Quality assurance in rectal cancer treatment

Dulk, M. den

Chapter 11

A multivariate analysis of limiting factors for stoma reversal in patients with rectal cancer entered into the total mesorectal excision (TME) trail: a retrospective study

Marcel den Dulk, Marije Smit, Koen C.M.J. Peeters, Elma Meershoek-Klein Kranenbarg, Harm J.T. Rutten, Theo Wiggers, Hein Putter, Cornelis J.H. van de Velde

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ABSTRACT

Background

In many patients with rectal cancer, defunctioning stomas are created to limit the consequences of anastomotic leakage. Although intended to be temporary, a substantial proportion of these stomas might never be reversed for various reasons. We aimed to describe stoma policy by use of data from the total mesorectal excision (TME) trial in patients with rectal cancer and to identify factors that limit stoma reversal.

Methods

924 Dutch patients with rectal cancer who underwent a low anterior resection were selected from the TME trial, a prospective, randomised multicentre trial studying the effects of short-term preoperative radiotherapy in 1861 patients who underwent TME. Creation of stomas and time to stoma reversal were analysed retrospectively by use of multivariate analysis.

Findings

In 523 of 924 (57%) patients, a primary stoma (defined as a stoma created at the time of TME) was constructed after a low anterior resection. Geographical differences in the number of primary stomas constructed were reported throughout the Netherlands. 19% of stomas that were created were never reversed. Postoperative complications and secondary constructed stomas (defined as a stoma created during a second or subsequent procedure after TME) were associated with a high likelihood of a permanent stoma. However, perioperative complications were not a limiting factor for stoma closure.

Interpretation

Postoperative complications are an important limiting factor for stoma reversal because, after occurrence of these complications, patients and surgeons might be reluctant to reverse the stoma, so a substantial proportion of these stomas are never closed. Future guidelines for stoma creation and closure should consider these factors.

INTRODUCTION

Stomas are created frequently in patients undergoing surgery for rectal cancer to limit the consequences of anastomotic leakage. Colostomies created after abdominoperineal resections are permanent. However, after a low anterior resection, a defunctioning stoma -such as a diverting colostomy- is constructed to protect the healing anastomosis, and these stomas are intended to be temporary. Although studies have not shown a substantial difference in the incidence of anastomotic leakage when comparing patients with and without a diverting stoma,[1,2] we have previously reported a substantial decrease in clinically evident anastomotic leakage in patients with stomas.[3] Furthermore, defunctioning stomas might mitigate the consequences of symptomatic anastomotic leakage, a notion that is supported by the decreased proportion of patients with a leak needing secondary surgery.[1-3]

The decision to create a stoma is affected by factors such as availability of high-quality stoma care, capability of stoma handling, and risk of stoma-related complications. Stoma complications occur in up to 30% of patients with a stoma.[4] These complications affect patients' daily activities and a relation between the number of stoma-care problems and the amount of restriction in social activities has been reported.[5] These stoma-related difficulties might be permanent because some of these stomas will never be closed.[6] The quality of life of a patient with a stoma is decided by multiple factors, such as patients' preferences and sociodemographical characteristics. Engel and coworkers found that patients undergoing a low anterior resection without creation of a stoma had better quality of life than did patients treated with an abdominoperineal resection and given a stoma.[7] By contrast, we previously reported that overall perceived health in patients who had undergone an abdominoperineal resection was not lower than that in patients who had been treated with a low anterior resection.[8] A recent Cochrane review[9] suggested that published studies challenged the assumption that patients who had undergone anterior resection fare better, but that data from larger, better designed and executed prospective trials are needed to answer the question of whether anterior resected patients had a better quality of life.

We aimed to describe the policy of stoma formation in patients entered into the TME trial for rectal cancer and to identify factors that limit reversal of these stomas.

METHODS

Patients and procedures

The TME trial included 1861 patients between 1 January 1996 and 31 December 1999.[10] This randomised multicentre trial asessed TME surgery with or without preoperative 5

x 5 Gy radiotherapy. Patients aged 18 years or over with clinically resectable adenocarcinoma of the rectum were randomly assigned to either radiotherapy followed by TME, or TME alone. The trial had no age limit. Radiotherapy, surgery, and pathology were standardised and strictly quality controlled, as described previously.[11] Both the decision to construct a stoma and the type of stoma were at the discretion of the surgeon, as defined in the protocol. A stoma created at the time of the TME procedure was defined as a primary stoma, and a secondary stoma was defined as a stoma created during a second (or following) procedure after the TME procedure. Follow-up of all patients was done according to trial protocol. The study was approved by all participating institutes and central and local ethics committees. All patients gave informed consent.

For the current analysis, all relevant data were collected at the time of trial. Only patients undergoing low anterior resection who were eligible for trial participation were studied in this analysis. Inclusion criteria have been reported previously.[10] Only Dutch patients were included because detailed and reliable information on patient and treatment characteristics was available for these patients, and data checking with hospital reports was done for these patients. Stomas created after a local recurrence were not included in the analysis. Exclusion criteria have been reported previously.[10]

Statistical analysis

Data were analysed with the SPSS package (version 12.0 for Windows; SPSS Inc., Chicago, IL, USA). Time to stoma reversal was analysed by use of the Kaplan-Meier method. Univariate log-rank and multivariate Cox regression analyses were used to study limiting factors for stoma reversal. The initial list of prognostic factors was based on clinical importance decided by the investigators (MdD, TW, CvdV). Each of these variables was retained for the multivariate analysis if either the univariate effect of that variable was significant or if the interaction with timing of stoma (primary versus secondary) was significant. In this selection process of variables, a *P*-value of ≤ 0.100 was deemed to be significant. For significant interactions, the results are presented separately for primary and secondary stomas, and the interaction was included in the multivariate Cox regression analysis. For non-significant interactions, the overall hazard ratio is shown. Except in the above mentioned selection process, a two-sided *P*-value of ≤ 0.050 was deemed to be statistically significant.

The following variables were studied as limiting factors for stoma closure: preoperative radiotherapy; sex; age; body-mass index; timing of stoma (primary versus secondary); type of stoma (ileostomy versus colostomy for primary stomas; end colostomy or ileostomy versus diverting stoma for secondary stomas); tumour-node-metastasis (TNM) stage; distance of the tumour to the anal verge; perioperative complications (including bleeding, organ injury, and tumour spill); postoperative infective complications (including wound infection, urinary tract infection, abscess, sepsis, and fever without

known cause); postoperative general complications (including thrombosis, embolism, cholecystitis, pulmonary, renal, neurological, and cardiac problems); postoperative surgical complications (for primary stomas only, including wound dehiscence, anastomotic leakage, ileus, postoperative bleeding, fistula, and perforation); and recurrence (either local recurrence defined as evidence of a tumour within the lesser pelvis or perineal wound, or distant recurrence defined as evidence of a tumour in any other area) after stoma creation as identified by: clinical assessment every 3 months in the first year and annually thereafter for at least 2 years; also, annual liver imaging and endoscopy. Overall recurrence status was entered as a time-dependent covariate.

RESULTS

Median follow-up of patients who were alive at the time of analysis was 7.1 years (range 2.5 to 9.8 years). Primary stomas were created in 523 of 924 (57%) patients who underwent low anterior resections (Figure 1). 329 (63%) of these stomas were ileostomies, and the remaining 194 patients (37%) received a colostomy. Characteristics of the patients

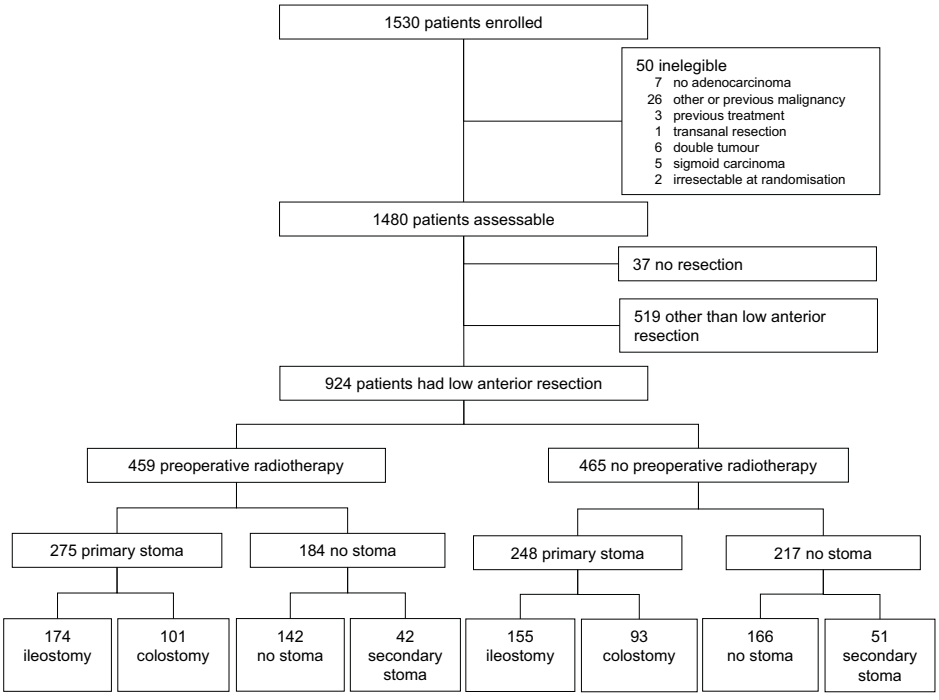


Figure 1. TME trial profile. Patients were randomised to TME surgery alone and TME surgery with preoperative radiotherapy at the time of inclusion.

Table 1. Characteristics of patients included in the analysis.

Variable	No primary stoma (%)	Primary stoma (%)
Preoperative radiotherapy		
No	217 (54)	248 (47)
Yes	184 (46)	275 (53)
Sex		
Male	234 (58)	336 (64)
Female	167 (42)	187 (36)
Age at randomisation (years)		
Mean	63.3	63.7
Standard deviation	11.2	10.6
TNM stage		
TNM Stage 0	11 (3)	9 (2)
TNM Stage I	120 (30)	165 (32)
TNM Stage II	106 (26)	124 (24)
TNM Stage III	141 (35)	204 (39)
TNM Stage IV	23 (6)	21 (4)
Distance tumour to anal verge		
< 5.0 cm	18 (4)	49 (9)
5.0-9.9 cm	174 (43)	288 (55)
≥ 10.0 cm	209 (52)	186 (36)
Type of anastomosis*		
End-to-side	257 (64)	293 (56)
End-to-end	55 (14)	52 (10)
Pouch	87 (22)	174 (33)

* Data missing for six patients. Percentages might not add up to 100% due to rounding.

and tumours are shown in Table 1. The Netherlands comprises nine comprehensive cancer centre regions, each serving a different part of the country. The geographical differences in primary stoma construction within the rectal cancer TME trial are shown in Figure 2.

Stomas were created at a secondary surgical procedure in 93 of 401 (23%) patients for reasons other than a recurrence. Stomas were created after a recurrence in four patients (0.4%), which were not included in this analysis. In one patient, a secondary stoma was created in conjunction with an abdominoperineal resection, which was done because of a positive resection margin. This patient was deemed to have had a permanent stoma and was, therefore, discarded from all further analyses. Of the 93 patients who had temporary stomas created at a secondary surgical procedure, 58 of 93 (62%) had diverting stomas, whereas 29 of 93 (31%) had end ileostomies or colostomies. The type of secondary stoma was unknown in six (6%) patients. The reasons for formation of secondary stomas are shown in Table 2. These secondary procedures were undertaken because of clinical anastomotic leakage in 61 of 93 (66%) patients. Taken together, 616 of 924 (67%) patients initially treated with a low anterior resection received a temporary stoma, either at initial or at secondary surgery.

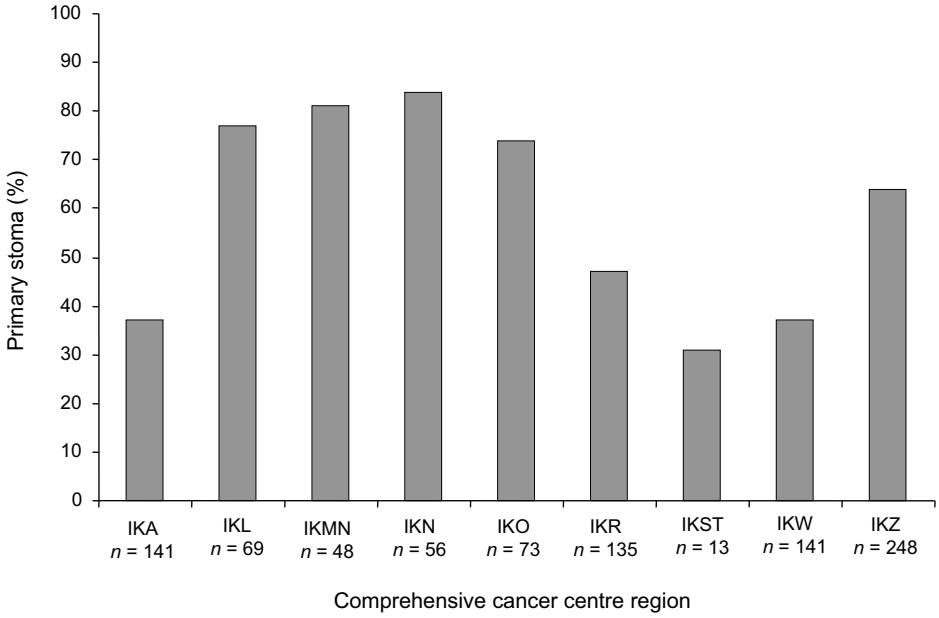


Figure 2. Primary stomas per comprehensive cancer centre region in the TME trial. IKA = comprehensive cancer centre Amsterdam; IKL = comprehensive cancer centre Limburg; IKMN = comprehensive cancer centre Middle Netherlands; IKN = comprehensive cancer centre North Netherlands; IKO = comprehensive cancer centre East; IKR = comprehensive cancer centre Rotterdam; IKST = comprehensive cancer centre Stedendriehoek Twente; IKW = comprehensive cancer centre West; IKZ = comprehensive cancer centre South.

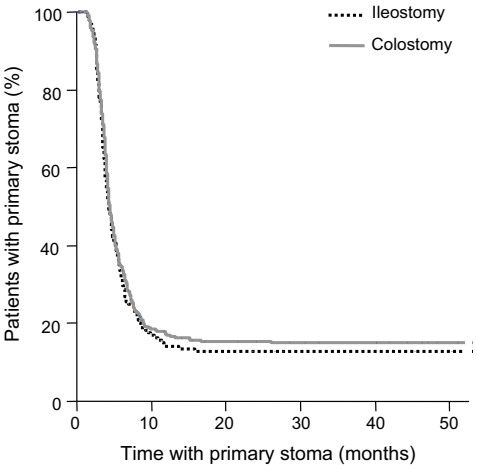
Table 2. Reasons for secondary-stoma creation.

Reason for secondary-stoma formation	n (%)
Anastomotic leakage	61 (66)
Abscess, sepsis or peritonitis	18 (19)
Fistula	6 (6)
Bleeding	1 (1)
Stenosis or ileus	2 (2)
Other	3 (3)
Unknown	2 (2)

Percentages might not add up to 100% due to rounding.

97% (95% CI 95%-98%) of stomas that were reversed were closed within the first year after surgery. The median time to stoma reversal was 4.1 months (range 1.3-33.1 months). 19.0% (16%-22%) of all stomas were not removed during follow-up. No significant difference was found between closure rate of ileostomies (15% not reversed [11%-19%]) and colostomies (13% not reversed [7%-18%]; $P = 0.474$; Figure 3).

Table 3 shows the univariate and multivariate analyses on limiting factors for stoma closure. In the univariate analysis, a relation between timing of the stoma, preopera-



Numbers at risk						
Ileostomy	329	48	36	32	30	24
Colostomy	194	26	15	12	12	10

Figure 3. Kaplan-Meier curve for stoma reversal of primary ileostomies and colostomies.

tive radiotherapy, and TNM stage was found. The results for these variables are shown separately for primary and secondary stomas in Table 3. Figure 4 shows the rate of stoma closure per age group ($P = 0.046$), and the rate of stoma closure for primary and secondary stomas. During follow-up, the closure rate was 86% (83%-89%) for primary stomas and 49% (37%-61%) for secondary stomas ($P < 0.0001$).

In the multivariate analysis, preoperative radiotherapy was significantly associated with a decreased likelihood of stoma reversal for secondary stomas, but not for primary stomas. Older age, secondary stoma construction, an end colostomy or ileostomy, any postoperative complication, and a recurrence were identified as limiting factors for stoma reversal. By contrast, no significant difference was reported for perioperative complications.

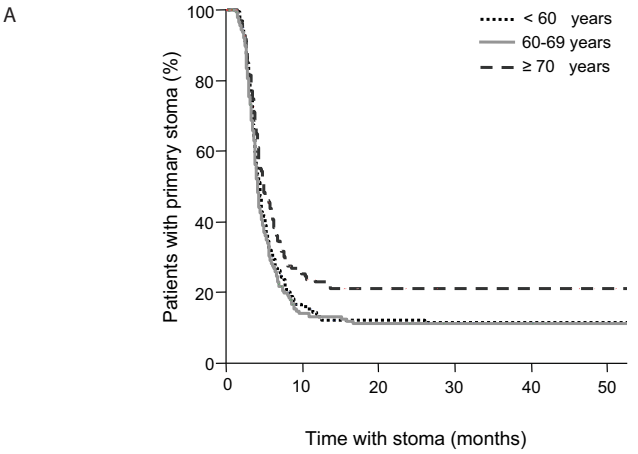
DISCUSSION

This study describes the policy on stoma construction used in the TME trial. As 84 of 102 hospitals in the Netherlands participated in this trial, the present study indicates common practise in the Netherlands. However, all extrapolations should be made carefully, because no information on treatment policy in the nontrial setting was studied and only Dutch patients entered into the TME trial are included in this analysis. We can assume that surgeons did not want to increase the risk of symptomatic anastomotic leakage, and so created more stomas in patients treated with preoperative radiotherapy

Table 3. Univariate log-rank and multivariate Cox regression analyses for factors limiting stoma reversal.

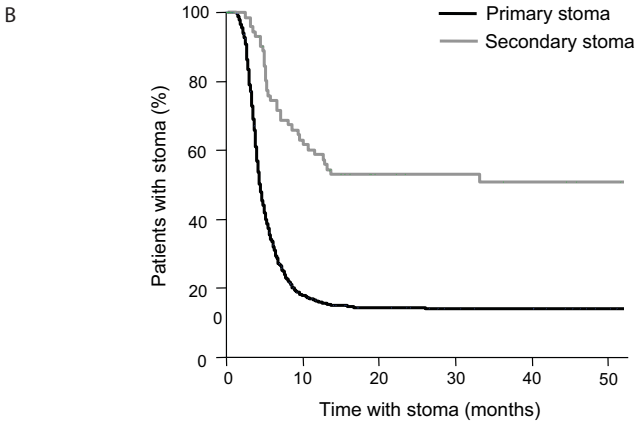
Variable	*n*	Univariate analyses			Multivariate analysis		
		HR	95% CI	*P*-value	HR	95% CI	*P*-value
Radiotherapy, primary stoma				0.960			0.244
No	248	1.00			1.00		
Yes	275	1.00	0.82 – 1.21		1.13	0.92 – 1.38	
Radiotherapy, secondary stoma				0.021			0.010
No	51	1.00			1.00		
Yes	42	0.41	0.19 – 0.87		0.34	0.15 – 0.77	
Sex*				0.923			----
Female	220	1.00					
Male	396	1.01	0.83 – 1.23				
Age				0.046			0.029
< 60 years	204	1.00			1.00		
60-69 years	226	1.03	0.82 – 1.28	0.815	1.10	0.88 – 1.38	0.394
≥ 70 years	186	0.77	0.61 – 0.99	0.038	0.79	0.62 – 1.02	0.071
Body mass index*†				0.369			----
< 25.0 kg/m^2	240	1.00					
25.0-29.9 kg/m^2	213	1.17	0.94 – 1.47	0.158			
≥ 30.0 kg/m^2	50	1.08	0.75 – 1.55	0.681			
Distance*				0.608			----
< 5.0 cm	57	1.00					
5.0 – 9.9 cm	330	1.01	0.72 – 1.42	0.939			
≥ 10 cm	229	1.12	0.79 – 1.59	0.536			
TNM stage, primary stoma				0.226			0.309
0-II	298	1.00			1.00		
III-IV	225	0.88	0.72 – 1.08		0.90	0.73 – 1.10	
TNM stage, secondary stoma				0.090			0.134
0-II	57	1.00			1.00		
III-IV	36	1.79	0.91 – 3.52		1.71	0.85 – 3.45	
Type of primary stoma*				0.474			----
Colostomy	194	1.00					
Ileostomy	329	0.93	0.76 – 1.14				
Type of secondary stoma‡				0.006			0.008
Diverting stoma	58	1.00			1.00		
End ileostomy or colostomy	29	0.13	0.03 – 0.55		0.14	0.03 – 0.59	
Perioperative complication				0.089			0.103
No	422	1.00			1.00		
Yes	194	0.84	0.68 – 1.03		0.84	0.68 – 1.04	
Infectious postoperative complication				<0.0001			0.0005
No	439	1.00			1.00		
Yes	177	0.50	0.39 – 0.63		0.65	0.51 – 0.83	
General postoperative complication				<0.0001			0.012
No	429	1.00			1.00		
Yes	187	0.61	0.49 – 0.77		0.73	0.57 – 0.93	
Surgical postoperative complication, primary stoma only				<0.0001			0.0001
No	350	1.00			1.00		
Yes	173	0.58	0.46 – 0.72		0.62	0.49 – 0.79	
Local or distant recurrence§				0.002			0.0001
No	431	1.00			1.00		
Yes	156	0.46	0.28 – 0.75		0.36	0.22 – 0.59	
Timing of stoma				<0.0001			0.0001
Primary	523	1.00			1.00		
Secondary	93	0.30	0.21 – 0.43		0.06	0.01 – 0.24	

HR = hazard ratio. HR < 1 indicates decreased likelihood of stoma reversal, whereas HR > 1 indicates increased likelihood of stoma reversal. *Multivariate analysis not done. †Data on height or weight were missing for 113 patients. ‡Unspecified for six patients. §Entered as time-dependent covariate, data missing for 29 patients (recurrence status unknown for one; recurrence status not applicable because of M1 disease in 28 at the time of surgery).



Numbers at risk

< 60 years	204	22	17	12	10	9
60-69 years	226	20	16	14	14	10
≥ 70 years	186	32	21	18	18	15



Numbers at risk

Primary stoma	523	74	51	44	42	34
Secondary stoma	93	44	29	27	25	23

Figure 4. Kaplan-Meier curves for stoma reversal per age group (A) and for primary and secondary stomas (B).

and for distally located tumours with, consequently, distally located anastomoses. Large geographical differences in primary stoma policy were detected -and similar findings have been reported in the UK[12]- but that such large differences exist is remarkable.

We report that 19% of temporary created stomas were not closed during follow-up. Of the stomas that were closed during follow-up, 97% were closed in the first year after construction. Therefore, if a stoma was not closed in the first year, it would probably become permanent. Although the outcome of temporary stomas in terms of the numbers closed has been studied before,[13,14] little is known about risk factors associated with

stoma closure. To our knowledge, this study is the first to analyse systematically factors that limit stoma reversal in a large population with a long follow-up.

Age was found to be a significant risk factor associated with a decreased likelihood of stoma reversal. In the TME trial, an upper age limit was not set, whereas most other randomised trials studying neoadjuvant treatment restricted the age of older participants.[15,16] Consequently, only few researchers report on older age as a limiting factor for stoma reversal. However, Kairaluoma and co-workers[13] also reported that age above 70 years was associated with fewer stoma closures due to fear of increased morbidity in older patients. Age has also been associated with increased morbidity and mortality after stoma closure,[17] although such an association could not be found in another study.[18] Fear of increased comorbidity in the elderly and patients' refusals to undergo more surgery might have resulted in the decreased frequency of stoma reversal in these patients. Additionally, patients with stomas who have had postoperative complications, such as infection, had their stomas reversed less frequently. By contrast, perioperative complications, such as bleeding, which were not perceived directly by the patient, could not be identified as a risk factor. Generally secondary stomas, which were created after complications, were less frequently removed. A reason for this could be that older patients and patients who have had postoperative complications after initial (curative) treatment of rectal cancer are more willing to accept a stoma than other patients. We have previously reported a similar finding for faecal incontinence:[19] a substantial proportion of patients treated with a low anterior resection had faecal incontinence. In our opinion, few secondary stomas are constructed in such patients, suggesting that patients accept faecal incontinence.

Other risk factors for not having stomas reversed might not be related directly to patients' or surgeons' motivation, but more related to surgical problems. The decision to create an end ileostomy or colostomy instead of a diverting stoma also highlights expected technical difficulties in creating a primary anastomosis. Accordingly, reversal of an end ileostomy or colostomy is less probable, and so these stomas are often permanent. Obviously, the development of a recurrence shifted treatment focus to a palliative setting in which the aim was to optimise quality of life and to prevent unnecessary surgery. Remarkably, other factors that might be associated with technical difficulties in reversing stomas, such as distance and TNM stage, were not identified as limiting factors in this study.

Although a side-to-end or colonic pouch anastomosis is recommended as an attempt to minimise the risk of anastomotic dehiscence,[20] an end-to-end anastomosis was created in only 107 of 924 patients. We previously showed that anastomosis type was not an independent factor for anastomotic dehiscence in the TME trial.[3] Similarly, in this study, the type of anastomosis was not associated with the necessity to create a secondary stoma (data not shown). However, the type of anastomosis and the decision

to create a stoma were left to the surgeons' discretion, which might have resulted in biased data. Preoperative radiotherapy was a risk factor for secondary stomas becoming permanent, but not for primary stomas -suggesting that the combination of preoperative radiotherapy and serious complications after primary surgery that necessitated a secondary stoma resulted in fewer stoma reversals.

The large difference in stoma reversal in patients having primary and secondary stomas might raise the question of whether all patients should have a stoma in the first operation. However, based on the findings in this study, we would not support this idea. Almost one-third of all patients treated with a low anterior resection in the rectal cancer TME trial never had a stoma. Also, only about 81% of stomas were reversed. Furthermore, the stomas themselves and second procedures to reverse stomas are associated with morbidity and mortality. Patients' preferences, morbidity -which sometimes even results in a new stoma- and mortality were not included in this analysis. Moreover, the costs associated with the stoma and its reversal are a burden for health-care systems.

A temporary diverting stoma is often created in an attempt to decrease the risk of clinical anastomotic leakage. However, data in published studies are inconsistent about the relation between defunctioning stoma usage and prevention of anastomotic leakage after surgical treatment of rectal cancer. Some studies have reported no significant difference in the frequency of anastomotic leakage if a diverting stoma is created,[1,2] whereas we and others have found a decreased incidence of clinically evident leakage.[3,21,22] More consistent evidence is available that suggests a diverting stoma reduces the clinical consequences of anastomotic leakage, for example, the finding that fewer patients with diverting stomas than those without such stomas need surgery when anastomotic leakage occurs.[1-3]

Other factors might support the argument for stoma construction. In the TME trial, patients with a stoma were more satisfied with their bowel function than those without a stoma (174 of 235 [74%] versus 199 of 362 [55%], $P < 0.001$).[19] Others, however, reported lower quality of life with a stoma.[7] Obviously, patients' preferences and sociodemographical characteristics, such as the availability of good stoma care and cultural acceptance of stomas, will decide the individual patient's quality of life to a certain extent. Eventually, the loss of quality of life due to a stoma needs to be counterbalanced with the patient's comorbidity, which might limit successful stoma reversal. Only in this way can an individualised decision be made on stoma reversal.

Our results do not suggest that the unreversed stomas should not have been made, but show that temporary stomas should be created as if they are permanent stomas; correct placement that helps life-long handling is of utmost importance. In an attempt to lower clinical anastomotic leakage and variability in surgical management of patients with rectal cancer, a working party has been developed in the Netherlands. This party will document prospectively surgical procedures in colorectal surgery in the Netherlands,

including the incidence of stoma formation and anastomotic leakage. This prospective audit should provide data that will guide surgeons towards a more standardised and evidence-based approach in stoma formation. Only then can treatment be further tailored to the individual patient with rectal cancer.

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