch-anal anastomosis, performed with the help of a Scott retractor, only rarely leads to internal anal sphincter defects, but three-dimensional endoanal ultrasonography shows alterations of the internal anal sphincter in 57% of the patients. No correlation was observed between these alterations and the functional outcome.

INTRODUCTION

Ileal pouch-anal anatomosis (IPAA) is the procedure of choice for patients with ulcerative colitis or familial adenomatous polyposis needing a proctocolectomy.[1] Total proctocolectomy with IPAA after transanal mucosectomy not only eliminates the disease but also preserves the anal sphincter. The coloanal anastomosis has also allowed restorative surgery with preservation of the anal sphincters.[2] It has been shown that addition of a pouch improves the functional outcome and quality of life.[3,4] In the past pouch-anal anastomoses were mainly handsewn using a Parks retractor at the dentate line after transanal mucosectomy. At present most surgeons prefer a double-stapled

IPAA or a double-stapled low colorectal anastomosis to prevent anal stretch and to preserve the transitional zone. In our institute we still perform a handsewn pouch-anal anastomosis. Since the recently developed Scott retractor appears to cause less sphincter damage than the Parks retractor during transanal manipulation, we always use this type of retractor to facilitate a handsewn pouch-anal anastomosis.[5]

Postoperative sphincter function is of key relevance for the long-term outcome after low transanally stapled anastomosis and after handsewn pouch-anal anastomosis. This necessitates the need for a better understanding of the effects of both techniques on sphincter anatomy and function. To examine the function of the anal sphincters many manometric studies have been conducted.[6-10] In most of these studies a significant reduction of maximum anal resting pressure (MARP) was observed after both procedures. Endoanal ultrasonography (EUS) is a well-established technique for visualizing the anal sphincters.[11,12] Recently, three-dimensional (3D) EUS, which can provide multiplanar imaging of the anal canal, has become available.[13,14] This yields more information on the anal sphincter complex and makes it easier to perform sphincter measurements such as volume measurements. Until now, four EUS studies have been performed in patients with a transanally stapled low colorectal anastomosis,[15-18] and only one in patients with a handsewn IPAA.[19]

The present study is the first one to use 3D EUS before and after surgery to evaluate the impact of transanal mucosectomy followed by handsewn pouch-anal anastomosis at the level of the dentate line on the integrity and the morphology of both sphincters.

PATIENTS & METHODS

All patients who underwent a colonic pouch-anal anastomosis (CPAA) or an IPAA between October 2001 and October 2003 were included in this prospective study after informed consent. Before and six months after surgery patients were asked to fill out a questionnaire to assess continence. In addition, all patients underwent anal manometry and 3D EUS at both occasions. The study was approved by the Ethics Committee of the Erasmus Medical Center.

Surgical Technique

All patients were operated on by one colorectal surgeon (WRS). To gain access to the anal canal a Scott retractor was used (Lone Star Retractor System, Lone Star Medical Products®, Inc., Houston, TX). This ring retractor, with multiple skin hooks on elastic bands, provides excellent exposure. Because no blades are inserted into the anal canal, the amount of stretch on both sphincters is minimized. The rectum was mobilized until the pelvic floor was reached. Just above the pelvic floor, the rectum was transected between two right-angled bowel clamps. The remaining mucosa was removed from the dentate line up to the upper margin of the transected mucosa.

CPAA

In patients with a tumor in the middle or distal third of the rectum, a side-to-end J-pouch-anal anastomosis was performed after total mesorectal excision. All these patients received preoperative radiotherapy. For the construction of the colonic J-pouch a stapler was used. The pouch was hand-sutured to the dentate line.

IPAA

In patients with ulcerative colitis or familial adenomatous polyposis, an IPAA was performed. In all these patients a handsewn S-pouch was constructed. After advancement into the anal canal, a handsewn pouch-anal anastomosis was performed.

Three-Dimensional Endoanal Ultrasonography (3D EUS)

For 3D EUS a Diagnostic Ultrasound System (type 3535, B-K Medical, Herlev, Denmark) with a 7-MHz rotating endoprobe (type 1850; focal range, 2-4.5 cm) covered by a water-filled hard sonolucent cone (diameter, 1.7 cm), producing a 360° view was used. The endoprobe was introduced into the rectum with the patient in the left lateral position. Serial radial images were taken of the distal part of the rectum, the puborectalis muscle (PR), the external anal sphincter (EAS) and the internal anal sphincter (IAS). Three-dimensional images were reconstructed by a 2D setup connected to a computer with frame-grabbing software. For this purpose, the probe was slowly withdrawn from the rectum in 30 seconds by means of a pullback device at a fixed speed of 2 mm/second. The data volume was viewed in a software program used for 3D reconstruction (Life Imaging System 2000, L3Di version 3.5.5, B-K Medical, Herlev, Denmark).

The anal sphincters were assessed for defects before surgery. In addition, the aspect of the IAS was carefully studied and any changes after surgery like thinning, an asymmetry, or fragmentation were noted. Volume measurements of the IAS and EAS were performed and IAS length and EAS length and thickness were determined.

Volume measurements were performed by determining the sum of the area of the IAS and EAS measured at 0.25-mm intervals. Only muscle without scarring was included in these measurements. The most proximal point of the IAS was defined as the first level at which the IAS is seen as a clear hypoechogenic ring and the most distal point was defined as the level where the IAS is last seen as a complete ring. For the most proximal point of the EAS, the level where the EAS is last seen as complete ring, distal to the PR sling, was used. In addition, for the most distal point of the EAS, the termination of the subcutaneous EAS was used.

For the anterior and posterior sphincter length, the distance between the lower and upper borders of the IAS and EAS was measured. The EAS thickness was measured at the 3 (left), 6 (posterior), 9 (right) and 12 o'clock (anterior) positions at the anatomic midpoint of the sphincter. Using these measurements the average EAS thickness could be determined.

Anal Manometry

A dynamic pull-through technique (2 mm/second) with a four-channel water-perfused (0.5 ml/minute) catheter (MMS system, Enschede, The Netherlands) was used for manometry. Each channel had a side-hole, and the side-holes were arranged around the circumference of the catheter, 90° to each other. No specific bowel preparation was used. To perform manometry patients were positioned in the left lateral position. Zero-pressure calibration was done at the anal orifice level before introducing the catheter. After introduction and stabilization in the rectum, the catheter was withdrawn. The high-pressure zone was registered; this was defined as an increase in pressure of more than 5 mmHg. Maximum anal resting pressure (MARP) was averaged across the four channels by use of the maximum plateau phase of all channels. After introducing the catheter a second time, the patient was asked to squeeze at 0.5-cm intervals. The maximum squeeze pressure was calculated by averaging the highest squeeze pressures recorded by each channel. The rectoanal inhibitory reflex was elicited by distending a rectal balloon with different volumes of air. Paradoxic straining was defined as an increase of 10 mmHg combined with a maximum resting pressure of more than 60 mmHg.

Fecal Incontinence Score

A questionnaire was used to determine the Rockwood Fecal Incontinence Severity Index (RFISI) score before and after surgery. This is a validated index based on a type × frequency matrix. The matrix includes four types of leakage commonly found in the fecal incontinent population - gas, mucus, liquid, and solid stools - and five frequencies - once to three times per month, once per week, twice per week, once per day, and twice per day. For the specification of the weighting scores, patient input was used. Scores range from zero (total continence) to 61 (complete incontinence to solid stool on a daily basis).

Statistical Analysis

Differences in RFISI score, manometry and 3D EUS measurements in both groups before and after surgery were compared using the Wilcoxon signed ranks test (median, *P* value). The Spearman's correlation coefficient (SCC) was used for correlation between manometry findings and 3D EUS measurements. The differences before and after surgery between the two groups were compared using the Mann-Whitney *U* test. All *P* values were calculated with exact methods. Two-sided *P* values less than 0.05 were considered to indicate statistically significant differences.

RESULTS

CPAA Group

Nineteen consecutive patients with rectal cancer entered the study. Four patients

were excluded; one patient was lost to follow-up, one died during follow-up, and in two patients a coloanal J-pouch anastomosis was not deemed suitable because of metastases found during the operation. In these patients a colostomy was created. The remaining 15 patients were evaluated (10 males; median age, 58 (range, 40-74) years). Five female patients had had a vaginal delivery. Two of these women had experienced a tear and two had undergone an episiotomy. No patients had undergone anal surgery previously. The median duration of the time interval between surgery and final evaluation was 6.8 (range, 4.7–13.4) months.

Three-dimensional EUS could be performed in all patients before and after surgery. Before the procedure an EAS defect was seen in one patient who had had four vaginal deliveries. During one of these deliveries she underwent an episiotomy. After the CPAA no new EAS defects were found. No significant changes were seen in EAS volume, length, or average thickness after surgery. The aspect of the IAS had changed in eight patients (53%), meaning that the IAS was thinner or asymmetric (Figure 1). A defect or fragmentation was not seen in any of these patients. A significant decrease was observed in IAS volume after surgery (P=0.009) but not in IAS length (Table 1). Maximum anal resting pressure decreased significantly after surgery (P<0.001). No difference was seen with respect to maximum anal squeeze pressure. A rectoanal inhibitory reflex was seen in all patients before surgery and in ten after surgery. Before surgery the median RFISI score was 4 (range, 0–30) and increased to 13 after

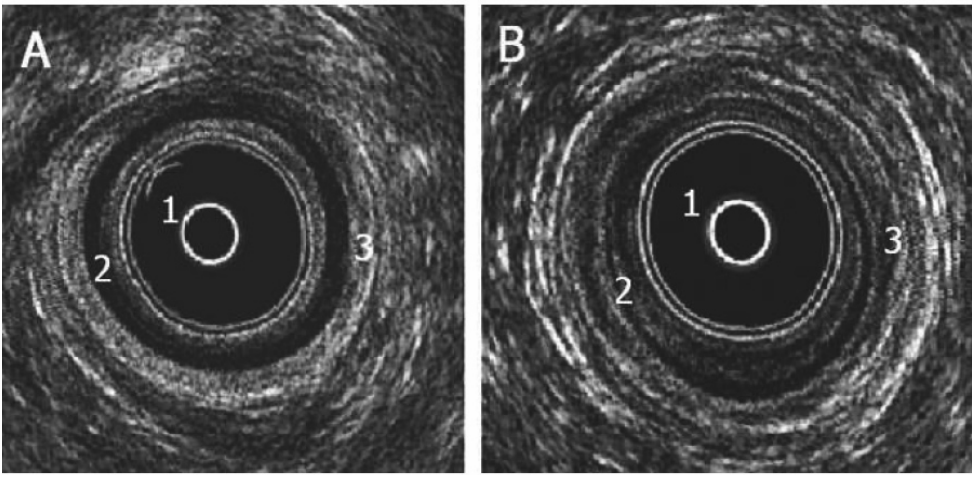

Figure 1.
IAS asymmetry after CPAA surgery. 3D EUS image before (A) and after (B) CPAA surgery showing the endoprobe (1), the IAS (2), and the EAS (3). In the postoperative image (B), asymmetry of the IAS can be seen. IAS = internal anal sphincter; EAS = external anal sphincter; CPAA = colonic pouch-anal anastomosis; 3D EUS = three dimensional endoanal ultrasonography.

Table 1.
EUS Measurements Before and After Colonic Pouch-Anal Anastomosis (n=13) and Ileal Pouch-Anal Anastomosis (n=11)

	IAS Volume (cm^3)		IAS Length (cm)		EAS Volume (cm^3)		EAS length (cm)		Average EAS thickness (cm)	
	Before	After	Before	After	Before	After	Before	After	Before	After
CPAA	0.9 (0.2-1.2)	0.6 (0.1-0.9)*	0.9 (0.3-1.6)	0.8 (0.2-1.5)	5.5 (2.2-10.9)	6.1 (2.7-10.8)	1.1 (0.3-1.8)	1.1 (0.3-1.8)	0.5 (0.3-0.6)	0.5 (0.4-0.6)
IPAA	0.5 (0.4-1.3)	0.5 (0.4-1.0)	1.0 (0.3-1.3)	0.8 (0.3-1.2)	5.6 (3.5-8.5)	5.1 (3.6-8.5)	1.2 (0.4-1.5)	1.0 (0.3-1.5)	0.5 (0.4-0.6)	0.5 (0.4-0.6)

Values are median (range).
* *P*=009

surgery (range, 0–31) (*P*=0.060). No correlation was found between the change in anal resting pressure and IAS volume (SSC=0.72, *P*=0.83) or between the RFISI score and MARP (SCC=0.140, *P*=0.32) or IAS volume (SCC=0.288, *P*=0.36).

IPAA Group

Sixteen patients with ulcerative colitis and one with familial adenomatous polyposis entered the study. Thirteen patients could be evaluated and four patients were excluded. In one patient surgery was postponed because of a perianal fistula requiring treatment. In another patient it was not possible to create a pouch and two patients were lost to follow-up. The median age of the 13 (8 males) who could be evaluated was 34 (range, 21-51) years. Eleven of these patients had undergone a subtotal colectomy with closure of the rectum stump before pouch surgery. In the other two patients a proctocolectomy and IPAA were performed in a single operation. One female patient had had a vaginal delivery, during which she had an episiotomy. None of the patients had undergone anal surgery previously. The median duration of the time interval between surgery and final evaluation was 8.2 (range, 6.0-19.3) months.

Before surgery 3D EUS could be performed in all 13 patients. An EAS defect was found in the female patient who had an episiotomy. After IPAA no new EAS defects were seen. The aspect of the IAS had changed in eight patients (62%). In six of these patients the IAS was thinner or asymmetrical, in one patient fragmentation of the IAS was observed (Figure 2), and in one patient an IAS defect was seen (Figure 3).

After the operation 3D EUS could be repeated in 11 patients. In two patients, the probe could not be introduced into the anal canal because of a stenotic anastomosis. No significant differences were seen for IAS and EAS volume or length and EAS thickness after surgery (Table 1). A significant decrease was seen in MARP and maximum anal squeeze pressure after surgery in this group (*P*=0.001 and *P*=0.006) (Table 2). The rectoanal inhibitory reflex was seen in all patients before

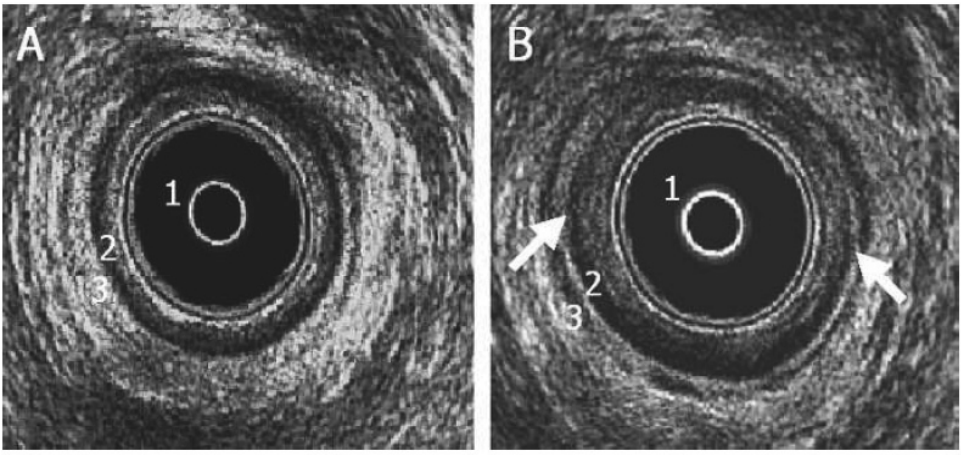

Figure 2.
Fragmentation of the IAS after IPAA surgery. 3D EUS image before (A) and after (B) IPAA surgery showing the endoprobe (1), the IAS (2), and the EAS (3). In the postoperative image (B), fragmentation of the IAS can be seen between the arrows. IAS = internal anal sphincter; EAS = external anal sphincter; IPAA = ileal pouch-anal anastomosis; 3D EUS = three dimensional endoanal ultrasonography.

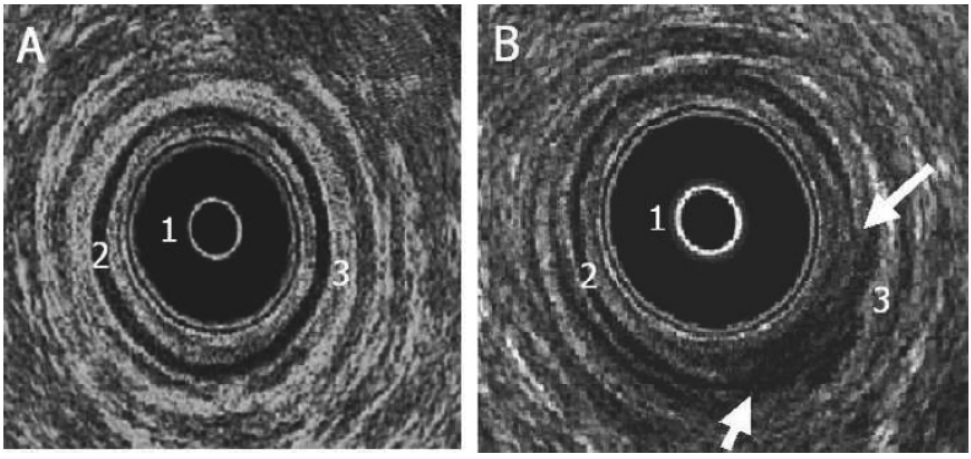

Figure 3.
IAS defect after IPAA surgery. 3D EUS image before (A) and after (B) IPAA surgery showing the endoprobe (1), the IAS (2), and the EAS (3). In the postoperative image (B), an IAS defect can be seen between the arrows. IAS = internal anal sphincter; EAS = external anal sphincter; IPAA = ileal pouch-anal anastomosis; 3D EUS = three dimensional endoanal ultrasonography.

Table 2.
Manometry Findings Before and After Colonic Pouch-Anal Anastomosis and Ileal Pouch-Anal Anastomosis.

	Maximum Anal Resting Pressure (mmHg)		Maximum Anal Squeeze Pressure (mmHg)	
	Before	After	Before	After
CPAA	83 (32–130)	41 (21–82)*	187 (59–363)	183 (55–307)
IPAA	85 (53–152)	44 (28–98)†	161 (73–450)	132 (70–356)‡

Values are median (range).
CPAA = colonic pouch-anal anastomosis; IPAA = ileal pouch-anal anastomosis.
* $P<0.001$.
† $P=0.001$.
‡ $P=0.006$.

surgery and in eight after surgery. The median RFISI score could not be determined before the procedure because 11 patients had a colostomy after subtotal colectomy. The postoperative RFISI score was 13 (range, 0–31). No correlation was found between the change in anal resting pressure and IAS volume (SSC=0.24, $P=0.49$) or between the RFISI score and anal resting pressure (SCC=−0.158, $P=0.30$) or IAS volume (SCC=0.559, $P=0.07$).

CPAA vs. IPAA Group

The patients in the CPAA group were significantly older than the patients in the IPAA group ($P<0.001$). Before surgery no differences were seen in manometric findings or 3D EUS measurements. The only significant difference between the two groups after surgery was the change in IAS volume. A larger decrease in IAS volume was seen in the CPAA group compared with that in the IPAA group ($P=0.04$).

DISCUSSION

The functional outcome after a pouch-anal anastomosis depends to a large extent on postoperative function of both sphincters. Many manometric studies have reported on postoperative anal sphincter function.[6-10] However, reports on anal sphincter imaging are scarce. Until now four studies have been conducted to evaluate the morphology of both sphincters after transanally stapled anastomosis.[15-18] Only one 2D EUS study has been conducted to examine the morphology of both sphincters after transanal mucosectomy followed by an IPAA hand-sutured at the level of the dentate line.[19]

The present study is the first one to use 3D EUS before and after surgery to evaluate the impact of transanal mucosectomy followed by a handsewn pouch-anal anastomosis on the integrity and the morphology of both sphincters. Unlike 2D EUS, 3D EUS produces a digital volume that may be reviewed and used to perform measurements in any plane. This technique provides more reliable measurements. Furthermore, as the length of the anal canal can be studied, volume measurements

of the anal sphincters can be performed. Volume measurements could provide more insight into anal sphincter morphology and disorders.

Our study has revealed that a pouch-anal anastomosis, hand-sutured to the dentate line with the help of a Scott retractor, does not affect the EAS because volume, length, and thickness of this muscle did not change. This finding is in agreement with those reported by others.[15,17] A defect in the IAS was found in two patients with an IPAA and in none with a CPAA. It seems likely that these defects are a result of direct injury to the IAS, sustained during transanal mucosectomy. The overall incidence of these IAS defects in the present series was 8%. A similar finding has been reported by Silvis *et al.*[19] These authors found similar defects in 11% of their patients. In their study a Parks retractor was used to gain access to the anal canal. Unfortunately, 2D EUS was performed only after the operation and not before.

The question is whether the risk of IAS defects is reduced by performing a transanally stapled anastomosis. Farouk *et al.* used 2D EUS and observed IAS defects in 18% of their patients after a stapled low anterior resection for rectal cancer.[17] Ho *et al.* also used 2D EUS and observed significant fragmentation of the IAS in 28% of the patients after a transanal stapled anastomosis.[15] In a recent study comparing transanally stapled J-pouches and coloplasty pouches, Ho *et al.* found fragmentation of the IAS in 6.3 and 8.3%, respectively.[16] Winter *et al.* assessed the effect of topical application of nitroglycerin (GTN) to facilitate stapler insertion in patients undergoing anterior resection.[18] In a randomized, controlled trial they found endosonographic evidence of sphincter abnormalities in 28.7% of patients in the control group. After topical application of GTN these abnormalities were observed in only 3.1% of the patients. Based on these data, it seems unlikely that the insertion and use of a stapler is less harmful for the IAS than a transanal mucosectomy.

Three-dimensional EUS enables the measurement of sphincter volume. In our patients who underwent a CPAA, a significant reduction of IAS volume was found after surgery. This finding was not observed in the patients who underwent an IPAA. The reduction of IAS volume in the CPAA group might be a result of the radiation therapy. It is also possible that the older age of the patients in this group contributes to this volume reduction.

Using 3D EUS we also studied other morphologic aspects of the IAS. After surgery the IAS did show alterations along the circumference in 53% of the patients after CPAA and in 62% of the patients after IPAA. These alterations were characterized by asymmetry and variations in thickness. Comparing IPAA patients with healthy volunteers, Silvis *et al.* observed significant differences regarding IAS thickness.[19] Our findings and those of Silvis *et al.* have not be documented in the four available reports on sphincter imaging after transanally stapled anastomosis.[15-18] The question is whether the changes in IAS morphology are a result of direct injury to the IAS during transanal mucosectomy or a result of damage to its nerve supply during rectal mobilization. Kroesen *et al.* performed 3D vector volume manometry before and after IPAA.[20] They found no isolated reduction of resting pressure in one of the sphincter segments.

Instead, they observed a global reduction in all segments, suggesting neurogenic injury rather than morphologic damage. Another manometric study in dogs revealed a significant drop in MARP after resection of the rectum followed by a handsewn colorectal anastomosis without any transanal manipulation.[21] Hallgren *et al.* investigated the changes in MARP during the different stages of restorative proctocolectomy and either handsewn or stapled pouch-anal anastomosis.[22] In both techniques the MARP was reduced in a sequential manner during the surgical procedure, with an immediate decrease in pressure after division of the superior rectal artery, a further reduction after full mobilization of the rectum, followed by another equally large drop at the final stage after construction of the anastomosis by either technique. All these findings indicate that the reduction of anal resting pressure is not only a result of direct injury to the IAS but also of neurogenic damage. This neurogenic injury might contribute to the morphologic changes observed in the present study.

Recently it has been shown that damage to the IAS during transanal manipulation can be reduced by the use of a Scott retractor. Zimmerman *et al.* conducted a randomized trial to compare the Parks retractor *vs.* the Scott retractor with regard to their impact on fecal continence after fistula repair.[5] MARP and RFISI deteriorated significantly after the use of a Parks retractor, whereas these changes were not observed when the repair was performed with a Scott retractor. In an earlier report Van Tets *et al.* also suggested that anal stretch resulting from the use of a Parks retractor is a major contributing factor in the impairment of fecal continence after hemorrhoidectomy.[23] Mean resting pressure decreased by 23% after using a Parks retractor compared with 8% when it was not used. These data do suggest that the use of a Scott retractor is less detrimental for the IAS than the use of a Parks retractor. Despite the use of a Scott retractor, changes in IAS morphology were observed in the majority of our patients. Further studies are warranted to answer the question of whether these changes in IAS morphology are caused by transanal manipulation or by neurologic damage.

CONCLUSION

After a handsewn pouch-anal anastomosis, performed with the help of a Scott retractor, distinct IAS defects are observed in only a minority of patients. The morphology of the IAS changed in 57% of the patients. These changes do not appear to adversely affect the functional outcome because the observed alterations and the manometric findings did not show any correlation with the RFISI scores.

REFERENCES

1. Parks AG, Nicholls RJ. Proctocolectomy without ileostomy for ulcerative colitis. Br Med J 1978; 2: 85-88.
2. Parks AG. Transanal technique in low rectal anastomosis. Proc R Soc Med 1972; 65: 975-976.
3. Parc R, Tiret E, Frileux P, Moszkowski E, Loygue J. Resection and colo-anal anastomosis with colonic reservoir for rectal carcinoma. Br J Surg 1986; 73: 139-141.
4. Lazorthes F, Fages P, Chiotasso P, Lemozy J, Bloom E: Resection of the rectum with construction of a colonic reservoir and colo-anal anastomosis for carcinoma of the rectum. Br J Surg. 1986; 73: 136-138.
5. Zimmerman DD, Gosselink MP, Hop WC, Darby M, Briel JW, Schouten WR. Impact of two different types of anal retractor on fecal continence after fistula repair: a prospective, randomized, clinical trial. Dis Colon Rectum 2003; 46: 1674-1679.
6. Vassilakis JS, Pechlivanides G, Zoras OJ, Vrachasotakis N, Chrysos E, Tzovaras G, Xynos E. Anorectal function after low anterior resection of the rectum. Int J Colorectal Dis 1995; 10: 101-106.
7. Choi HJ, Saigusa N, Choi JS, Shin EJ, Weiss EG, Nogueras JJ, Wexner SD: How consistent is the anal transitional zone in the double-stapled ileoanal reservoir? Int J Colorectal Dis 2003; 18: 116-120.
8. Hallbook O, Nystrom PO, Sjodahl R. Physiologic characteristics of straight and colonic J-pouch anastomoses after rectal excision for cancer. Dis Colon Rectum 1997; 40: 332-338.
9. Reilly WT, Pemberton JH, Wolff BG, Nivatvongs S, Devine RM, Litchy WJ, McIntyre PB. Randomized prospective trial comparing ileal pouch-anal anastomosis performed by excising the anal mucosa to ileal pouch-anal anastomosis performed by preserving the anal mucosa. Ann Surg 1997; 225: 666-676.
10. Sailer M, Fuchs KH, Fein M, Thiede A. Randomized clinical trial comparing quality of life after straight and pouch coloanal reconstruction. Br J Surg 2002; 89: 1108-1117.
11. Law PJ, Bartram CI. Anal endosonography: technique and normal anatomy. Gastrointest Radiol 1989; 14: 349-353.
12. Stoker J, Rociu E, Wiersma TG, Lameris JS. Imaging of anorectal disease. Br J Surg 2000; 87: 10-27.
13. Gold DM, Bartram CI, Halligan S, Humphries KN, Kamm MA, Kmiot WA. Three-dimensional endoanal sonography in assessing anal canal injury. Br J Surg 1999; 86: 365-370.
14. Williams AB, Spencer JA, Bartram CI. Assessment of third degree tears using three-dimensional anal endosonography with combined anal manometry: a novel technique. Bjog 2002; 109: 833-835.
15. Ho YH, Tsang C, Tang CL, Nyam D, Eu KW, Seow-Choen F. Anal sphincter injuries from stapling instruments introduced transanally: randomized, controlled study with endoanal ultrasound and anorectal manometry. Dis Colon Rectum 2000; 43: 169-173.
16. Ho YH, Brown S, Heah SM, Tsang C, Seow-Choen F, Eu KW, Tang CL. Comparison of J-pouch and coloplasty pouch for low rectal cancers: a randomized, controlled trial investigating functional results and comparative anastomotic leak rates. Ann Surg 2002; 236: 49-55.
17. Farouk R, Duthie GS, Lee PW, Monson JR. Endosonographic evidence of injury to the internal anal sphincter after low anterior resection: long-term follow-up. Dis Colon Rectum 1998; 41: 888-891.
18. Winter DC, Murphy A, Kell MR, Shields CJ, Redmond HP, Kirwan WO. Perioperative Topical Nitrate and Sphincter Function in Patients Undergoing Transanal Stapled Anastomosis: A Randomized, Placebo-Controlled, Double-Blinded Trial. Dis Colon Rectum 2004; 47: 697-703.
19. Silvis R, van Eekelen JW, Delemarre JB, Gooszen HG. Endosonography of the anal sphincter after ileal pouch-anal anastomosis. Relation with anal manometry and fecal continence. Dis Colon Rectum 1995; 38: 383-388.
20. Kroesen AJ, Runkel N, Buhr HJ. Manometric analysis of anal sphincter damage after ileal pouch-anal anastomosis. Int J Colorectal Dis 1999; 14: 114-118.
21. Molloy RG, Moran KT, Coulter J, Waldron R, Kirwan WO. Mechanism of sphincter impairment following low anterior resection. Dis Colon Rectum 1992; 35: 462-464.
22. Hallgren T, Fasth S, Delbro D, Nordgren S, Oresland T, Hulten L. Possible role of the autonomic nervous system in sphincter impairment after restorative proctocolectomy. Br J Surg 1993; 80: 631-635.
23. Van Tets WF, Kuijpers JH, Tran K, Mollen R, van Goor H. Influence of Parks' anal retractor on anal sphincter pressures. Dis Colon Rectum. 1997 Sep; 40: 1042-5.

CHAPTER 9

The effect of neo-rectal wall properties on functional outcome after colonic J-pouch-anal anastomosis

Gosselink MP, Zimmerman DD, West RL,
Hop WC, Kuipers EJ and Schouten WR.
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ABSTRACT

It has been suggested that normal function of both anal sphincters is essential for a good functional outcome after colonic J-pouch-anal anastomosis (CPAA). However, CPAA patients may have impaired continence despite adequate sphincter function. The present study was designed to identify those factors, which contribute to the functional outcome after a handsewn CPAA. Forty patients were studied before and 1 year after pouch surgery. Fecal continence was evaluated using the Rockwood fecal incontinence severity index (RFISI). At both occasions, maximum anal resting pressure (MARP) and maximum anal squeeze pressure (MASP) were recorded. In addition, sensory perception threshold-volumes (SPT-V) and compliance were assessed using an 'infinitely' compliant polyethylene bag connected to an electronic barostat assembly. The median RFISI score 1 year after surgery was higher than the median RFISI score before surgery (13 vs 7 ($p < 0.01$). The median MARP dropped significantly ($p<0.01$) whereas the median MASP remained unaffected. The mean compliance, calculated at three different sensation levels, and the pouch sensory perception threshold-volumes (PSPT-V) were lower than those of the original rectum ($p<0.05$). The reduction of MARP showed no correlation with the post-operative change in RFISI scores. Low PC and low PSPT-V were associated with higher RFISI scores. Low pouch compliance and low SPT-V adversely affect functional outcome after a handsewn colonic J-pouch-anal anastomosis.

INTRODUCTION

After total meso-rectal excision for rectal cancer, surgeons often try to avoid an abdomino-perineal resection by performing a trans-anally double-stapled low colorectal anastomosis (LRA), often without a pouch. The functional outcome after such a LRA is not as good as previously thought,[1,2] especially after pre-operative radiotherapy.[3,4] It has been shown that the addition of a pouch improves the functional outcome and quality of life.[5,6] A poor functional outcome after LRA or straight colo-anal anastomosis without a pouch is characterised by a high defecation frequency, urgency and impaired continence, especially during the first 2 years after the operation. Decrease in internal and external anal sphincter functions due to direct injury of the nervous supply,[7,8] abolishment of the recto-anal inhibitory reflex[9,10] and the level of the anastomosis[11] have been related to functional impairment after LRA. In a recent study, we demonstrated that poor functional outcome after handsewn colonic J-pouch-anal anastomosis (CPAA) utilising a Scott retractor was not due to alterations of the anal sphincters.[12] The question therefore is whether other factors such as pouch compliance and pouch sensory perception attribute to functional outcome. A recent meta-analysis conducted by Heriot *et al.* revealed that pouch sensory perception threshold-volumes (PSPT-V) are larger in patients with a CPAA than in those with a straight anastomosis.

However, no difference was found for resting or squeeze pressure.[5]

Although functional outcome after CPAA is better than after low colorectal anastomosis without a pouch, a number of patients with a CPAA have impaired continence despite adequate sphincter function. The aim of our study was to investigate whether compliance and sensory perception are different in a colonic J-pouch compared to the original rectum. In addition, a possible relationship between compliance and sensory perception and functional outcome was evaluated.

PATIENTS AND METHODS

Between January 1999 and June 2003, 46 consecutive patients entered the study after signing informed consent. Forty patients presented with cancer located in the middle or lower third of the rectum. Six patients had a large villous adenoma of the rectum, which was unsuitable for endoscopic resection. Before the operation, all 46 patients underwent anal manometry and barostat measurements. One year after surgery, these measurements were repeated in 40 patients. In addition, patients were asked to fill out a questionnaire to assess faecal continence at both occasions. In six patients, this post-operative evaluation could not be performed. Two patients had died within 1 year after the operation. The cause of their death was not related to the procedure or their underlying cancer. In the other four patients, the surgeon had decided to perform an abdomino-perineal resection during surgery. Nine patients who were evaluated 1 year after the operation received pre-operative radiotherapy. The radiotherapy was applied through a posterior–anterior field and 2 lateral fields with a total dosage of 25 Gray (5×5 Gray). The target volume of the radiotherapy consists of the primary tumour and the mesentery with the vascular supply containing the peri-rectal, pre-sacral and internal iliac nodes. Eight patients with stage III rectal cancer and 1 patient with stage II rectal cancer received adjuvant chemotherapy; 6 months of 5-fluorouracil given along with leucouvorin. None of the patients had any detectable signs of local recurrence or distant metastases at 1-year follow-up. There was no history of neurological disease, connective tissue disorder or diabetes mellitus in any of the patients. The study was approved by the ethical committee of the Erasmus MC.

Surgery

All patients were operated on by one colorectal surgeon (W.R.S). A total meso-rectal excision was performed with central ligation of the inferior mesenteric artery and vein including autonomic nerve preservation. The left part of the colon was mobilised proximally to the splenic flexure. The rectum was mobilised until the pelvic floor was reached. Just above the pelvic floor, the rectum was transected between two right-angled bowel clamps. To gain access to the anal canal, a Scott retractor was used (Lone Star Retractor System, Lone Star Medical Products, Houston, TX, USA). The remaining mucosa was removed from the dentate line up to the upper margin of

the transected mucosa. For the construction of the 5- to 7-cm-long colonic J-pouch, the distal part of the descending colon was used. All epiploic appendices were removed to reduce the amount of fatty mass. The colonic J-pouch was anastomosed to the dentate line with interrupted sutures Maxon 3.0 (United States Surgical Corporation, Norwalk, CT, USA). None of the patients had a temporary diverting ileostomy or trans-anal drains. All patients were immobilised for 5 days. During this period, metronidazole and cefuroxime were administered intravenously three times daily.

Anal manometry

Between 1999 and October 2001, a micro-tip pressure transducer (Millar Instruments, Houston, TX, USA) with an outside diameter of 1.7 mm and after October 2001, a dynamic pull-through technique (2 mm/s) with a 4-channel water-perfused (0.5 ml/min) catheter (MMS system, Enschede, The Netherlands) were used for manometry. No specific bowel preparation was used. To perform manometry, patients were positioned in the left lateral position. Zero pressure calibration was done at the anal orifice level before introducing the catheter. After introduction and stabilisation in the rectum, the catheter was withdrawn. The high-pressure zone was registered; this was defined as an increase in pressure of more than 5 mmHg. Maximum anal resting pressure (MARP) was averaged across the four channels by using the maximum plateau phase of all channels. After introducing the catheter a second time, the patient was asked to squeeze at 0.5-cm intervals. The maximum squeeze pressure was calculated by averaging the highest squeeze pressures recorded by each channel. The recto-anal inhibitory reflex was elicited by distending a rectal balloon with different volumes of air. Paradoxical straining was defined as an increase of 10 mmHg combined with a maximum resting pressure of more than 60 mmHg.

Barostat measurement

For this study, both ends of a thin, 'infinitely' compliant polyethylene bag were fastened hermetically to 1 side of a polyvinyl catheter (7 mm in the outer diameter and marked at each 10 cm) proximal and distal of 5 holes, covering a distance of 5 to 7 cm from the end of the catheter.[13] Before surgery, this bag was attached at a distance of 5 to 7 cm from the end of the catheter. After pouch construction, the bag was fastened at 4-5 cm. The bag is fastened at both ends of the polyvinyl catheter to prevent axial expanding thereby allowing the bag to fully engage the circumference of the rectal wall. No tension is created in the walls of the bag in the interval between 0-600 cc of air and therefore, distension pressure is transferred entirely on the rectal wall.

The catheter was linked to a strain gauge and a computer-controlled air injection system (G&J Electronics, Ontario, Canada). The device was switched on at least 45 min before the measurement to allow the device to warm up. This time allows for the temperature drift of the pressure transducer to reach its maximum.

All patients and control subjects were asked to attempt to empty their bladder and rectum before measurement.

With the patient in left lateral position, the bag was inserted into the rectum, 10 cm from the anal canal. This was accomplished with the help of the scale on the catheter. Before each measurement, approximately 50 cc of air was injected into and aspirated from the bag to un-fold it. After this, the bag was inflated with air to selected pressure-plateaus (range 0-60 mmHg; rising in cumulative steps of 2 mmHg at a stimulation duration of 10 s) with the help of the computer-controlled electromechanical barostat system. Volume changes at the various levels of distending pressures were recorded and expressed in cc of air.

Subjects were instructed to report when they experienced the first sensation of content in the rectum (FS), earliest urge to defaecate (EUD) and maximum tolerable volume (MTV). The various levels of distending pressures needed to evoke these different sensations were noted. First, the entire pressure-volume curves of all patients, before and after surgery, and control subjects were plotted and compared. Second, the compliance of the rectal wall was calculated by taking the slope of the pressure-volume curve ($\Delta V/\Delta p$) at the three different sensation levels.

Fecal incontinence score

A questionnaire was used to determine the Rockwood Fecal Incontinence Severity Index (RFISI) score before and after surgery.[14] This is a validated index based on a type X frequency matrix. The matrix includes four types of leakage commonly found in the faecal incontinent population: gas, mucus, liquid and solid stools and five frequencies: once to three times per month, once per week, twice per week, once per day and twice per day. For the specification of the weighting scores, patient input was used. Scores range from 0 (total continence) to 61 (complete incontinence to solid stool on a daily basis).

Statistical analysis

Differences in the RFISI score, ano-rectal manometry and barostat measurements before and after surgery were evaluated using the Wilcoxon signed ranks test (median, p value). Nominal data before and after surgery were compared with McNemar's test. Spearman's correlation coefficients were used for the evaluation of the changes in ano-rectal manometry and barostat findings vs RFISI score. Comparison of changes between patient groups was conducted using the Mann–Whitney test. The limit of statistical significance was set at $p=0.05$ (two-sided).

RESULTS

Demographic characteristics and oncological data of all patients are listed in Table 1. Minor complications occurred in 4 out of 40 (10%) patients. Two patients developed urinary retention. Another patient was treated for symptoms of urinary tract infection. A fourth patient suffered from abdominal wound infection. None of the patients

Table 1.
Baseline characteristics.

Number of patients	40
Median age (years) (range)	57 (41 - 74)
Median time-interval after surgery (months)	12 (10 - 15)
Male / female	26 / 14
Tumour stage	
Villous adenoma (%)	7 (17)
Stage I = T1-2 N0 M0 (%)	9 (23)
Stage II = T3-4 N0 M0 (%)	16 (40)
Stage III = T1-4 N1 M0 (%)	8 (20)
Preoperative radiotherapy (%)	9 (23)
Postoperative chemotherapy (%)	5 (13)

experienced post-operative clinical anastomotic leakage.

One year after surgery, the median Rockwood Fecal Incontinence Severity Index (RFISI) score was found to be increased (pre-operative=6, post-operative=13; $p<0.01$) (Table 2). With respect to the increase of this score, no differences were found between

Table 2.
RFISI-scores and anorectal manometric findings before and one year after pouch construction.

	Preoperative	Postoperative	Statistical Significance
RFISI-score	6 (0 - 30)	13 (0 - 44)	P<0.001
MARP (mmHg)	65 (32 - 130)	45 (21 - 88)	P<0.001
MASP (mmHg)	163 (59 - 363)	151 (55 - 324)	*P*=0.194
RAIR	100%	58%	*P*<0.01

Values are median (range). RFISI-score, Rockwood Fecal Incontinence Severity Index; MARP, Maximum anal resting pressure; MASP, Maximum anal squeeze pressure; RAIR, rectoanal inhibitory reflex.

patients with and without pre-operative radiotherapy (15 and 12, respectively).

Comparing pre-operative and post-operative manometric measurements, the median MARP was found to be significantly lower ($p<0.02$), 1 year after the operation. The median maximum anal squeeze pressure (MASP) remained the same. The observed changes in MARP showed no correlation with the post-operative alterations in RFISI scores. The reduction of MARP was significantly greater in the patients who received pre-operative radiotherapy (25% vs 43%, $p=0.02$). The MASP was not affected by pre-operative radiotherapy. The results of the anal manometry and barostat measurements in patients with or without radiotherapy are shown in Table 3. Before operation, the

Table 3.
RFISI scores, anorectal monometric findings and barostat measurements 1 year after pouch construction in patients with or without pre-operative radiotherapy.

	Without Preoperative Radiotherapy	Preoperative Radiotherapy	Statistical Significance
Number of patients	31	9	
RFISI-score	12 (0 - 40)	15 (0 - 30)	*P*=0.29
MARP (mmHg)	49 (29 - 88)	37 (21 - 79)	P<0.02
MASP (mmHg)	156 (55 - 324)	135 (67 - 280)	*P*=0.20
RAIR	61%	44%	*P*=0.32
Volume FS	54 (17 - 100)	42 (8 - 78)	*P*=0.37
Volume EUD	116 (32 - 193)	92 (25 - 210)	*P*=0.11
Volume MTV	166 (71 - 280)	138 (40 - 255)	*P*=0.23
Compliance FS	3.7 (1.6)	5.1 (2.1)	*P*=0.52
Compliance EUD	4.3 (1.2)	3.2 (0.8)	*P*=0.07
Compliance MTV	4.9 (0.9)	3.8 (1.1)	*P*=0.09

Values are presented as the median (range). Median volume thresholds (and range) and compliance (mean value and standard deviation) for (neo)rectal filling sensations during isobaric phasic distention (median values and range). RFISI score: Rockwood Faecal Incontinence Severity Index, MARP: maximum anal resting pressure, MASP: maximum anal squeeze pressure, RAIR: recto-anal inhibitory reflex, FS: first sensation, EUD: earliest urge to defaecate, MTV: maximum tolerated volume.

recto-anal inhibitory reflex (RAIR) was present in all patients. One year after surgery, this reflex was detected in 58% of the patients (p<0.01). The presence or absence of this reflex did not influence the final RFISI score (*p*=0.11).

During rectum distension with stepwise increasing pressures, the pressure–volume curves showed an S-shaped form in all patients. One year after the operation, the neo-rectal pressure–volume curves showed a similar S-shaped form. The PSPT-V for the FS, EUD and MTV were significantly lower than those obtained in the original rectum (all p<0.02) (Figure 1). Comparing patients with and without pre-operative radiotherapy, no differences were found in the PSPT-V. At 1-year follow-up, the mean compliance calculated from $\Delta V/\Delta p$ at the different sensation levels was significantly lower than the compliance of the original rectum (Figure 2). Pouch compliance was not affected by pre-operative radiotherapy (Table 3).

There was a significant correlation between the increase in RFISI score and the post-operative decrease in SPT-V for EUD and MTV (*p*=0.02 and *p*=0.002, respectively). The increase in RFISI scores also correlated with the post-operative reduction in compliance calculated at each point of individual perception thresholds (FS, *p*=0.01; EUD, p=0.005; MTV, *p*=0.003) (Figure 3).

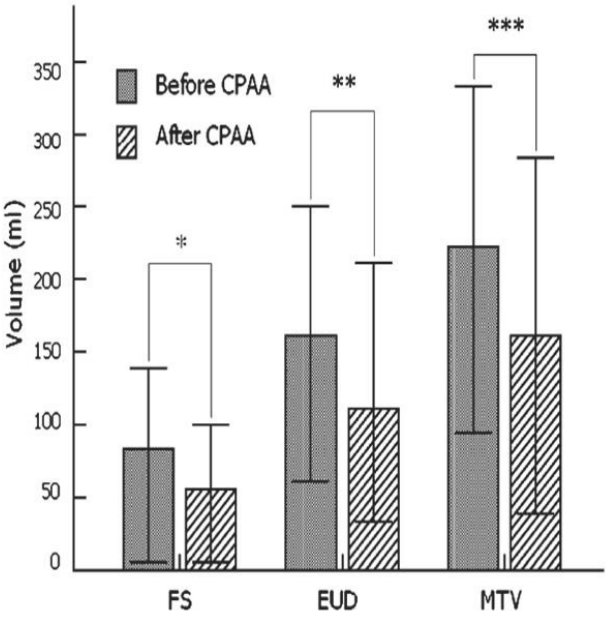

Figure 1.
Volume thresholds for (neo)rectal filling sensations during isobaric phasic distention (median values and range). FS first sensation, EUD earliest urge to defaecate, MTV maximum tolerated volume, CPAA colonic J-pouch-anal anastomosis. *p=0.008, **p=0.018 and ***p=0.009 (Wilcoxon signed rank test).

DISCUSSION

After total meso-rectal excision for rectal cancer, surgeons often try to avoid an abdomino-perineal resection by performing a trans-anal double-stapled low colorectal anastomosis, often without a pouch. The functional outcome after such an anastomosis is not as good as previously thought,[1] especially after pre-operative radiotherapy.[3,4] In most patients, a poor functional outcome is characterised by a high defecation frequency, urgency and impaired continence, especially during the first 2 years after the operation. The exact incidence of these defecation disturbances is unknown. A recent study indicated that 1 year after a double-stapled side-to-end colorectal anastomosis without a pouch, 30% of the patients still experience problems with their bowel function, adversely affecting their daily life.[15] A straight colo-anal anastomosis without a pouch is associated with similar problems. Almost all patients encounter defecation disturbances during the first 2 years after the procedure. In approximately one third of the patients, these problems become a permanent disability.[16-18] During the last

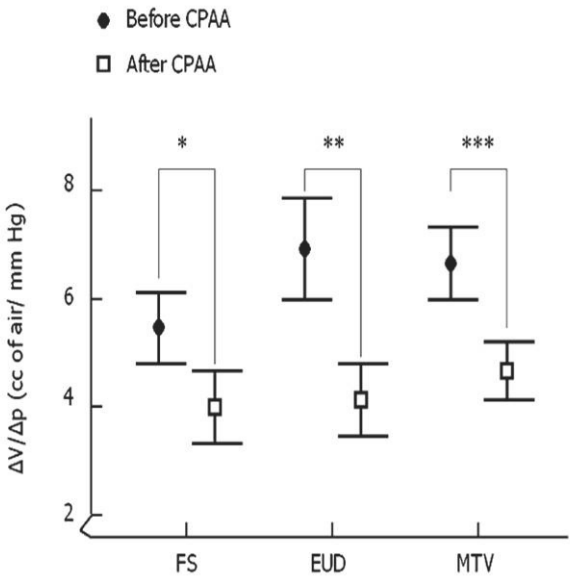

Figure 2.
Compliance, calculated at each point of sensory perception threshold, during isobaric phasic distention (mean values and standard deviation). FS first sensation, EUD earliest urge to defecate, MTV maximum tolerated volume, CPAA colonic J-pouch-anal anastomosis. *p=0.036, **p=0.001 and ***p=0.001 (Wilcoxon signed rank test).

two decades it has become clear that the addition of a pouch improves the functional outcome and quality of life after colo-anal anastomosis.[5,6] This statement is supported by the findings of our study. The median post-operative RFISI score observed in our patients was 13. It seems likely that this minor deterioration of continence did not affect the quality of life of our patients because it has been reported that only a score of over 30 has a detrimental effect on quality of life.[19]

It has been shown that total meso-rectal excision results in a sustained reduction of maximum anal resting pressure, irrespective of the level and the type of the anastomosis.[1,6,20-23] Based on this finding, it seems unlikely that this pressure drop affects the functional outcome. In the present study, we observed an overall pressure drop of 30%. However, this significant reduction of MARP showed no correlation with post-operative alteration in RFISI scores. The patients who received pre-operative radiotherapy encountered an even more pronounced pressure drop of 52%. A similar finding has been reported by other authors.[24,25] According to these authors, irradiation is associated with internal anal sphincter damage, thereby resulting in impaired ano-rectal function. However, all their patients underwent a low colorectal anastomosis without a pouch. Two recent studies have revealed that the detrimental effect of pre-

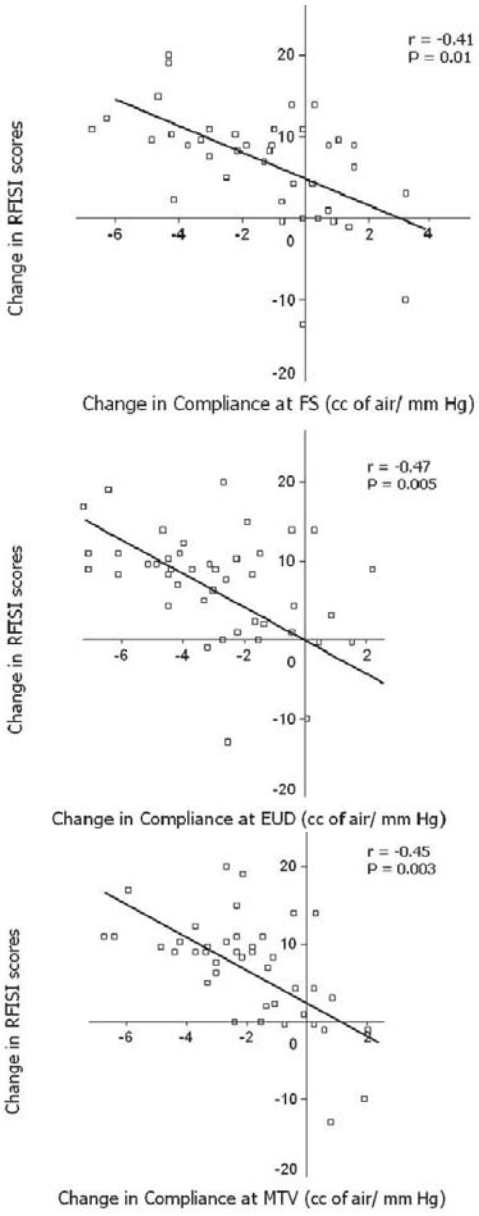

Figure 3.
Correlation analysis showing the inverse relationship between the change in RFISI scores and the changes in compliance calculated at each point of sensory perception. FS first sensation, EUD earliest urge to defecate, MTV maximum tolerated volume, RFISI Rockwood Fecal Incontinence Severity Index.

operative radiotherapy on functional outcome is less explicit in patients who underwent a colonic J-pouch-anal anastomosis.[26,27] Our present study confirms these findings. We could not demonstrate any correlation between the reduction of MARP and the functional outcome in our patients who received pre-operative radiotherapy.

At 1-year follow-up, we did not find a significant reduction in MASP and thereby no correlation with the final RFISI score. In a previous study, we have shown that a pouch-anal anastomosis, hand-sutured to the dentate line with the help of a Scott retractor, does not affect the EAS. The volume, length and thickness of this muscle did not change and MASP remained un-affected.[2] Zimmerman *et al.* conducted a randomised trial to compare the Parks retractor vs the Scott retractor with regards to their impact on fecal continence after fistula repair.[28] MARP and RFISI scores deteriorated significantly after the use of a Parks retractor whereas these changes were not observed when the repair was performed with a Scott retractor. In ileoanal pouch surgery, it has been speculated that functional outcome could be improved by preserving the anal transition zone. The anal transition zone, thought to be important in continence, contains nerve endings that differentiate solid and liquid stools from gas. However, three prospective, randomised trials have demonstrated no significant difference in functional results for patients in whom a mucosectomy was performed vs those patients in whom the proximal anal canal mucosa was preserved.[29-31]

Based on our manometric findings it is obvious that other factors contribute to the functional outcome after a colonic J-pouch-anal anastomosis. During the last decade, several studies have evaluated compliance and SPT-V in patients with and without a colonic pouch. With respect to the influence of compliance and sensory perception on functional outcome, the reported data are rather conflicting. Four studies suggest that the better outcome after a CPAA is due to a higher compliance with associated higher SPT-V.[22,32-34] In contrast, three other studies revealed that the neo-rectal wall properties had no detectable influence on functional outcome.[35-37] The authors of these three studies suggested that the better functional outcome in patients with a CPAA might be due to the design of the pouch with its anisoperistaltic limb resulting in the reversal of propulsive movements. In the present study, we investigated the influence of neo-rectal wall properties on the functional outcome among patients with a uniform pouch design. We did not compare patients with and without a pouch. Even in our patients with a uniform pouch design, we found a significant correlation between neo-rectal wall properties and functional outcome: the higher the compliance, the better the outcome. However, the configuration of the pouch may not be too large because long-term evacuation problems may occur. The optimal pouch size used for reconstruction was evaluated in 2 prospective randomised trials comparing a long (10 cm) vs a short (5-6 cm) J-pouch.[38,39] In both studies, the short pouch was accompanied by a better evacuation function and a reduced use of laxatives or suppositories. In our study, the mean length of the J-pouch varied between 5 and 7 cm. Three of our patients complained of evacuation difficulties after CPAA. These patients were successfully treated with retrograde colonic irrigation, as described

in a previous study.[40] Data reported by van Duijvendijk *et al.* also illustrate the impact of compliance and sensory perception.[41] They examined the influence of pre-operative radiotherapy on the functional outcome after trans-anally double-stapled low colorectal anastomosis by comparing patients with and without radiotherapy. They found that in the patients who received radiotherapy, compliance was significantly lower, which was associated with a higher defecation frequency and fecal incontinence. In our study, we were not able to demonstrate this detrimental effect of pre-operative radiotherapy. All our colonic pouches were constructed of the non-irradiated distal part of the descending colon. These pouches were sutured to the dentate line after removing the entire irradiated rectum. Based on our findings, it seems preferable to create a colonic pouch-anal anastomosis rather than to leave an irradiated rectal remnant for a low colorectal anastomosis. Our r-squared values do suggest that compliance and sensory perception are not the only factors contributing to the functional outcome after a colonic J-pouch-anal anastomosis. Another study is warranted to investigate these other factors.

In the treatment of patients with cancer located in the middle or lower third of the rectum, total meso-rectal excision is now being established as the therapeutic gold standard. After this procedure, a trans-anally double-stapled anastomosis can only be constructed at the level of or just above the pelvic floor. Most surgeons believe that the preservation of a short rectal remnant is beneficial for the patient. However, it has been shown that this does not offer any functional advances.[11,42] Moreover, most surgeons under-estimate the high risk of anastomotic leakage after the construction of such a low anastomosis. Recently, a population-based study from Sweden revealed that the incidence of this serious complication was 24% when the anastomosis was located within 6 cm from the anal verge.[43] Such an anastomotic leakage in this region is associated not only with a high morbidity, but also with a significant mortality.[44] It has also been reported that an anastomotic leakage adversely effects disease-free survival.[45] The reported incidence of anastomotic leakage after colonic J-pouch-anal anastomosis varies between 0% and 9%, which seems to be much lower than after a double-stapled low rectal anastomosis.[46,47] This is in agreement with our own experience. None of our patients received a temporary diverting ileostomy. Nevertheless, we did not observe any anastomotic breakdown after the procedure. Further studies that address this issue are needed.

During the last decade, it has been demonstrated that the transverse coloplasty pouch, as described by Z'Graggen *et al.* from Bern, is a good alternative for the colonic J-pouch.[48] There is growing evidence that both pouches have similar wall properties and comparable functional outcome.[36,49,50] Mantyh *et al.* compared neo-rectal wall properties and functional results among patients receiving a transverse coloplasty pouch, a colonic J-pouch or a straight anastomosis.[49] Compliance and sensory perception were found to be higher in patients with a pouch than in patients with a straight anastomosis. This was associated with a better functional outcome. Based on these findings and those obtained from the present study, it is obvious that both neo-

rectal compliance and neo-rectal sensory perception are major contributing factors to a good functional outcome after total mesorectal excision. In our opinion, all patients who are scheduled for total mesorectal excision should be offered either a colonic J-pouch or a coloplasty pouch, especially to overcome the poor early post-operative function after straight colo-anal anastomosis.

REFERENCES

1. Williamson ME, Lewis WG, Finan PJ, Miller AS, Holdsworth PJ, Johnston D. Recovery of physiologic and clinical function after low anterior resection of the rectum for carcinoma: myth or reality? Dis Colon Rectum 1995; 38(4): 411–8.
2. Gosselink MP, Busschbach JJ, Dijkhuis CM, Stassen LP, Hop WC, Schouten WR Quality of life after total mesorectal excision for rectal cancer. Colorectal Dis 2006; 8(1): 15–22.
3. Welsh FK, McFall M, Mitchell G, Miles WF, Woods WG. Pre-operative short-course radiotherapy is associated with faecal incontinence after anterior resection. Colorectal Dis 2003; 5(6): 563–8.
4. Pollack J, Holm T, Cedermark B, Holmstrom B, Mellgren A. Long-term effect of preoperative radiation therapy on anorectal function. Dis Colon Rectum 2006; 49(3): 345–52.
5. Heriot AG, Tekkis PP, Constantinides V, Paraskevas P, Nicholls RJ, Darzi A et al. Meta-analysis of colonic reservoirs versus straight coloanal anastomosis after anterior resection. Br J Surg 2006; 93(1): 19–32.
6. Sailer M, Fuchs KH, Fein M, Thiede A. Randomized clinical trial comparing quality of life after straight and pouch coloanal reconstruction. Br J Surg 2002; 89(9): 1108–17.
7. Miller AS, Lewis WG, Williamson ME, Holdsworth PJ, Johnston D, Finan PJ. Factors that influence functional outcome after coloanal anastomosis for carcinoma of the rectum. Br J Surg 1995; 82(10): 1327–30.
8. Molloy RG, Moran KT, Coulter J, Waldron R, Kirwan WO. Mechanism of sphincter impairment following low anterior resection. Dis Colon Rectum 1992; 35(5): 462–4.
9. Lewis WG, Holdsworth PJ, Stephenson BM, Finan PJ, Johnston D. Role of the rectum in the physiological and clinical results of coloanal and colorectal anastomosis after anterior resection for rectal carcinoma. Br J Surg 1992; 79(10):1082–6.
10. Otto IC, Ito K, Ye C, Hibi K, Kasai Y, Akiyama S et al. Causes of rectal incontinence after sphincter-preserving operations for rectal cancer. Dis Colon Rectum 1996; 39(12): 1423–7.
11. Matzel KE, Stadelmaier U, Muehldorfer S, Hohenberger W. Continence after colorectal reconstruction following resection: impact of level of anastomosis. Int J Colorectal Dis 1997; 12(2): 82–7.
12. Gosselink MP, West RL, Kuipers EJ, Hansen BE, Schouten WR. Integrity of the anal sphincters after pouch-anal anastomosis: evaluation with three-dimensional endoanal ultrasonography. Dis Colon Rectum 1995; 48(9): 1728–35.
13. Gosselink MJ, Hop WC, Schouten WC. Rectal compliance in females with obstructed defecation. Dis Colon Rectum 2001; 44(7): 971–7.
14. Rockwood TH, Church JM, Fleshman JW, Kane RL, Mavrantonis C, Thorson AG et al. Patient and surgeon ranking of the severity of symptoms associated with fecal incontinence: the fecal incontinence severity index. Dis Colon Rectum 1999; 42(12): 1525–32.
15. Machado M, Nygren J, Goldman S, Ljungqvist O. Similar outcome after colonic pouch and side-to-end anastomosis in low anterior resection for rectal cancer: a prospective randomized trial. Ann Surg 2003; 238(2): 214–20.
16. Lazorthes F, Chiotasso P, Gamagami RA, Istvan G, Chevreau P. Late clinical outcome in a randomized prospective comparison of colonic J pouch and straight coloanal anastomosis. Br J Surg 1997; 84(10): 1449–51.
17. Dehni N, Tiret E, Singland JD, Cunningham C, Schlegel RD, Guiguet M et al. Long-term functional outcome after low anterior resection: comparison of low colorectal anastomosis and colonic J-pouch-anal anastomosis. Dis Colon Rectum 1998; 41(7): 817–22 (discussion 822–3).

18. Seow-Choen F, Goh HS. Prospective randomized trial comparing J colonic pouch-anal anastomosis and straight coloanal reconstruction. Br J Surg 1995; 82(5): 608–10.
19. Cavanaugh M, Hyman N, Osler T. Fecal incontinence severity index after predictor of quality of life. Dis Colon Rectum 2002; 45: 349–53.
20. O'Riordain MG, Molloy RG, Gillen P, Horgan A, Kirwan WO. Rectoanal inhibitory reflex following low stapled anterior resection of the rectum. Dis Colon Rectum 1992; 35(9): 874–8.
21. Vassilakis JS, Pechlivanides G, Zoras OJ, Vrachasotakis N, Chrysos E, Tzovaras G et al. Anorectal function after low anterior resection of the rectum. Int J Colorectal Dis 1995; 10(2): 101–6.
22. Hallbook O, Nystrom PO, Sjodahl R. Physiologic characteristics of straight and colonic J-pouch anastomoses after rectal excision for cancer. Dis Colon Rectum 1997; 40(3): 332–8.
23. Rasmussen OO, Petersen IK, Christiansen J. Anorectal function following low anterior resection. Colorectal Dis 2003; 5(3): 258–61.
24. Gervaz P, Rotholtz N, Pisano M, Kaplan E, Secic M, Coucke P et al. Quantitative short-term study of anal sphincter function after chemoradiation for rectal cancer. Arch Surg 2001; 136(2):192–6.
25. Kusunoki M, Shoji Y, Yanagi H, Kamikonya N, Sakanoue Y, Hishikawa Y et al.
Anorectal function after preoperative intraluminal brachytherapy and colonic J pouch-anal anastomosis for rectal carcinoma. Br J Surg 1993; 80(7): 933–5.
26. Amin AI, Hallbook O, Lee AJ, Sexton R, Moran BJ, Heald RJ. A 5-cm colonic J pouch colo-anal reconstruction following anterior resection for low rectal cancer results in acceptable evacuation and continence in the long term. Colorectal Dis 2003; 5(1): 33–7.
27. Dehni N, McNamara DA, Schlegel RD, Guiguet M, Tiret E, Parc R. Clinical effects of preoperative radiation therapy on anorectal function after proctectomy and colonic J-pouch-anal anastomosis. Dis Colon Rectum 2002; 45(12): 1635–40.
28. Zimmerman DD, Gosselink MP, Hop WC, Darby M, Briel JW, Schouten WR. Impact of two different types of anal retractor on fecal continence after fistula repair: a prospective, randomized, clinical trial. Dis Colon Rectum 2003; 46(12): 1674–9.
29. Seow-Choen A, Tsunoda A, Nicholls RJ. Prospective randomized trial comparing anal function after handsewn ileoanal anastomosis versus stapled ileoanal anastomosis without mucosectomy in restorative proctocolectomy. Br J Surg 1991; 78(4): 430–4.
30. Luukkonen P, Jarvinen H. Stapled versus hand sutured ileoanal anastomosis in restorative proctocolectomy: a prospective randomized trial. Arch Surg 1993; 128(4): 437–40.
31. Reilly WT, Pemberton JH, Wolff BG et al. Randomized prospective trial comparing ileal pouch-anal anastomosis performed by excising the anal mucosa to ileal pouch-anal anastomosis. Ann Surg 1997; 225(6): 666–76.
32. Lin JK, Wang HS, Yang SH, Jiang JK, Chen WS, Lin TC. Comparison between straight and J-pouch coloanal anastomoses in surgery for rectal cancer. Surg Today 2002; 32(6): 487–92.
33. Hida J, Yoshifuji T, Tokoro T, Inoue K, Matsuzaki T, Okuno K et al. Comparison of long-term functional results of colonic J-pouch and straight anastomosis after low anterior resection for rectal cancer: a five-year follow-up. Dis Colon Rectum 2004; 47(10): 1578–85.
34. Araki Y, Isomoto H, Tsuzi Y, Matsumoto A, Yasunaga M, Yamauchi K et al. Functional results of colonic J-pouch anastomosis for rectal cancer. Surg Today 1999; 29(7): 597–600.
35. Ho YH, Tan M, Seow-Choen F. Prospective randomized controlled study of clinical function and anorectal physiology after low anterior resection: comparison of straight and colonic J pouch anastomoses. Br J Surg 1996; 83(7): 978–80.
36. Ho YH, Brown S, Heah SM, Tsang C, Seow-Choen F, Eu KW et al. Comparison of J-pouch and coloplasty pouch for low rectal cancers: a randomized, controlled trial investigating functional results and comparative anastomotic leak rates. Ann Surg 2002; 236(1): 49–55.
37. Furst A, Burghofer K, Hutzel L, Jauch KW. Neorectal reservoir is not the functional principle of the colonic J-pouch: the volume of a short colonic J-pouch does not differ from a straight coloanal anastomosis. Dis Colon Rectum 2002; 45(5): 660–7.

38. Lazorthes F, Gamagami R, Chiotasso P, Istvan G, Muhammad S. Prospective, randomized study comparing clinical results between small and large colonic J-pouch following coloanal anastomosis. Dis Colon Rectum 1997; 40(12): 1409–13.
39. Hida J, Yasutomi M, Fujimoto K, Okuno K, Ieda S, Machidera N et al. Functional outcome after low anterior resection with low anastomosis for rectal cancer using the colonic J-pouch. Prospective randomized study for determination of optimum pouch size. Dis Colon Rectum 1996; 39(9): 986–91.
40. Gosselink MP, Darby M, Zimmerman DD, Smits AA, van Kessel I, Hop WC et al. Long-term follow-up of retrograde colonic irrigation for defaecation disturbances. Colorectal Dis 2005; 7(1): 65–69.
41. van Duijvendijk P, Slors JF, Taat CW, van Tets WF, van Tienhoven G, Obertop H et al. Prospective evaluation of anorectal function after total mesorectal excision for rectal carcinoma with or without preoperative radiotherapy. Am J Gastroenterol 2002; 97(9): 2282–9.
42. Montesani C, Pronio A, Santella S, Boschetto A, Aguzzi D, Pirozzi R, D'Amato A, Vestri A. Rectal cancer surgery with sphincter preservation: functional results related to the level of anastomosis. Clinical and instrumental study. Hepatogastroenterology 2004; 51(57): 718–21.
43. Matthiessen P, Hallbook O, Andersson M, Rutegard J, Sjodahl R. Risk factors for anastomotic leakage after anterior resection of the rectum. Colorectal Dis 2004; 6(6): 462–9.
44. Eriksen MT, Wibe A, Norstein J, Haffner J, Wiig JN, Norwegian Rectal Cancer Group. Anastomotic leakage following routine mesorectal excision for rectal cancer in a national cohort of patients. Colorectal Dis 2005; 7: 51–7.
45. Walker KG, Bell SW, Rickard MJ, Mehanna D, Dent OF, Chapuis PH, Bokey EL. Anastomotic leakage is predictive of diminished survival after potentially curative resection for colorectal cancer. Ann Surg 240 2004; (2): 255–9.
46. Dehni N, Parc R, Church JM. Colonic J-pouch-anal anastomosis for rectal cancer. Dis Colon Rectum 2003; 46(5): 667–75.
47. 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.
48. Z'Graggen K, Maurer CA, Birrer S, Giachino D, Kern B, Buchler MW. A new surgical concept for rectal replacement after low anterior resection: the transverse coloplasty pouch. Ann Surg 2001; 234(6): 780–5 (discussion 785–7).
49. Mantyh CR, Hull TL, Fazio VW. Coloplasty in low colorectal anastomosis: manometric and functional comparison with straight and colonic J-pouch anastomosis. Dis Colon Rectum 2001; 44(1): 37–42.
50. Remzi FH, Fazio VW, Gorgun E, Zutshi M, Church JM, Lavery IC et al. Quality of life, functional outcome, and complications of coloplasty pouch after low anterior resection. Dis Colon Rectum 2005; 48(4): 735–43.

CHAPTER 10

Summary and discussion / Samenvatting

SUMMARY AND DISCUSSION

For patients with distal rectal cancer, the colonic J-pouch-anal anastomosis (CPAA) provides an alternative to a double stapled low colorectal anastomosis or permanent colostomy. In patients with ulcerative colitis, the ileal pouch-anal anastomosis (IPAA) offers the opportunity to life without a definitive ileostomy, whereas in patients with familial adenomatous polyposis this procedure is an alternative to the ileo-rectal anastomosis. The aim of this thesis was to study the functional outcome after both procedures.

Introduction

Chapter 1 provides a general introduction to the surgical treatment of ulcerative colitis and rectal cancer. In addition, the outline of the thesis is presented.

Treatment and prevention of pouchitis

Pouchitis is the most frequent late complication after IPAA in patients with ulcerative colitis. We evaluated the pouch flora in patients with ulcerative colitis during episodes of pouchitis, during subsequent treatment with metronidazole or ciprofloxacin and during pouchitis-free periods. During pouchitis episodes, we found a significant decrease of anaerobes and a significant increase of aerobic bacteria. The total number of bacteria was ten times lower in patients with pouchitis. This finding is in contrast with the current opinion that pouchitis is caused by bacterial overgrowth. The increase in the numbers of aerobes during pouchitis was mainly due to the increase of the numbers of coliforms. In 57% of the samples this coliform was a pathogenic Escherichia coli. Although the total number of anaerobes was lower during pouchitis, we found a significant increase of the pathogen Clostridium perfringens. This pathogen was found in 95% of the samples. This study strongly suggests a role of dysbiosis in pouchitis. Treatment with metronidazole resulted in a significant reduction of the anaerobic flora with a complete eradication of the pathogen Clostridium perfringens. During treatment with metronidazole the total number of aerobes was left unchanged. The same holds for the numbers of the pathogen Escherichia coli. In contrast, when the patient was treated with ciprofloxacin, not only Clostridium perfringens, but also all coliforms, including hemolytic strains of Escherichia coli, disappeared. The greater part of the anaerobic flora was left undisturbed during the administration of ciprofloxacin. At the end of the treatment with ciprofloxacin, the pH of the feces regained almost normal values. In patients, treated with ciprofloxacin, larger reductions in "Pouchitis Disease Activity Index" score were observed when compared with patients treated with metronidazole. These findings indicate that treatment with ciprofloxacin, which eradicates both pathogens, is more beneficial than treatment with metronidazole, which is only effective when no pathogenic Escherichia

coli are present.

From the microbiological point of view, ciprofloxacin has another advantage: it does not disturb the greater part of the anaerobic flora. These anaerobes contribute to the stability of the pouch flora and provide resistance against colonization by pathogens. After treatment with metronidazole, the flora remains instable and pathogens may colonize the pouch again. This probably explains the frequent relapses, observed after pouchitis therapy with metronidazole. Based on our findings we advocate the use of ciprofloxacin in the treatment of pouchitis.

The fact that pouchitis occurs almost exclusively in patients with ulcerative colitis and not in patients with familial adenomatous polyposis suggests an underlying genetic predisposition. It has been reported that in patients with a diverting ileostomy, the characteristic signs of pouchitis do not occur until the ileostomy is closed. This finding and the observation that pouchitis generally responds to antibiotic therapy, supports the hypothesis that bacterial antigens cause the inflammatory process. Clostridium perfringens and Escherichia coli may be considered as a part of the normal pouch flora. When the stability of the flora is disturbed, the number of these bacteria may increase to a harmful level. Taking these factors into account, pouchitis likely involves a dysregulated immune response to altered luminal bacteria (dysbiosis) in a genetically susceptible host.

There is a gap in knowledge on the composition of the gut flora. Cultivation-based methods are limited by difficulties in providing growth conditions suitable for all types of bacteria. It has been shown that only 40% of the bacterial species in fecal samples can be cultivated by conventional means. Terminal restriction fragment length polymorphism (T-RFLP) combined with the construction of 16S rRNA gene libraries have been used successfully for characterization of bacterial communities in human feces. Taking these technological developments into account, the interaction between immunologists, microbiologists and clinicians will be even of greater importance in the future.

Probiotics are defined as living microorganisms with health promoting properties beyond their intrinsic nutritional value. It has been shown that probiotics contribute to the maintenance of the microbiological homeostasis, and increase the resistance against colonization of pathogens, by interference with bacterial adherence and modulation of proinflammatory cytokines. We investigated the efficacy of the probiotic bacterium *Lactobacillus rhamnosus* GG in delaying the first onset of pouchitis. When administered orally, *Lactobacillus rhamnosus* GG adheres to the mucous membrane of the intestine and may help to restore the balance of the gastro-intestinal microflora and to promote gut-barrier functions. This probiotic also activates the innate immune response and enhances adaptive immunity, especially during infections. Between 1989 and 2001, a consecutive series of 127 patients presenting with ulcerative colitis underwent an IPAA at the Erasmus MC in Rotterdam. Patients operated during the time period between 1986 and 1996 never used *Lactobacillus rhamnosus* GG and served as a historical control group. Patients operated during the time period between 1996 and 2001 started

immediately after the operation with the daily intake of *Lactobacillus rhamnosus* GG. The cumulative incidence of the first episode of pouchitis was significant lower in the group of patients, who used *Lactobacillus rhamnosus* GG, without side effects. Based on the results of this study, we recommend a daily intake of *Lactobacillus rhamnosus* GG (dose 1–2 × 1010 bacteria), equivalent to one cup of 350 ml Vifit®, shortly after pouch surgery. Probiotics, like Vifit®, VSL#3® en Yakult®, have an advantage over antibiotics, given that they would eliminate the concern of development of bacterial resistance because of chronic antibiotic use. Patient adherence will be crucial for the efficacy of probiotics; daily intake is necessary to prevent dysbiosis in the pouch.

The pathophysiological relationship between pouchitis and other inflammatory bowel diseases is unknown. Though the efficacy of probiotics in the prevention of pouchitis offers an interesting perspective, it is not possible to extrapolate directly to treatment of other inflammatory bowel diseases. Pouchitis patients represent an antibiotics-sensitive subgroup and also have a smaller reservoir of bacteria to affect and alter. Large, well designed, multicenter, controlled clinical trials are necessary to determine whether probiotics should have a place in the treatment of other inflammatory bowel diseases as well.

The role of the colonic J-pouch in the treatment of rectal cancer

Most patients with cancer in the middle or lower third of the rectum are potential candidates for a sphincter saving procedure, such as double-stapled low colo-rectal anastomosis, a straight colo-anal anastomosis or a colonic J-pouch anal anastomosis. We evaluated the surgical management of rectal cancer in 521 eligible patients, operated between 2001 and 2003, in the region of the Comprehensive Cancer Centre Rotterdam with 2.3 million inhabitants, representative for the whole Dutch population. We found that only half of the patients with distal rectal cancer underwent a sphincter saving procedure. In most cases transanal double-stapled low colo-rectal anastomosis was performed. In only 4% a CPAA was constructed. The leakage rate after CPAA was significantly lower than the leakage rate after the low colorectal anastomosis. This difference is difficult to explain, and is probably surgeon dependent. Higher leakage rates after TME as compared to "conventional surgery" have been explained by the devascularization of the anorectal stump during the dissection of the distal mesorectum.

In our opinion the technique of choice for rectal cancer in the lower one third of the rectum should be the handsewn method. The level of the handsewn anastomosis is located in the anal canal, so the anastomosis is not compromised by the poor vascularity of the distal rectum. A possible abscess will spontaneously drainage out through the anus and will not spread into the upper part of the rectum. Furthermore, sometimes even a transanal approach for pouch-anal dehiscence may be attempted. A protective effect of a covering ileostomy in preventing anastomotic leakage could not be demonstrated. We suggest that a diverting stoma is not necessary when performing a handsewn CPAA.

After total mesorectal excision for rectal cancer, many surgeons try to avoid an abdominoperineal resection (APR) by performing a transanally double stapled low colo-rectal anastomosis (LRA). This policy is mainly based on the assumption that the quality of life after such LRA is higher than after APR. It has been shown that during the first 2 years after CPAA the quality of life is better than that after a LRA. We assessed the quality of life among disease-free survivors after APR, LRA and CPAA. The quality of life of 204 patients who had undergone surgery for cancer in the middle or lower third of the rectum was examined using one generic and two disease-specific questionnaires. The median follow-up was 31 months. The quality of life after CPAA was found to be better than after APR and LRA. This difference was not only due to the better functional outcome, but also to the lower incidence of disturbed micturition and sexual problems in the CPAA group. Quality of life after APR was similar to that after LRA. In the past, rectal cancer surgery has focused mainly on avoidance of local recurrence and preservation of the anal sphincter complex. These goals were, and still are, important. However, for a patient who suffers from stool incontinence, straining and frequent bowel movements after sphincter-saving rectal resection, the creation of a permanent colostomy might be a better option. In contrast with current opinions, our study revealed that the quality of life after LRA is not better than the quality of life after APR. This finding underlines the importance of preoperative counselling of an enterostomal therapist to discuss the advantages and disadvantages of a permanent colostomy. Our findings and those reported by others indicate that a CPAA is associated with a better functional outcome and thereby a better quality of life as compared to a double stapled LRA. However, the construction of a colonic J-pouch has not gained universal acceptance. Prospective studies comparing quality of life after CPAA and LRA are lacking. Based on the better functional outcome and thereby the better quality of life and the lower leakage rate, we prefer a CPAA instead of a LRA in all patients with cancer located in the middle or the lower third of the rectum.

Continence mechanisms after pouch surgery

A small number of patients with either an IPAA or CPAA suffer from soiling, frequent bowel movements or evacuation difficulties. Between 1989 and 2001, 127 patients underwent IPAA for either ulcerative colitis or familial adenomatous polyposis in our hospital. In the same time period, complete rectal excision and CPAA was performed in 62 patients. Eleven patients (6%) experienced disabling defecation disturbances after pouch surgery, not responding to medical treatment and biofeedback. These patients were offered retrograde bowel irrigation (RBI) on an ambulatory basis. Eight patients presented with nocturnal incontinence after IPAA and 3 patients presented with obstructed defecation after CPAA. For many patients with disabling defecation disturbances after pouch surgery, the creation of a stoma is the only option left. We evaluated the long-term feasibility and outcome of retrograde

bowel irrigation in patients with disabling defecation disturbances after pouch surgery. All patients reported retrograde bowel irrigation to be effective and beneficial. None of these patients ceased this therapy during the time period of follow-up. Despite this, 63% of them experienced irrigation related problems. If creation of a stoma is considered, especially in patients with disabling defecation disturbances after pouch surgery, it might be worthwhile to offer these patients first retrograde bowel irrigation. In our opinion, this is the first treatment of choice, since it is minimally invasive, easy to learn, safe and has only minor side effects.

It is well known that anal sphincter function is impaired after pouch surgery. Until recently, surgeons used Parks anal retractor during pouch surgery to gain access to the anal canal and to perform a handsewn anastomosis. In recent years, it has been suggested that the use of a Scott retractor, a ring retractor with multiple skin hooks on elastic bands, results in less sphincter damage. We performed a randomized controlled trial comparing the effect of the Parks anal retractor and the Scott retractor on the anal sphincter complex. After transanal surgery with the use of a Parks retractor, there was a significantly larger decrease of maximum anal resting pressure than after surgery with a Scott retractor. Furthermore, the use of a Parks retractor resulted in impairment of continence which was not observed in the patients in whom the Scott retractor was used. Based on these results we advocate the use of a Scott retractor to gain access to the anal canal and to perform a handsewn anastomosis for pouch surgery.

It has been argued that transanal mucosectomy followed by handsewn pouch-anal anastomosis at the level of the dentate line, damages the anal sphincters. We studied the integrity and the morphology of both sphincters before and after pouch surgery, using three-dimensional endoanal ultrasonography (3D-EUS). Handsewn pouch-anal anastomosis, performed using a Scott retractor, only rarely caused external anal sphincter defects, but 3D-EUS showed alterations of the internal anal sphincter in 57% of the patients. These alterations were characterized by asymmetry or thinning. No correlation was observed between these alterations and the functional outcome. The question remains whether the decrease in the IAS volume in the CPAA group is due to direct damage to the sphincter or to damage to its nerve supply during rectal mobilization.

Although the overall functional outcome as well as the quality of life are good after colonic J-pouch anal anastomosis, we observed some patients with impaired continence despite adequate sphincter function. Therefore, we investigated whether compliance and sensory perception are altered after a handsewn colonic J-pouch anastomosis. One year after surgery, the maximum anal resting pressure (MARP) was significantly reduced, whereas the maximum anal squeeze pressure remained unaffected. The reduction of MARP did not correlate with the functional outcome. The mean compliance, calculated at three different sensation levels, as well as the pouch sensory perception threshold (PSPT)-volumes were lower than those of the

original rectum. Low pouch compliance and low PSPT-volumes were associated with a worse functional outcome. Based on these findings it is obvious that both neo-rectal compliance and neo-rectal sensory perception are major contributing factors to a good functional outcome after total mesorectal excision. In our opinion, all patients, who are scheduled for total mesorectal excision, should be offered a colonic pouch.

While the functional outcome after pouch surgery is good in most patients, it is clear that a pouch is not functionally identical to the original rectum. Therefore, the development of alternative restorative procedures focused on rectum preservation might be worthwhile. The ileo-neorectal anastomosis has been introduced as a promising alternative to the conventional IPAA. This procedure restores oral-anal continuity by replacing rectal mucosa by a vascularised ileal mucosa graft without pelvic dissection. Despite its elegant concept, the functional outcome after this procedure is less favourable as expected, probably due to low compliance of the neorectum. Complete remission or partial response after neoadjuvant radiochemotherapy might enable local excision for rectal cancer, instead of a CPAA. Because of insecurities in the clinical assessment of complete remission, a full thickness excision by transanal endoscopic microsurgery offers the opportunity to accurately determine the degree of local regression and to excise the remaining tumor cells. The histopathological findings of the specimen, excised by transanal endoscopic microsurgery, might determine the optimal postoperative therapeutic strategy. After sphincter-saving surgery, rectum-saving surgery might be the next challenge for colorectal surgeons.

SAMENVATTING

Het moeten leven met een stoma betekent, ondanks de goede stomahulpmiddelen die tegenwoordig beschikbaar zijn voor de patiënt, een ingrijpende veandering in het dagelijks functioneren. Totale proctocolectomie gevolgd door een ileo pouch-anale anastomose (IPAA) bij patiënten met colitis ulcerosa of familiaire adenomateuze polyposis heeft als voordeel dat de patiënt een definitief stoma wordt bespaard, terwijl toch de gehele dikke darm kan worden verwijderd. Het is aangetoond dat na een rectumresectie bij patiënten met kanker in het middelste of onderste eenderde deel van de endeldarm, een colo-anale anastomose met een J-pouch (CPAA) een beter functioneel resultaat geeft dan een rechttoe-rechtaan colo-anale anastomose. Het onderzoek dat in dit proefschrift wordt beschreven, had tot doel na te gaan welke factoren het functionele resultaat beïnvloeden na deze vormen van pouch chirurgie.

Hoofdstuk 1 vormt de inleiding van dit proefschrift. Het bevat een historisch overzicht van de chirurgische behandeling van colitis ulcerosa en het rectum carcinoom. Tevens wordt in dit hoofdstuk de struktuur van het proefschrift beschreven.

De meest voorkomende lange termijn complicatie na een IPAA is pouchitis. In hoofdstuk 2 wordt het effect van metronidazol en ciprofloxacine op de pouchflora besproken. Wij hebben de pouchflora bestudeerd bij patiënten tijdens episoden van pouchitis, tijdens pouchitis vrije episoden en gedurende de behandeling van pouchitis met metronidazol of ciprofloxacine. Het totaal aantal bacteriën per gram bleek tien maal minder in patiënten met pouchitis. Tijdens een pouchitis aanval zagen wij een significante afname van het aantal anaerobe bacteriën, maar wel een significante toename van het aantal aerobe bacteriën. De toename van het aantal aërobe bacteriën tijdens pouchitis bleek voornamelijk veroorzaakt te worden door een significante toename van het aantal coliformen. In 57% van de kweken was dit een pathogene Escherichia coli. Alhoewel het totale aantal anaeroben lager was tijdens pouchitis, vonden wij binnen deze groep een significante toename van de pathogeen Clostridium perfringens. Deze pathogeen werd gevonden in 95% van de kweken. Clostridium perfringens is een pathogene, anaerobe sporenvormer die onder andere fosfolipase C maakt dat celmembranen kan afbreken. De opvallende verandering van de pouchflora tijdens pouchitis was geassocieerd met een toename van de pH in de pouch. Dit is een belangrijke bevinding gezien het feit dat een lage pH beschermt tegen de afbraak van mucus. Behandeling met metronidazol resulteerde in een significante afname van de anaerobe flora en deed de Clostridium perfringens verdwijnen. Metronidazol heeft echter geen effect op het aantal aeroben en ook het aantal pathogene Escherichia coli's veranderde niet. Echter, bij patiënten die behandeld werden met ciprofloxacine in plaats van metronidazol bleek dat de aantallen aeroben voornamelijk afnamen ten gevolge van een daling van de coliformen, inclusief de pathogeen Escherichia coli. Ook de Clostridium perfringens verdween, terwijl het totale aantal anaeroben niet afnam. Na de behandeling met ciprofloxacine, was de pH in de pouch gelijk aan de

pH van patiënten zonder pouchitis. Beide antibiotica veroorzaakten een significante afname van de de pouchitis activity index. Deze afname was groter na de behandeling met ciprofloxacine. Het is duidelijk dat behandeling met ciprofloxacine, dat beide pathogenen doet verdwijnen, de voorkeur verdient boven de behandeling met metronidazol, dat alleen effectief is als het pathogeen Escherichia coli niet aanwezig is. Vanuit microbiologisch standpunt heeft ciprofloxacine een ander belangrijk voordeel: het laat de anaerobe flora ongestoord. Deze anaerobe bacteriën zorgen voor een stabiele pouchflora en zorgen voor kolonisatieresistentie tegen pathogenen. Gezien onze resultaten, adviseren wij ciprofloxacine voor de behandeling van pouchitis.

In hoofdstuk 3 wordt het effect beschreven van *Lactobacillus rhamnosus* GG op het voorkomen van pouchitis. Wij gebruikten in eerste instantie gevriesdroogde *Lactobacillen rhamnosus* GG. Toen er op de Nederlandse markt een *Lactobacillen rhamnosus* GG bevattend voedingsmiddel werd geïntroduceerd, werd dit aan de patiënten voorgeschreven. Tussen 1986 en 2001, ondergingen 127 patiënten met colitis ulcerosa een IPAA in het Erasmus MC. Wij gebruikten een historische controle groep: patiënten geopereerd tussen 1986 en 2001. Deze hebben nooit *Lactobacillus rhamnosus* GG gebruikt. Patiënten geopereerd na 1996, begonnen onmiddellijk na de operatie met het dagelijks innemen van *Lactobacillus rhamnosus* GG. Behalve in de duur van follow-up, waren er geen verschillen tussen de twee groepen in patiënt-karakteristieken, operatie-indicatie en functioneel resultaat. De cumulatieve incidentie van de eerste pouchitis aanval was 29 procent in de historische groep, vergeleken met slechts 7% in de groep welke direkt na de operatie *Lactobacillus rhamnosus* GG ging gebruiken. Op basis van deze gegevens adviseren wij voor de preventie van pouchitis de dagelijkse inname van een geschikt probioticum direkt vanaf de operatie.

Bij patiënten met kanker in het middelste of onderste eenderde deel van het rectum verrichten chirurgen in Nederland een "total mesorectal excision". Meestal wordt hierna geprobeerd de continuïteit te herstellen middels een dubbel gestapelde anastomose zonder pouch, omdat gedacht wordt dat de kwaliteit van leven beter is wanneer er geen stoma wordt aangelegd. Het is echter aangetoond dat het functioneel resultaat beter is na een CPAA dan na een reconstructie zonder pouch. In hoofdstuk 4 worden de resultaten beschreven van een onderzoek naar de chirurgische behandeling van 521 patiënten met een rectumcarcinoom in de periode 2001 tot en met 2003, in de regio van het Integraal Kankercentrum Rotterdam. Deze regio telt ongeveer 2,3 miljoen inwoners. Het bleek dat slechts de helft van de patiënten met kanker in het middelste of onderste eenderde deel van het rectum een sphincter-sparende operatie onderging. Meestal was hierbij sprake van een dubbel gestapelde anastomose zonder pouch. Bij 4 procent van de patiënten werd een CPAA verricht. Het aantal naadlekkages na CPAA was significant lager vergeleken met een dubbel gestapelde anastomose zonder pouch.

In hoofdstuk 5 worden de uitkomsten beschreven van een onderzoek naar de kwaliteit van leven bij patiënten na een dubbel gestapelde anastomose zonder pouch (DGA), na een colo-anale anastomose met een J-pouch (CPAA) en na een abdominale perineale resectie (APR). De kwaliteit van leven bij de 204 patiënten met een carcinoom in het onderste tweederde deel van het rectum werd geëvalueerd door middel van drie internationaal erkende gestandaardiseerde vragenlijsten, de generieke vragenlijst EQ-5D en de ziektespecifieke vragenlijsten EORTC QLQ C-30 / CR-36. De mediane follow-up was 31 maanden. Het functioneel resultaat werd gescoord volgens de methode van Rockwood. De kwaliteit van leven was aanmerkelijk beter bij de patiënten na een CPAA, vergeleken na een DGA en een APR. Dit verschil kwam niet alleen door een beter functioneel resultaat na de CPAA, maar ook door een lagere incidentie van mictie- en sexuele problemen. De kwaliteit van leven na de DGA was gelijk aan die na een APR.

Een kleine groep patiënten heeft last van invaliderende defaecatie problemen na een IPAA of een CPAA. Voor deze patiënten is het aanleggen van een permanent stoma meestal de enige mogelijkheid om van de klachten af te komen. In ons ziekenhuis bieden wij alle patiënten met invaliderende defaecatie problemen na pouchchirurgie, die niet reageren op medicatie en fysiotherapie, retrograde darmspoelingen aan. In hoofstuk 6 wordt het lange termijn resultaat van zulke darmspoelingen geëvalueerd. Tussen 1989 en 2001, ondergingen 127 patiënten een IPAA en 62 een CPAA in ons ziekenhuis. Elf patiënten (6%) hadden last van invaliderende defaecatieproblemen. Al deze patiënten gebruikten de darmspoelingen regelmatig en vonden de therapie effectief. Geen enkele patiënt staakte de therapie gedurende de mediane follow-up van 4,7 jaar. Dit, ondanks het feit dat 63% van hen technische problemen ondervond zoals buikkramp of verlies van spoelvloeistof gedurende de dag. Indien het aanleggen van een stoma wordt overwogen vanwege invaliderende defaecatie problemen na pouch chirurgie, is het daarom aan te bevelen de patiënt eerst nog met darmspoelingen te behandelen.

Een stoornis in het continentiemechanisme is een gevreesde complicatie na anorectale chirurgie. Het gebruik van een anaalspreider zou hiervan een oorzaak kunnen zijn. In hoofdstuk 7 worden de resultaten beschreven van een prospectieve studie waarin de gevolgen van het gebruik van twee verschillende anale spreiders met elkaar vergeleken wordt. Na gebruik van de Parks spreider bleek een significant grotere daling in de maximale anale rustdruk op te treden dan na gebruik van de Scott spreider. Bij de patiënten die geopereerd werden met behulp van de Parks spreider trad een significante verslechtering van de continentie op. Dit werd niet gevonden bij de patiënten die met behulp van een Scott spreider werden geopereerd. Derhalve adviseren wij een Scott retractor bij het aanleggen van een handgelegde pouch-anale anastomose.

In hoofdstuk 8 worden de uitkomsten gepresenteerd van een onderzoek om na te gaan of, en zo ja in welke mate, de anale kringspieren schade oplopen tijdens het aanleggen van een handgelegde pouch-anale anastomose met behulp van een Scott retractor. Om deze vraag te kunnen beantwoorden werd gebruik gemaakt van 3-dimensionale endo-anale echografie. Tussen 2001 en 2003 ondergingen 36 patiënten een darm-reconstructie middels een handgelegde pouch-anale anastomose. Voorafgaand aan, en zes maanden na de operatie werden verschillende morfologische aspecten van de kringspieren onderzocht bij 28 patiënten (15 patiënten met een CPAA en 13 patiënten met een IPAA). Tevens werd bij hen anorectale manometrie verricht. Het functionele resultaat werd geëvalueerd aan de hand van de Rockwood fecale incontinentie scoringslijst (RFIS). Zes maanden na de ingreep was de interne sfincter (IS) bij alle patiënten met een CPAA circulair intact. Bij twee patiënten met een IPAA werd een klein defect in de IS gevonden. Bij alle patiënten bleef de lengte van de IS gelijk. Bij de patiënten met een CPAA was het volume van de IS significant gedaald. Dit fenomeen trad niet op bij patiënten met een IPAA. De symmetrie was duidelijk verstoord bij 8 patiënten met een CPAA (53%) en bij 9 patiënten met een IPAA (73%). In beide groepen bleven dikte, lengte en volume van de externe sfincter hetzelfde. Zes maanden na de operatie was de maximale anale rustdruk significant gedaald in beide groepen. Maximale anale knijpkracht was alleen gereduceerd in de patiëntengroep met een IPAA. De postoperatieve RFIS scores waren niet gecorreleerd, noch aan de geobserveerde veranderingen van de IS, noch aan de manometrische bevindingen. Op grond van bovenstaande bevindingen lijkt het aanleggen van een handgelegde pouch-anale anastomose met behulp van een Scott retractor geen enkel nadelig effect te hebben op de externe sfincter en leidt dit bijna nooit tot een defect in de interne sfincter. Wel verandert de symmetrie van de interne sfincter bij 62% van de patiënten. Deze veranderingen vertoonden geen relatie met de functionele uitkomsten.

Schade aan de anale sfincters heeft een nadelig effect op de functionele uitkomst na een CPAA. Er zijn echter patiënten die, ondanks adequate sfincterfunctie, toch moeite hebben om de ontlasting op te houden na een dergelijke operatie. In hoofdstuk 9 worden de resultaten gepresenteerd van een onderzoek naar andere factoren die het functionele resultaat na deze ingreep beïnvloeden. Bij 40 patiënten werd voorafgaande aan, en een jaar na een CPAA het functionele resultaat geëvalueerd aan de hand van de RFIS. Tevens werd bij hen anorectale manometrie verricht. Compliantie en sensibiliteit van het (neo)rectum werden bepaald met behulp van een oneindig compliant polyethyleen meetzakje, aangesloten op een elektronisch barostat systeem. De mediane RFIS liet een significante vermindering van het continentie vermogen zien na de operatie. De maximale anale rustdruk was significant gedaald. De maximale knijpkracht bleef onveranderd. De gemiddelde compliantiecurve van de pouch was significant lager dan die van de oorsprokelijke endeldarm. Dit betekent een afname van de uitzetbaarheid. De sensibiliteit was significant verhoogd vergeleken met de oorspronkelijke endeldarm. De postoperatieve RFIS was niet gecorreleerd

aan de manometrische bevindingen. Een lagere compliantiecurve en een verhoogde sensibiliteit bleken gepaard te gaan met een minder goed functioneel resultaat na een CPAA. Op grond van bovenstaande bevindingen lijkt het advies gerechtvaardigd na "total mesorectal excision" de continuïteit te herstellen middels een colo-anale J-pouch anastomose.

Appendices

LIST OF ABBREVIATIONS

3D-EUS	three-dimensional endoanal ultrasonography
APR	abdominal perineal resection
CPAA	colonic J-pouch-anal anastomosis
EAS	external anal sphincter
EUD	earliest urge to defecate
FS	first sensation of content in the rectum or pouch
IAS	internal anal sphincter
IPAA	ileal pouch-anal anastomosis
LRA	low colo-rectal anastomosis
MARP	maximum anal resting pressure
MASP	maximum anal squeeze pressure
MTV	maximum tolerable volume
PC	pouch compliance
PDAI	pouchitis disease activity index
PSPT	pouch sensory perception threshold
RAIR	recto-anal inhibitory reflex
RBI	retrograde bowel irrigation
RFISI	Rockwood Fecal Incontinence Severity Index
TME	total mesorectal excision
UC	ulcerative colitis

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CURRICULUM VITAE

Martijn Pieter Gosselink werd geboren op 2 februari 1976 te Voorburg. Na het eindexamen Gymnasium, aan het Grotius College in Delft, studeerde hij Beleid en Management Gezondheidszorg (doctoraalexamen 2004) en geneeskunde (doctoraalexamen 2001) aan de Erasmus Universiteit Rotterdam. Gedurende zijn studietijd was hij student-onderzoeker bij de vakgroep Interne Organisatie van de Economische Faculteit onder leiding van prof. dr. J. Paauwe (1995-1996) en deed hij patiëntgebonden onderzoek bij de "Colorectal Research Group" op de afdeling Heelkunde onder leiding van dr. W.R. Schouten (1998-heden). De eerste chirurgische praktijkervaring deed hij op als lid van het chirurgisch studententeam: de "Nel Kreeft-brigade" (2000-2002). In 2004 behaalde de auteur het arts-examen aan het Erasmus MC. Hierna volgde een aanstelling als arts-onderzoeker op de afdeling Immunologie (prof. dr. R. Benner). In 2005 was hij arts-assistent chirurgie in het IJsselland Ziekenhuis in Capelle aan den IJssel (opleider dr. I. Dawson). Sinds 1 april 2006 is hij in opleiding tot chirurg in het Medisch Centrum Rijnmond Zuid (opleiders dr. E. van der Harst en dr. P.P.L.O. Coene).

PUBLICATIES

Zimmerman DDE, Briel JW, Gosselink MP, Schouten WR. Anocutaneous advancement flap repair of transsphincteric fistulas. *Dis Colon Rectum*. 2001; 44: 1474-80.

Zimmerman DD, Gosselink MP, Briel JW, Schouten WR. The outcome of transanal advancement flap repair of rectovaginal fistulas is not improved by an additional labial fat flap transposition. *Tech Col Proct*. 2002; 6: 37-42.

Gosselink MP, van der Grinten TED, Capaciteitsplanning. *TVZ*. 2003; 15; 107: 94-8.

Zimmerman DD, Delemarre JB, Gosselink MP, Hop WC, Briel JW, Schouten WR. Smoking affects the outcome of transanal mucosal advancement flap repair of transsphincteric fistulas. *Br J Surg*. 2003; 90: 351-4.

Zimmerman DD, Gosselink MP, Hop WC, Darby M, Briel JW, Schouten WR. Impact of two different types of anal retractor on fecal continence after fistula repair: a prospective, randomized, clinical trial. *Dis Colon Rectum*. 2003; 46: 1674-9.

Gosselink MP, Schouten WR, van Lieshout LMC, Hop WC, Laman JD, Ruseler-van Embden JGH. Delay of the first onset of pouchitis by oral intake of the probiotic strain Lactobacillus rhamnosus GG. *Dis Colon Rectum*. 2004; 47: 876-84.

Gosselink MP, Schouten WR, van Lieshout LMC, Hop WC, Laman JD, Ruseler-van Embden JGH. Eradication of pathogenic bacteria and restoration of the normal pouch flora: comparison of metronidazole and ciprofloxacin in the treatment of pouchitis. *Dis Colon Rectum*. 2004; 47: 1519-25.

Gosselink MP, Darby M, Zimmerman DDE, Smits AAA, van Kessel I, Hop WC, Briel JW, Schouten WR. Long term follow-up of retrograde colonic irrigation for defecation disturbances. *Colorectal Dis*. 2005; 7: 65-9.

Gosselink MP, Darby M, Zimmerman DDE, Gruss HJ, Schouten WR. Treatment of anal fissure by application of L-Arginine gel: a phase II study in 15 patients. *Dis Colon Rectum*. 2005; 48: 832-7.

Zimmerman DD, Gosselink MP, Mitalas LE, Delemarre JBV, Hop WC, Briel JW, Schouten WR. Smoking impairs rectal mucosal bloodflow - a pilot study. Possible implications for transanal flap repair. *Dis Colon Rectum* 2005; 48: 1228-32.

Schouten WR, Gosselink MP. Long-term outcome following loose-seton technique for external sphincter preservation in complex anal fistula. *Tech Col Proct*. 2005; 9: 79.

Gosselink MP, West RL, Kuipers EJ, Hansen BE, Schouten WR. Integrity of the anal sphincters after pouch-anal anastomosis: evaluation with three-dimensional endoanal ultrasonography. *Dis Colon Rectum.* 2005; 48: 1728-35.

Gosselink MP, Busschbach JJ, Dijkhuis CM, Stassen LPF, Hop WC. Schouten WR. Quality of life after total mesorectal excision for rectal cancer. *Colorectal Dis.* 2005; 8: 15-22.

Prins HA, Gosselink MP, Mitalas LE, Buise MP, Teerlink T, Esser C, Schouten WR. The effect of oral administration of L-arginine on anal resting pressure and anodermal blood flow in healthy volunteers. *Tech Col Proct.* 2005; 9: 229-32.

Oom DM, Gosselink MP, van Dijl VR, Zimmerman DD, Schouten WR. Puborectal sling interposition for the treatment of rectovaginal fistulas. *Tech Col Proct.* 2006; 10: 125-30.

Vermaas M, Gosselink MP, Ferenschild FTJ, van den Aardweg E, Lont HE, Kemperman H, van der Harst E, Tetteroo GW, Oostenbroek RJ, Dijkhuis CM, Eggermont AMM, de Wilt JHW. Regionale rsultaten van de behandeling van het rectum carcinoom in de regio van het IKR na introductie van nieuwe consensusrichtlijnen. *NTVH* 2006; 6: 168-72.

Oom DM, Gosselink MP, Schouten WR. Muscle interposition in patients with fistulas between the rectum and urethra or vagina. *Dis Colon Rectum.* 2007; 50: 548-9.

Vermaas M, Gosselink MP, Ferenschild FT, van den Aardweg E, Lont HE, Kemperman HW, van der Harst E, Tetteroo GW, Oostenbroek RJ, Dijkhuis CM, Eggermont AM, de Wilt JH. Introduction of preoperative radiotherapy in the treatment of operable rectal cancer in the Southwest region of The Netherlands. *Eur J Surg Oncol.* 2007; 33: 862-7.

Gosselink MP, Zimmerman DD, West RL, Hop WC, Kuipers EJ, Schouten WR. Impact of neo-rectal wall properties on functional outcome after colonic J-pouch anal-anastomosis. *Int J Colorectal Dis.* 2007; 22: 1353-60.

Doornebosch PG, Tollenaar RA, Gosselink MP, Stassen LP, Dijkhuis CM, Schouten WR, van de Velde CJ, de Graaf EJ. Quality of life after transanal endoscopic microsurgery and total mesorectal excision in early rectal cancer. *Colorectal Dis.* 2007; 9: 553-8.

Mitalas LE, Gosselink MP, Zimmerman DD, Schouten WR. Repeat transanal advancement flap repair: impact on the overall healing rate of high transsphincteric fistulas and on fecal continence. *Dis Colon Rectum.* 2007; 50: 1508-11.

Oom DM, van Dijl VR, Gosselink MP, van Wijk JJ, Schouten WR. Enterocele repair by abdominal obliteration of the pelvic inlet: long-term outcome on obstructed defaecation and symptoms of pelvic discomfort. *Colorectal Dis*. 2007; 9: 845-50.

Vermeulen J, Akkersdijk GP, Gosselink MP, Hop WC, Mannaerts GH, van der Harst E, Coene PP, Weidema WF, Lange JF. Outcome after emergency surgery for acute perforated diverticulitis in 200 cases. *Dig Surg*. 2007; 24: 361-6.

Gosselink MP, Oom DM, Zimmerman DD, Schouten RW. Martius flap: an adjunct for repair of complex, low rectovaginal fistula. *Am J Surg*. 2008; in press.

Oom DM, Gosselink MP, van Wijk JJ, van Dijl VR, Schouten WR. Rectocele repair by anterolateral rectopexy; long-term functional outcome. *Colorectal Dis*. 2008; in press.

Doornebosch PG, Gosselink MP, Neijenhuis PA, Schouten WR, Tollenaar RA, de Graaf EJ. Impact of transanal endoscopic microsurgery on functional outcome and quality of life. *Int J Colorectal Dis*. 2008; in press.

Mitalas LE, Gosselink MP, Zimmerman DD, Schouten WR. Required length of follow-up after transanal advancement flap repair of high transsphincteric fistulas. Accepted for publication in *Colorectal Dis*. 2008; in press.

Alexander SM, Mitalas LE, Gosselink MP**,** Oom DM, Zimmerman DD, Schouten WR. Obliteration of the fistulous tract with BioGlue adversely affects the outcome of transanal advancement flap repair. Submitted for publication.

Oom DM, Gosselink MP, Schouten WR. Enterocele: diagnosis and treatment. Submitted for publication.

Bruin de AF, Gosselink MP, Wijffels NA, Coene PP, van der Harst E. Local application of gentamicin reduces deep perineal wound infection after short-term preoperative radiotherapy followed by abdominoperineal resection for rectal cancer. Submitted for publication.

Boeken

Wie zorgt voor U? Capaciteitsplanning en arbeidsbeleving in de gezondheidszorg. Stand van zaken en politiek debat. 2002. Gosselink MP (redactie).
ISBN 90-9016052-3.

Hospitolk. Beknopte taalgids voor de medische zorg. 2004. Gosselink MP en Siccama R (redactie).
ISBN 90-808589-1-9.