Original article

Risk factors for anastomotic failure after total mesorectal excision of rectal cancer

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Background: **Anastomotic leakage is a major complication of rectal cancer surgery. The aim of this study was to investigate risk factors associated with symptomatic anastomotic leakage after total mesorectal excision (TME).**

Methods: **Between 1996 and 1999, patients with operable rectal cancer were randomized to receive short-term radiotherapy followed by TME or to undergo TME alone. Eligible Dutch patients who underwent an anterior resection (924 patients) were studied retrospectively.**

Results: **Symptomatic anastomotic leakage occurred in 107 patients (11·6 per cent). Pelvic drainage and the use of a defunctioning stoma were significantly associated with a lower anastomotic failure rate. A significant correlation between the absence of a stoma and anastomotic dehiscence was observed in both men and women, for both distal and proximal rectal tumours. In patients with anastomotic failure, the presence of pelvic drains and a covering stoma were both related to a lower requirement for surgical reintervention.**

Conclusion: **Placement of one or more pelvic drains after TME may limit the consequences of anastomotic failure. The clinical decision to construct a defunctioning stoma is supported by this study.**

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Introduction

Symptomatic anastomotic leakage is the most important surgical complication of rectal cancer surgery. Leakage after low anterior resection can result in significant morbidity and mortality[1–5], and may be associated with a higher local recurrence rate[6–8]. Since the introduction of total mesorectal excision (TME) by Heald[9], TME has become the accepted standard for rectal cancer surgery. The low recurrence and improved survival rates in TME series support the value of removing the fatty tissue around the rectum, known as the mesorectum[10–12]. However, concern has been expressed about the increased risk of symptomatic anastomotic leakage associated with TME[13,14]. The increase in sphincter-saving procedures and the subsequently higher proportion of patients with distal bowel anastomoses may contribute to an increased incidence of anastomotic failure. In addition, TME potentially endangers the blood supply to the remaining rectum, and may compromise anastomotic healing. Finally, removal of the mesorectum leaves a large pelvic space in which a haematoma may accumulate and lead to pelvic sepsis. To avoid the severe complications of anastomotic failure it is crucial to take all possible measures to prevent symptomatic anastomotic leakage. The aim of this study was to identify risk factors for symptomatic anastomotic leakage in patients undergoing TME for rectal cancer.

The Editors have satisfied themselves that all authors have contributed significantly to this publication

Patients and methods

Study population

The database of the Dutch TME trial was used. This was a large international multicentre trial that investigated the efficacy of short-term preoperative radiotherapy (5 × 5 Gy) in patients with rectal cancer treated by TME. From January 1996 to December 1999, 1861 patients with histologically proven adenocarcinoma of the rectum but with no evidence of distant metastases were included in the trial and randomized to receive preoperative irradiation followed by TME surgery or TME alone. Patients were eligible for randomization when the tumour was located below the level of S1–2 and was 15 cm or less from the anal verge, measured during withdrawal of a flexible coloscope. In addition, the tumour had to be clinically resectable (R0 resection). Results of the Dutch TME trial have been published previously[15].

In the present retrospective analysis, only data that had been collected prospectively during the TME trial were used. Only Dutch patients (1530 patients) were considered as their details and treatment characteristics, as well as surgical complications and deaths, were known to be complete and had been checked extensively during trial accrual by the study coordinators[16].

Surgery

Within the context of the TME trial, an extensive structure of workshops, symposia and instruction videos was developed to ensure optimal surgical quality and standardization of the TME technique[17]. In the protocol, the construction of a defunctioning stoma was recommended according to the surgeon's discretion, as was the decision to drain the remaining pelvic cavity. In addition, a side-to-end or colonic pouch anastomosis was advised, in an attempt to minimize the risk of anastomotic dehiscence. All surgical characteristics as well as operative and postoperative complications were recorded on a data form by the operating surgeon. These forms were compared with the operating report and discharge letters by the surgical trial coordinator, and checked for inconsistencies. When the data were unclear or incomplete, additional information was requested.

Symptomatic anastomotic leakage, the endpoint of this analysis, was defined as clinically apparent leakage (gas, pus or faecal discharge from the pelvic drain, or peritonitis) or extravasation of endoluminally administered water-soluble contrast on radiography or computed tomography. An abscess around the anastomosis was also recorded as a leakage. Radiological examination was performed only when there was clinical suspicion of anastomotic leakage.

Data collection and statistics

All forms were sent to the central data centre in Leiden. After checking, data were entered into a database and analysed with SPSS® statistical software (version 11.5 for Windows) (SPSS, Chicago, Illinois, USA). The χ^2 test was used to compare proportions; a two-sided P value of 0·050 was considered significant. The influence of independent variables on the risk of clinical anastomotic leakage was calculated using single-variable regression analysis. All variables associated with leakage with $P < 0{\cdot}100$ were entered in a multiple regression analysis. $P \leq 0{\cdot}050$ was considered statistically significant.

Results

Of the 1530 randomized Dutch patients, 1480 were eligible for enrolment into the clinical trial. Reasons for ineligibility were no adenocarcinoma (seven patients), other or previous malignancy (26), previous treatment (three), transanal resection (one), double tumour (six), sigmoid carcinoma (five) and tumour considered irresectable at randomization (two). Of all eligible patients, 441 underwent an abdominoperineal resection, 78 had a Hartmann procedure and in 37 patients no tumour resection was performed. The remaining 924 patients, who were evaluated in the present analysis, underwent an anterior resection according to the TME principle.

Five hundred and seventy patients (61·7 per cent) were men and 354 (38·3 per cent) were women; their median age was 64·0 (range 23–92) years. The average distance of the tumour from the anal verge was 8·4 (range 0–18) cm. Some 459 patients (49·7 per cent) were assigned to preoperative radiotherapy, the remaining patients to surgery alone. Clinical symptomatic anastomotic leakage was detected in 107 patients (11·6 per cent).

Patients who received preoperative irradiation did not have an increased risk of anastomotic leakage compared with non-irradiated patients (10·9 *versus* 12·3 per cent; $P = 0{\cdot}517$). However, a defunctioning stoma was constructed more often in irradiated patients (59·9 *versus* 53·3 per cent; $P = 0{\cdot}044$).

A defunctioning ileostomy or colostomy was constructed in 523 (56·6 per cent) of patients. Forty-three patients (8·2 per cent) with a stoma had a leakage, compared with 64 (16·0 per cent) of the 401 patients without a stoma ($P < 0{\cdot}001$). The presence of one or more pelvic drains after surgery was strongly associated with a lower leakage rate: 76 (9·6 per cent) of 792 patients with pelvic drainage had leakage, compared with 31 (23·5 per cent) of 132 patients without a drain ($P < 0{\cdot}001$). Men had more leakage than women (13·2 *versus* 9·0 per cent),

Table 1 Single-variable regression analysis of symptomatic anastomotic leakage

	No. with leakage ($n = 924$)*	Relative risk†	P**
Sex			
F	32 of 354 (9·0)	1·00	
M	75 of 570 (13·2)	1·53 (0·99, 2·36)	0·057
Age		0·99 (0·97, 1·01)	0·417
Distance of tumour from anal verge (cm)			
≥ 10·1	46 of 395 (11·6)	1·00	
5·1–10·0	52 of 462 (11·3)	0·96 (0·63, 1·47)	0·858
≤ 5·0	9 of 67 (13)	1·18 (0·55, 2·53)	0·676
Preoperative radiotherapy			
No	50 of 459 (10·9)	0·88 (0·58, 1·31)	0·517
Yes	57 of 465 (12·3)	1·00	
Intraoperative bleeding			
No	97 of 833 (11·6)	1·00	
Yes	10 of 91 (11)	0·93 (0·47, 1·87)	0·853
Preoperative organ injury			
No	100 of 850 (11·8)	1·00	
Yes	7 of 74 (9)	0·78 (0·35, 1·75)	0·553
Closure of anastomosis‡			
Double stapled	92 of 808 (11·4)	1·00	
Single stapled	9 of 69 (13)	1·17 (0·56, 2·43)	0·679
Handsewn	5 of 46 (11)	0·95 (0·37, 2·46)	0·914
Type of reconstruction§			
Pouch	22 of 261 (8·4)	1·00	
End-to-end anastomosis	17 of 107 (15·9)	2·05 (1·04, 4·04)	0·038
Side-to-end anastomosis	68 of 550 (12·4)	1·53 (0·93, 2·54)	0·098
Diverting stoma			
Yes	43 of 523 (8·2)	1·00	
No	64 of 401 (16·0)	2·12 (1·41, 3·20)	< 0·001
Omentoplasty			
Yes	26 of 197 (13·2)	1·00	
No	81 of 725 (11·2)	0·83 (0·52, 1·33)	0·431
Pelvic drainage			
Yes	76 of 792 (9·6)	1·00	
No	31 of 132 (23·5)	2·89 (1·81, 4·61)	< 0·001
Operating time¶		1·00 (0·99, 1·00)	0·942
TNM stage			
0	1 of 20 (5)	1·00	
I	31 of 285 (10·9)	2·32 (0·30, 17·93)	0·420
II	29 of 230 (12·6)	2·74 (0·35, 21·26)	0·335
III	38 of 345 (11·0)	2·35 (0·31, 18·07)	0·411
IV	8 of 44 (18)	4·22 (0·49, 36·32)	0·190

Values in parentheses are *percentages and †95 per cent confidence intervals. ‡One, §six and ¶seven patients missing. TNM, tumour node metastasis. **Chi-square test for comparison of proportions, and Student's t-test for continuous variables.

although this difference was not statistically significant ($P = 0·057$). A colonic pouch was constructed in 261 patients. Patients with a pouch had a leakage rate of 8·4 per cent, compared with 12·4 per cent in patients with an side-to-end anastomosis and 15·9 per cent in those with an end-to-end anastomosis ($P = 0·092$).

The correlation between tumour location and leakage rate was not significant: leakage rates for tumours 5·0 cm or less from the anal verge, between 5·1 and 10·0 cm, and more than 10·1 cm were 13, 11·3 and 11·6 per cent respectively ($P = 0·872$). However, when the tumour was located more proximally, a protective stoma was constructed less often; faecal diversion was performed in 73, 62·3 and 47·1 per cent respectively ($P < 0·001$).

The single-variable regression analysis included a number of other continuous and dichotomous parameters that may be associated with clinical anastomotic leakage. The absence of a diverting stoma, non-placement of pelvic drains, and the formation of an end-to-end or end-to-side anastomosis showed a significant association with anastomotic failure (*Table 1*).

Multiple regression analysis was performed to exclude confounding due to interaction between the covariates. Absence of a defunctioning stoma and lack of pelvic drainage remained the only two significant risk factors. Male sex was not significant ($P = 0·055$) (*Table 2*). The absence of a protective stoma was significantly associated with increased anastomotic dehiscence rates in both men and women (*Table 3*). Moreover, this association was also observed in patients with low or high rectal tumours (*Table 3*).

Management of symptomatic anastomotic leakage

Fifteen (14·0 per cent) of 107 patients with anastomotic leakage died within 30 days of surgery. The mortality rate related to anastomotic leakage did not differ significantly

Table 2 Multiple regression analysis of symptomatic anastomotic leakage

	Relative risk	P
Diverting stoma		
Yes	1·00	
No	1·89 (1·24, 2·90)	0·003
Sex		
F	1·00	
M	1·55 (0·99, 2·42)	0·055
Type of reconstruction		
Pouch	1·00	
End-to-end anastomosis	1·70 (0·85, 3·41)	0·135
Side-to-end anastomosis	1·43 (0·85, 2·39)	0·176
Pelvic drainage		
Yes	1·00	
No	2·53 (1·57, 4·09)	< 0·001

Values in parentheses are 95 per cent confidence intervals.

Table 3 Symptomatic anastomotic leakage in patients with and without a protective stoma according to sex and tumour location

	Anastomotic leakage		
	Stoma ($n = 523$)	No stoma ($n = 401$)	P*
Sex			
M	34 of 336 (10·1)	41 of 234 (17·5)	0·011
F	9 of 187 (4·8)	23 of 167 (13·8)	0·003
Distance of tumour from anal verge (cm)			
≤ 5·0	4 of 49 (8)	5 of 18 (28)	0·040
5·1–10·0	27 of 288 (9·4)	25 of 174 (14·4)	0·100
≥ 10·1	12 of 186 (6·5)	34 of 209 (16·3)	0·002

Values in parentheses are percentages. *Chi-square test.

between patients with and without diversion (six of 43 *versus* nine of 64; $P = 0·987$), nor between patients with or without pelvic drainage (nine of 76 *versus* six of 31; $P = 0·310$). Seventy-nine patients had surgical reintervention for a suspected anastomotic failure: in 44 patients a defunctioning stoma was constructed, in eight an end-colostomy was fashioned and in 13 patients a Hartmann procedure was performed. In 21 patients the reintervention consisted of abscess drainage only. Fifteen of the 86 patients who had a surgical reintervention died, compared with none of the other patients with leakage.

The need for surgical reintervention after detection of anastomotic failure was significantly lower for patients with pre-existing pelvic drainage than for those without a drain (56 of 76 *versus* 30 of 31 respectively; $P = 0·006$). A diverting stoma was also associated with a lower rate of surgical reintervention, as only 26 of 43 patients with a stoma underwent reoperation compared with 60 of 64 patients without a stoma ($P < 0·001$).

Discussion

In this large study population, symptomatic anastomotic leakage was detected in 11·6 per cent of patients, which is comparable with previous reports[1,12,13,18]. Before the start of the randomized trial, some surgeons expected increased surgical morbidity as a result of irradiation. In an earlier report it was shown that preoperative hypofractionated radiotherapy is a safe treatment with no increase in the surgical complication rate[19]. There was no significant association between leakage and short-term preoperative radiotherapy, which has become part of the standard regimen for rectal cancer treatment in many European countries.

Data in the present analysis were derived from a prospective randomized trial that investigated the efficacy of short-term preoperative radiotherapy in patients with rectal cancer treated by TME. The trial was not set up to answer any question regarding anastomotic leakage. Therefore, any statement based on data from the trial must be made carefully. However, the present analysis is informative and has identified risk factors for anastomotic leakage.

In the multiple regression analysis, the absence of pelvic drainage after TME and absence of a defunctioning stoma were the only two factors significantly associated with anastomotic dehiscence. After TME surgery, there is a large presacral space in which a haematoma or seroma may develop that constitutes an excellent medium for bacteria[20]. Any infection may extend to, involve and drain into the anastomosis and cause dehiscence. Pelvic drainage may prevent this process. Nevertheless, several trials have failed to show benefit of pelvic drainage[21–25]. However, these trials included heterogeneous populations of patients having either colonic[23,24] or colorectal[22,25] resections, many of whom did not undergo TME[21,25]. Thus the results cannot automatically be applied to patients after TME. Furthermore, the trials were often underpowered to detect small differences that may be clinically relevant to surgeons and their patients[22]. It is the present authors' view that there are few drawbacks to pelvic drainage and, although not investigated prospectively, the present findings suggest that it is wise to establish drainage of the presacral space after TME.

The creation of a stoma should effectively divert the faecal stream from a healing anastomosis, thereby mitigating the consequences of anastomotic failure. It is generally accepted that low rectal anastomoses after TME are particularly vulnerable to anastomotic failure[1,26]. In the present series, however, patients with both low and high rectal tumours were found to be at substantial risk of anastomotic leakage, and both patient categories may benefit from faecal diversion. In the present study, the decision to construct a defunctioning stoma was left to the discretion of the surgeon. Clearly, this decision is not made solely in an attempt to prevent leakage; other factors, such as the possible reduced quality of life after stoma formation[27] and the subsequent need to close a temporary stoma[28], play an important role in the decision. Indeed, temporary protective stomas tend to be left *in situ* for longer than is initially anticipated. After a median follow-up of 5 years, 19·2 per cent of the present patients with a 'temporary diversion' still had a stoma (data not shown).

One possible important risk factor for anastomotic leakage is the performance of the individual surgeon[29–32], a confounding factor that is hard to measure but may be crucial. In the present study surgeons had varying strategies

with regard to pelvic drainage or stoma construction, and it could be argued that patients with drains and a protective stoma might have had a higher *a priori* risk of anastomotic dehiscence. However, this was found not to be the case, so strengthening the relationship between drainage, faecal diversion and lower rates of anastomotic failure.

Construction of a temporary stoma and the placement of one or more drains in the presacral space were significantly associated with decreased clinical anastomotic leakage in patients with rectal cancer treated with TME. Moreover, these two measures were associated with a reduction in the proportion of leaks requiring surgical reintervention, and thus with a less severe clinical course in patients with anastomotic leakage. In an attempt to minimize the risk of clinical leakage, the construction of a defunctioning stoma seems advisable for patients with both proximal and distal rectal tumours, regardless of sex. Placement of at least one drain after TME for rectal cancer is recommended.

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