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Risk factors for anastomotic failure after TME surgery for rectal cancer

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ABSTRACT

Background: Anastomotic leakage is a major complication after rectal cancer surgery. We investigated risk factors that were associated with symptomatic anastomotic leakage after total mesorectal excision.

Method: Between 1996 and 1999 patients with operable rectal cancer were randomised between short-term radiotherapy followed by TME and TME alone. Eligible Dutch patients who underwent an anterior resection (n = 924) were retrospectivally studied.

Results: Leakage occurred in 107 patients (11.8%). Pelvic drainage and the use of a protective stoma were significantly associated with decreased anastomotic failure rates. A significant correlation between the absence of a stoma and anastomotic dehiscence was present in both male and female patients, and not only for distal, but also for proximal rectal tumours. In case of anastomotic failure, the presence of pelvic drains and a covering stoma were both related to a reduction in leaks requiring surgical reintervention.

Conclusion: It is recommendable to place one or more pelvic drains after TME to limit the consequences of anastomotic failure. A covering stoma is significantly associated with decreased anastomotic dehiscence and re-intervention rates in patients with both low and high rectal tumours, regardless their gender. The decision to construct a temporary stoma may be supported by this study.

INTRODUCTION

Symptomatic anastomotic leakage is the most important surgical complication following rectal cancer surgery. Leakage after low anterior resection can result in significant morbidity and mortality[1-5] and may be associated with a higher incidence of local recurrence[6-8]. Since the introduction of total mesorectal excision (TME) by Heald et al.[9], TME has become the accepted standard for rectal cancer surgery. The low recurrence rates and improved survival rates in TME series support the idea of removing the fatty tissue around the rectum, also known as the mesorectum[10-12]. However, concern has been expressed about the increased risk of symptomatic anastomotic leakage associated with the introduction of TME[13,14]. The rise in sphincter saving procedures and the subsequent higher proportion of patients with distal bowel anastomoses might contribute to an increase of anastomotic failure. Also, TME potentially endangers the blood supply to the remaining rectum, thus jeopardizing anastomotic healing. Finally, removing the mesorectum leaves a large pelvic space for accumulation of a haematoma, which bears the risk of infection and sepsis. To avoid severe complications of anastomotic failure like peritonitis, septic shock and even death, it is crucial to take all possible measures to prevent symptomatic anastomotic dehiscence. The aim of this study was to identify risk factors for symptomatic anastomotic leakage in rectal cancer patients who undergo TME surgery.

PATIENTS AND METHODS

Study population

In the current study we used the database of the "Dutch TME trial", a large international multicenter trial that investigated the efficacy of short term preoperative radiotherapy (5x5 Gy) in TME treated rectal cancer patients. From January 1996 until December 1999 1861 patients with histologically proven adenocarcinoma of the rectum without evidence of distant metastases were included in the study and randomised between preoperative irradiation followed by TME surgery or TME alone. Patients were eligible for randomisation when the tumour was located below the level of S1/2 and 15 centimetres or less from the anal verge, being measured during withdrawal of a flexible coloscope. Also, the tumour had to be clinically resectable which meant that the tumour, on examination by the surgeon, was considered to be mobile and resectable without leaving behind any residual tumour (i.e. a R0 resection). Results of this trial have been published previously[15].

In the present retrospective analysis, only data that had been collected prospectively during the course of the TME trial were used. Only Dutch patients (n = 1530) were considered as data of only these patients regarding patient and treatment characteristics, as well as surgical complications and mortality, are complete and were checked extensively during trial accrual by the study coordinators[16].

Surgery

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

Regarding the endpoint of this analysis, symptomatic anastomotic leakage was defined as clinically apparent leakage (i.e. gas, pus or faecal discharge from the pelvic drain, or peritonitis) or extravasation of endoluminal administered water soluble contrast on X-ray or CT-scan. An abscess around the anastomosis was also recorded as a leakage. Radiological examination was performed only in case of suspicion of anastomotic leakage.

Data Collection and Statistics

All case reports forms were sent to the central data centre in Leiden. After elaborate checking, data were entered in a database and analysed with SPSS statistical software (version 11.5 for Windows, SPSS, Chicago). Chi-square tests were used to compare proportions. A two-sided P-value of 0.05 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 $P < 0.1$ were entered in a multiple regression analysis. A P-value of 0.05 or less was considered significant.

RESULTS

Of all 1530 randomised Dutch patients, 1480 patients were eligible for enrolment into the clinical trial. Reasons for ineligibility were no adenocarcinoma (n=7), other/previous malignancy (n=26), previous treatment (n=3), transanal resection (n=1), double tumour (n=6), sigmoid carcinoma (n=5) and tumour not considered resectable at randomisation (n=2). Of all eligible patients 441 underwent an abdominoperineal resection, 78 patients 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 seventy patients (61.7%) were male and 354 (38.3%) were female. Median age was 64.0 years (range 23-92). The average distance of the tumour from the anal verge

was 8.4 cm (range 0-18 cm). Four hundred and fifty nine patients (49.7%) were assigned to preoperative radiotherapy, the remaining patients to surgery alone. In 107 patients (11.8%) a clinical symptomatic anastomotic leakage was detected.

Patients who received pre-operative irradiation did not have an increased risk of anastomotic leakage compared to non-irradiated patients (10.9% versus 12.3%, P = 0.517). However, in irradiated patients the operating surgeon decided more often to construct a defunctioning stoma (59.9% versus 53.3%, P = 0.044).

A protective ileo- or colostoma was constructed in 56.6% of the patients. Eight point two percent of the patients with a stoma had a leakage compared to 16.0% of the patients without a stoma (P < 0.001). Leaving behind one or more pelvic drains after surgery was strongly associated with decreased leakage rates: in patients with pelvic drainage, anastomotic leakage was diagnosed in 9.6% of the patients, compared to 23.5% of the patients without a drain (P < 0.001). Male patients suffered more often from leakage (13.2% versus 9.0%) although this difference was not statistically significant (P = 0.057). The construction of a pouch was done in 261 patients. Patients with a pouch had a leakage rate of 8.4% compared to 12.4% in patients with an side-end anastomosis and 15.9% in patients with an end-end anastomosis (P = 0.092).

The correlation between tumour location and leakage rate was not significant: leakage rates for tumours 5 cm or less located from the anal verge, between 5.1 and 10 cm, and for tumours at more than 10.1 cm were 13.4%, 11.3% and 11.6% respectively (P = 0.872). However, if the tumour was located more proximally, a protective stoma was less often was constructed: faecal diversion was performed in 73.1%, 62.3% and 47.1% respectively (P < 0.001).

In the single variable regression analysis, a number of other continuous and dichotomous parameters were analysed that were possibly associated with clinical anastomotic leakage. The absence of a diverting stoma, the lack of one or more of pelvic drains left behind after surgery, male gender and the formation of an end-end or end-side anastomosis appeared to be significantly associated with the occurrence of anastomotic failure (table 1).

Multiple regression analysis was performed to exclude confounding due to interaction between the covariates. The absence of a defunctioning stoma and the lack of pelvic drainage remained the only two significant risk factors. Male gender was a non-significant risk factor with a P-value of 0.055 (table 2). The absence of a protective stoma was significantly associated with increased anastomotic dehiscence rates in both male and female patients (table 3). Moreover, this association is also present in patients with both low and high rectal tumours (table 3).

Management of symptomatic anastomotic leakage

Fifteen of the 107 patients (14.0%) with anastomotic leakage died within 30 days after surgery. Mortality related to anastomotic leakage did not differ significantly between patients with and without diversion (14.0% vs. 14.1%, P = 0.987), nor between patients with

Table 1. Single variable regression analysis of symptomatic anastomotic leakage. Values in parentheses are percentages. * n = 1 is missing. ** n = 6 missing. *** n = 7 missing. ETE: end-to end anastomosis. STE: side-to-end anastomosis

	Number of patients (%)	Relative risk	95% CI	P-value
Sex				
Female	32/354 (9.0)	1.00		
Male	75/570 (13.2)	1.53	0.99-2.36	0.059
Age		0.99	0.97-1.01	0.417
Distance tumour from anal verge				
≥10.1 cm	46/395 (11.6)	1.00		
5.1-10.0 cm	52/462 (11.3)	0.96	0.63-1.47	0.858
≤5 cm	9/67 (13.4)	1.18	0.55-2.53	0.676
Pre-operative radiotherapy				
Yes	57/465 (12.3)	1.00		
No	50/459 (10.9)	0.88	0.58-1.31	0.517
Intra-operative bleeding				
No	97/833 (11.6)	1.00		
Yes	10/91 (11.0)	0.93	0.47-1.87	0.853
Peroperative organ injury				
No	100/850 (11.8)	1.00		
Yes	7/74 (9.5)	0.78	0.35-1.75	0.553
Stapler*				
Double stapler	92/808 (11.4)	1.00		
No, hand-sewn	5/46 (10.9)	0.95	0.37-2.46	0.914
Single stapler	9/69 (13.0)	1.17	0.56-2.43	0.679
Type of reconstruction**				
Pouch	22/261 (8.4)	1.00		
ETE	17/107 (15.5)	2.05	1.04-4.04	0.038
STE	68/550 (12.4)	1.53	0.93-2.54	0.098
Diverting stoma				
Yes	43/523 (8.2)	1.00		
No	64/401 (16.0)	2.12	1.41-3.20	<0.001
Omentumplasty				
Yes	26/197 (13.2)	1.00		
No	81/725 (11.2)	0.83	0.52-1.33	0.431
Pelvic drainage				
Yes	76/792 (9.6)	1.00		
No	31/132 (23.5)	2.89	1.81-4.61	<0.001
Operation time***		1.00	0.99-1.00	0.942
TNM stage				
0	1/20 (5.0)	1.00		
I	31/285 (10.9)	2.32	0.30-17.93	0.420
II	29/230 (12.6)	2.74	0.35-21.26	0.335
III	38/345 (11.0)	2.35	0.31-18.07	0.411
IV	8/44 (18.2)	4.22	0.49-36.32	0.190

Table 2. Multiple regression analysis of symptomatic anastomotic leakage. Values in parentheses are percentages

	Relative risk	95% CI	P-value
Diverting stoma			
Yes	1.00		
No	1.89	1.24-2.90	0.003
Sex			
Female	1.00		
Male	1.55	0.99-2.42	0.055
Type of reconstruction			
Pouch	1.00		
ETE	1.70	0.85-3.41	0.135
STE	1.43	0.85-2.39	0.176
Pelvic drainage			
Yes	1.00		
No	2.53	1.57-4.09	<0.001

Table 3. Number of patients with symptomatic anastomotic leakage distributed according to gender, tumour location and the use of a protective stoma. Values in parentheses are percentages

	Diverting stoma	No diverting stoma	P-value
Gender			
Male	34/336 (10.1)	41/234 (17.9)	0.011
Female	9/187 (4.8)	23/167 (13.8)	0.003
Tumour location			
≤5 cm	4/49 (8.2)	5/18 (27.8)	0.040
5.1-10.0 cm	27/288 (9.4)	25/174 (14.4)	0.100
≥10.1 cm	12/186 (6.5)	34/209 (16.3)	0.002

or without pelvic drainage (11.8% vs. 19.4%, P = 0.310). Seventy nine patients underwent a surgical reintervention due to a (suspected) anastomotic failure: in 44 patients a diversion was constructed after all, in 8 patients an end-colostomy, 13 patients underwent a Hartmann procedure and in 14 patients the reintervention consisted of abscess drainage only. Fifteen out of 79 patients that had a surgical reintervention died as none died in the patient group without reintervention.

The need for surgical reintervention after detecting anastomotic failure was significantly lower for patients with pelvic drainage (56 out of 76 patients (73.7%) than for patients without drain (30/31, 96.8%, P = 0.006). A diverting stoma was also associated with lower rates of surgical reintervention as only 26 out of 43 patients (60.5%) with a stoma underwent surgery for the second time, compared to 60 out of 64 patients without a stoma (93.8%, P < 0.001).

DISCUSSION

In this large study population, symptomatic anastomotic leakage was detected in 11.8%, which is comparable with previous reports[1,12,13,18]. Before the start of the randomised trial, some surgeons expected increased surgical morbidity due to irradiation. In an earlier report it was shown that preoperative hypofractionated radiotherapy is a safe treatment without a rise in surgical complications[19]. There was no significant association between leakage and preoperative short term radiotherapy, which has become part of the standard regime for rectal cancer treatment in many European countries.

Data in the current analysis were derived from a prospective randomised trial that investigated the efficacy of short term preoperative radiotherapy in TME treated rectal cancer patients. 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 most carefully. However, the performed analysis is informative and can identify risk factors for anastomotic leakage reliably.

In the multiple regression analysis, the lack of pelvic drains left behind after TME surgery, as well as the absence of a defunctioning stoma were the only two significant factors associated with anastomotic dehiscence. The possible acting mechanism of pelvic drainage and defunctioning in preventing clinical leakage can be explained biologically. After TME surgery, the large presacral space is a significant collector of fluids that may constitute an excellent medium for bacteria[20]. Infection of this haematoma may extend to, involve and drain into the anastomosis and cause dehiscence. The accumulation of these fluids is likely hindered by pelvic drainage. Nonetheless, several trials that investigated the usefulness of placing a drain after colorectal surgery do not favour pelvic drainage [21,22,22-25]. However, these trials often describe a heterogeneous population with either colonic[23,24] or colorectal resection[22,25] that did not undergo TME surgery[21,25]. Therefore, the results of these trials cannot be extrapolated automatically to TME treated rectal cancer patients. Also, the performed trials are often underpowered and hence not able to detect small differences that may be clinically relevant to both surgeons and their patients[22]. Furthermore, there are hardly any drawbacks from pelvic drainage: drains are easily left behind after rectal surgery and hardly burden the patient. Although not prospectively investigated, these data on TME rectal cancer patients suggest that it is recommendable to leave behind one or more pelvic drains after rectal surgery.

A covering stoma diverts the faecal stream from a healing anastomosis. In case of an anastomotic dehiscence, no faeces can be transported through a defective anastomosis into the abdominal cavity. In this way, the consequences of anastomotic failure are mitigated. 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 at substantial risk for anastomotic leakage and both patient categories may benefit from faecal diversion, as well as both male and female patients do. In this trial, the

decision to construct a defunctioning stoma was left to the discretion of the individual surgeon. Clearly, this decision is not solely made in an attempt to prevent leakage. Other factors, like the possible decreased quality of life after stoma formation[27], and the need to close a temporary stoma[28] play an important role as well. Indeed, temporary protective stomas tend to remain longer in situ than initially anticipated. In fact, after a median follow up of 5 years, 19% of the analysed patients with a so called temporary diversion, still has a stoma.

One possible important risk factor for anastomotic leakage is the performance of the individual surgeon[29-32]. This confounding factor is hard to measure but may be crucial. In this study population, it was examined whether each individual surgeon had a common policy of creating a protective stoma or placing pelvic drains when performing TME surgery on rectal cancer patients. There was a variable surgical strategy, i.e. most patients without pelvic drainage or a protective stoma were operated upon by surgeons who choose to place drains and divert the faecal steam in other patients, most likely based on intraoperative risk assessment of the likelihood of anastomotic dehiscence (data not shown). Thus, one could argue that patients with drains and a protective stoma would have a higher a priori risk of anastomotic dehiscence. This is however refuted by the present analysis, which strengthens the significant correlation between drainage, faecal diversion and lower rates of anastomotic failure.

In conclusion, the construction of a temporary stoma and the placement of one or more drains in the pelvic area are significantly associated with decreased anastomotic failure rates in rectal cancer patients treated with TME surgery. Moreover, these two measures are associated with a reduction in the rate of leaks requiring secondary surgery and thus with a mild clinical course in case of anastomotic dehiscence. In an attempt to minimise the risk of clinical leakage, stoma formation seems advisable, for patients with both proximal and distal rectal tumours, regardless their gender. However, individual patient characteristics have to be taken into account as well when deciding to construct a stoma. Considering the minimal burden to both patients and surgeons, we recommend placement at least one drain after TME for rectal cancer.

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