Transanal endoscopic microsurgery in rectal cancer

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CHAPTER 3

Transanal endoscopic microsurgery versus total mesorectal excision of T1 rectal adenocarcinomas with curative intention

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INTRODUCTION

In rectal cancer, total mesorectal excision (TME) is the gold standard. This optimised and standardized surgical technique, combined with preoperative radiotherapy, has improved outcome. [1, 2] Counterbalancing this improvement is the high rate of (severe) morbidity and even mortality. [3-6] Local excision of rectal adenocarcinomas is a much safer procedure and transanal excision (TE) is the technique most commonly used. However, transanal endoscopic microsurgery (TEM) is nowadays considered the method of choice. [7] Only in T1 rectal adenocarcinomas TEM is considered adequate if curation is intended.

Quirke showed that standardized processing of resection specimens for rectal adenocarcinomas revealed a higher percentage of incomplete excision, which significantly correlated to an increased risk on both local and distant recurrences and on decreased survival. [8] This resulted in the concept of TME and adjustment of histological examination of the specimen. Although TEM is being implemented in several national guidelines for T1 rectal adenocarcinomas, the role of pathological assessment of the specimen has been limited mainly to basic histopathologic criteria. [9] Excision margin status after both TE and TEM, has been demonstrated to be a predictor for local recurrence, however, this has only been shown in case studies. [10-12] Most studies comparing outcome after local excision for T1 rectal adenocarcinomas with TME do not focus on excision margin status. Moreover, standardized pathological assessment lacks, and this may have caused the varying outcome. [13-18]

As the incidence of T1 and T2 rectal cancer will most likely increase in the near future, because of introduction of population-based screening programs, this warrants a thorough analysis of oncologic outcome following TEM for T1 rectal adenocarcinomas. [19] The aim of this prospective study was to compare the impact of margin status, assessed with standardized pathology after TEM and TME for T1 rectal cancer.

PATIENTS AND METHODS

The Dutch TME trial started in 1996, and 1530 Dutch patients with mobile rectal adenocarcinomas were randomly assigned either to short term preoperative radiotherapy followed by TME or to TME alone. The study protocol included standardized processing of the specimen, described in detail elsewhere. [20] Only T1 rectal adenocarcinomas were considered eligible for this study. In the IJsselland hospital, a tertiary referral centre for TEM and participating in the Dutch TME trial, patients with T1 rectal adenocarcinomas were also deemed feasible for TEM. Selection was based upon the same study protocol, with complementary rigid rectoscopy and endorectal ultrasound (ERUS). Eligibility for the current study was in accordance with the Dutch TME trial protocol with some exceptions. Patients who underwent TME and had synchronous distant metastases, only discovered at laparotomy, were not excluded, because if TEM had

been therapy of choice, metastases would not have been disclosed. Furthermore, patients who previously underwent pelvic operations or resections of left-sided large bowel or rectum were not excluded. For TEM patients World Health Organisation Performance Score (WPS) was not a criterion (in the Dutch TME trial WPS limited to 2 or less was an inclusion criterion). TEM patients were only eligible if there were no signs of lymph node metastases on MRI and/or ERUS and excision margins were negative.

If T1 rectal cancer only emerged at histology of the excised specimen following TEM, patients were offered follow-up only or immediate additional TME. In case excision margins were positive following TEM, patients also were offered immediate TME or intensive follow up after repeat TEM, in order to obtain negative excision margins. The TEM technique is described in detail elsewhere. [21] Tumor size after TEM as well as TME was assigned as the largest diameter. TEM specimens were pinned on a corkboard before fixation. Fixation, serial transverse slicing, embedding, staining, sectioning and examination of the specimens were done according to descriptions detailed elsewhere. [8, 20]

Both groups were followed according to the Dutch TME trial protocol. Moreover, rigid rectoscopy and endorectal ultrasound were performed at every visit except for the colonoscopy visit in the TEM patients. Endpoints studied were morbidity, mortality, margin status, local recurrence, distant recurrence, overall survival and cancer specific survival. Local recurrence was defined as evidence of a tumor within the lesser pelvis. Distant recurrence was defined as evidence of a tumor in any other area. In all patients in this study informed consent had been obtained.

Data were analyzed with SPSS statistical software (version 14.0 for Windows, SPSS, Chicago). Chi-square tests were used to compare proportions. Mann-Whitney tests were used to compare continue variables. Univariate analyses of cumulative probability of local and distal recurrence, as well as overall and cancer-specific survival were carried out by the Kaplan-Meier method, and the evaluation of differences between the two groups was performed with the log-rank test. The Cox proportional hazards model was used to calculate hazard ratios and 95% confidence intervals in the univariate and multivariate analyses. A two-sided p-value of 0.05 or less indicated statistical significance.

RESULTS

Of the 1530 Dutch patients entered in the TME trial, a total of 76 patients with T1 rectal adenocarcinomas were present (5%). One patient was excluded because of a second malignancy. Seventy-five patients were eligible for this study. In 1 patient excision margin was positive (1.3%). In 86 patients TEM was performed for T1 rectal adenocarcinomas. In 5 patients excision margins were positive (5.8%). Six patients, including 2 patients with incomplete margins, chose for additional TME and were excluded. Eighty patients were entered in the study, including the remaining 3 patients with initial positive excision margins. TEM was repeated in these patients,

no residual tumor tissue was found and excision margin was considered negative. Patient, tumor and operation characteristics are depicted in Table 1. Both groups were comparable, except that TEM patients had higher WPS pre-operatively ($p < 0.001$).

TEM proved to be safer compared to TME reflected by operating time, blood loss, hospital stay, morbidity, re-operations and stoma formation (all $p < 0.001$). Complications after TEM were present in 5 patients (5.8%). In three patients a urinary tract infection occurred, and one patient with a cardiac history suffered from cardiac pain and dysrythmia leading to medical treatment on the coronary care unit. In one patient, following a segmental resection, anastomotic stenosis with disabling complaints occurred. Hegar dilation proved unsuccesful, necessitating renewed TEM for correction. Histopathologic evaluation only showed fibrosis. After TME, 48 patients suffered from 72 complications (64%). The majority was severe, necessitating re-operations in 13.3% of all patients (anastomotic leakage 6.9%, re-bleeding 9.3% and ileus 6.7%). In 58 patients a primary anastomosis was constructed, with a diverting ileostomy in 44. In two patients a Hartmann's procedure was performed and in 15 patients an abdomino-perineal excision. A stoma was constructed during re-operation in another 2 patients. Ten out of 44 diverting ileostomies have never been reversed and in 5 patients after reversal again a stoma was constructed resulting in 43% of the TME patients having a definite stoma at the time of evaluation. Following TEM, five (6%) patients had a colostomy, because of a local recurrence necessitating salvage surgery. (Table 2) There was no mortality after TEM, and after TME 4% of patients died ($p = 0.07$). Median follow-up after TEM was 42 months (range, 1-127) and after TME 84 months (range, 30-115). Local recurrence rate was 24% after TEM compared to 0% after TME patients ($p < 0.0001$; Figure 1). Details of local and distant recurrences following TEM and TME are given in Table 2. After TEM 15 local recurrences were observed of which 13 were diagnosed within the first 18 months (86.7%). Median time to local recurrence was 10 months (range, 5-50). In 12 patients (80%) salvage surgery was performed, limited to TME, without mortality and without renewed local recurrences.

Distant metastases developed in 6 patients. None of the TEM patients without local recurrence developed distant metastases or died cancer-related. After TME 6 patients developed distant recurrences. Overall survival was 75% after TEM and 77% after TME ($p = 0.9$; Figure 2). Cancer specific survival was 90% after TEM and 87% after TME ($p = 0.5$; Figure 3). In regard to both overall survival and cancer-specific survival, neither surgical technique used, age, gender or WPS were risk factors.

DISCUSSION

After TME for rectal adenocarcinomas, morbidity varies from 10 to 62%, and mortality varies from 3.3 to 25.8%. [1-6] Morbidity is often severe, especially if preoperative radiotherapy is added. Long-term functional outcome is poor, having major impact on quality of life. Reduced

Table 1. Patient-, tumor- and operation characteristics of the patients enrolled in the study.

	TEM	TME	
Number of patients	80	75	
Age (yrs)	71 (44-92)	67 (48-83)	ns
Female: male	32: 48	27: 48	ns
WPS 0: 1: 2/3	42: 18: 20	60: 14: 0	p < 0.001
Tumor diameter (cm)	3.0 (0.5-13)	2.5 (0.5-7.5)	ns
Tumor distance from dentate line (cm)	8.0 (0-15)	7.0 (0-15)	
0-5	17	14	ns
5-10	44	34	
10-15	18	25	
Operating time (min)	40 (10-125)	180 (70-360)	p < 0.001
Blood loss (ml)	0 (0-250)	1000 (50-15000)	p < 0.001
Hospital stay (days)	3 (2-13)	14 (7-121)	p < 0.001
Morbidity (%)	5 (5.1)	48 (64)	
-surgical complications			
-abdominal wound dehiscence	0	1 (1.3)	
-perineal wound dehiscence	0	1 (1.3)	
-intestinal necrosis	0	1 (1.3)	
-ileus	0	5 (6.7)	
-anastomotic leakage	0	4 (6.9)	
-re-bleeding	0	7 (9.3)	
-other	1 (1.2)	3 (4)	
-infections			
-abdominal wound	0	8 (10.7)	
-perineal wound	0	2 (2.7)	
-urinary tract	3 (3.4)	10 (13.3)	All p < 0.001
-intra-abdominal abscess	0	2 (2.6)	
-sepsis	0	4 (5.3)	
-other	0	2 (2.6)	
-febris e causa ignota	0	1 (1.3)	
-general complications			
-venous thrombosis	0	1 (1.3)	
-pulmonary	0	6 (8)	
-embolism	0	3 (4)	
-cardiac	1 (1.2)	2 (2.6)	
-other	0	7 (9.3)	
-delirium	0	1 (1.3)	
-multi organ failure	0	1 (1.3)	
Re-operations (%)	1 (1.2)	10 (13.3)	p < 0.001
Stoma formation (%)	0	61 (81.3)	
-at first operation	0	59 (78.7)	p < 0.001
-at re-operation	0	2 (2.6)	
Mortality (%)	0	3 (4.0)	P = 0.07

WPS = World Health Organization Performance Score; data given are numbers or medians with ranges between parentheses. Morbidity = number of patients with one or more complications.

morbidity and mortality is often the motive for local excision in rectal adenocarcinomas. Morbidity is predominantly minor, occasionally leading to re-operation and formation of a stoma and without functional disorders having impact on quality of life. [22] Morbidity and mortality in

Table 2. Characteristics of local and distant recurrences after TEM or TME for T1 rectal cancer.

Primary surgery	LR	LR-free interval (months)	Salvage therapy	pTNM (salvage surgery)	R0 vs. other	DR	Interval (months)	FU (months)	Survival status
TEM	Yes	5	LAR	pT3N0	R0	-	-	16	Alive
TEM	Yes	5	APR	pT2N0	R0	-	-	34	DNCR
TEM	Yes	6	APR	pT2N0	R0	-	-	33	DNCR
TEM	Yes	7	LAR	pT2N0	R0	-	-	69	Alive
TEM	Yes	10	APR	pT3N0	R0	-	-	69	Alive
TEM	Yes	10	LAR	pT3N0	R0	-	-	16	Alive
TEM	Yes	11	LAR	pT3N1	R0	-	-	19	Alive
TEM	Yes	12	LAR	pT3N0	R0	-	-	20	Alive
TEM	Yes	40	CTh,APR	pT0N0	R0	-	-	49	Alive
TEM	Yes	5	LAR	pT3N0	R0	Liver,lung	5	13	DCR
TEM	Yes	12	LAR, CTh	pT3N2	R1	Liver	27	39	DCR
TEM	Yes	19	Hp	pT2N0	R0	Liver	19	40	DCR
TEM	Yes	5	None	cT3	-	Liver	5	15	DCR
TEM	Yes	20	CTh	cT4	-	Liver	22	30	DCR
TEM	Yes	50	CTh	cT4	-	Lung	50	52	Alive
TME	No	-	-	-	-	Skin	5	7	DCR
TME	No	-	-	-	-	Peritoneal	0	20	DCR
TME	No	-	-	-	-	Liver, bone	28	29	DCR
TME	No	-	-	-	-	Liver, lung, brain	29	34	DCR
TME	No	-	-	-	-	Liver	23	39	DCR
TME	No	-	-	-	-	Lung	16	57	DCR

APR= abdomino-perineal resection; AR= anterior resection; Cth= chemotherapy; Hp= Hartmann's procedure; - = not applicable; p= pathological; c= clinical; R0= microscopic radical; R1= microscopic irradical; DCR= died cancer-related; DNCR= died not cancer-related.

this study are in line with literature and again demonstrate the safety of TEM and the consequences of TME. This is even reinforced by the fact TEM patients had worse WPS compared to TME patients.

However, morbidity should not be the main endpoint measured when choosing between two operation techniques for rectal adenocarcinomas. After local excision of rectal adenocarcinomas, outcome varies strikingly, even when limited to T1 rectal adenocarcinomas. As a result, it is looked at with caution and most authors emphasize its adoption only in carefully selected patients. [23]

Microscopic radical excision is a prerequisite to diminish recurrences after TME for rectal cancer. [8] Standardized histological examination revealed a higher percentage of incomplete resection with significant correlation to an increased risk on both local and distant recurrences and on decreased survival. This resulted in the concept of TME and adjustment of histological examination of the TME specimen. Excision margin status after local excision is also a significant prognostic factor. In 1990 Graham concluded that after local excision positive excision margins were

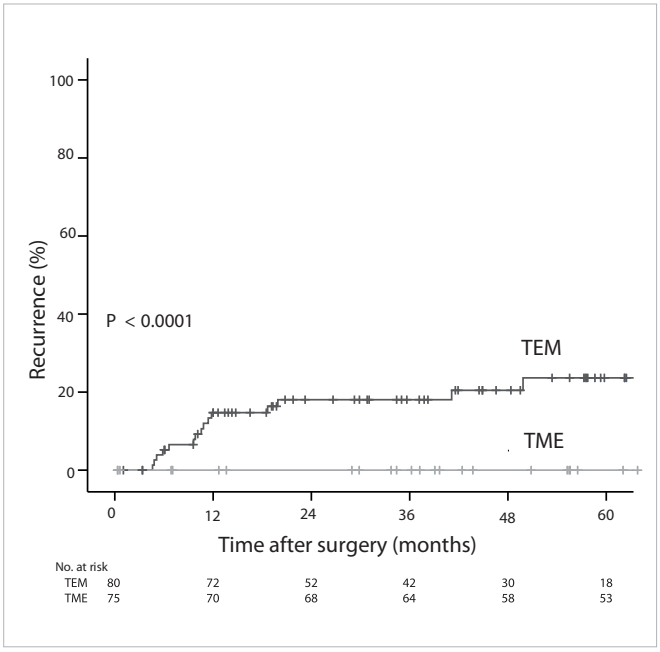

Figure 1. Local recurrence rates after TEM and TME for T1 rectal cancer.

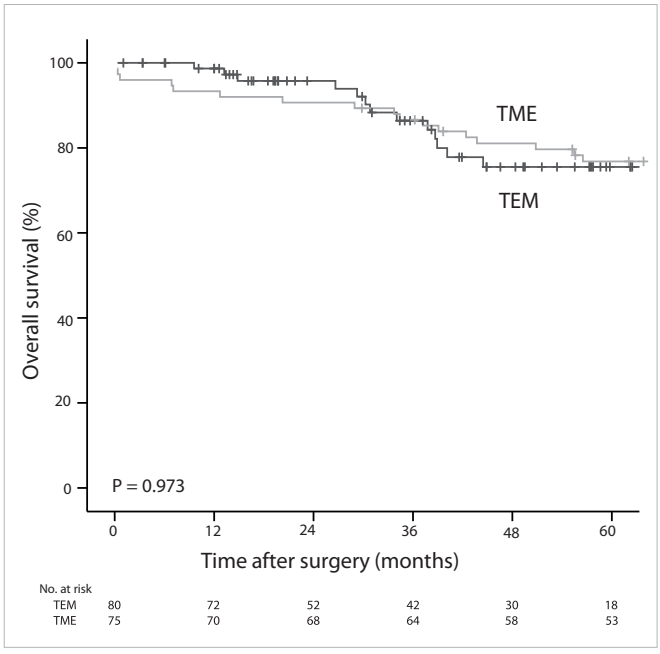

Figure 2. Overall survival after TEM and TME for T1 rectal cancer.

associated with increased local recurrence rates and decreased survival. [11] Also in case studies on TEM, excision margin status has proven to be a predictor for recurrence. [10, 12] However, comparative studies, focusing on TE or TEM and TME for T1 rectal adenocarcinomas, are subject to possible bias as patient selection criteria and (neo-) adjuvant strategies are not elucidated. Furthermore, the method of histological investigation remains unclear and the presence of incomplete or doubtful margins was not an exclusion criterion.

Unprotocollized histopathologic evaluation leads to underestimation of positive excision margins. [12, 24] With TEM, even with standardized histopathologic evaluation, negative excision margins can be obtained in over 90% of specimens. [25] This may be one of the most contributing factors to improved oncologic outcome following TEM, compared to after TE. [16] This hypothesis warranted the current study.

Regarding survival, we found that if negative excision margins are confirmed by thorough, protocollized histopathologic evaluation, no differences between TEM or TME occurred. This is in line with all other comparative studies of TEM and TME. [16-18] Following TME never a local recurrence occurred, and after TEM, despite a 100% negative excision margin status, local recurrence rate was 24%. This is higher than the 4.1 to 10% observed by other TEM centres and even higher to the 4 to 18% after TE. A possible explanation for this result has yet to be clarified.

Focussing on prevention of local recurrence after local excision of rectal cancer is caused by the fact that local recurrences after radical excision are difficult to treat with many renewed local recurrences and poor prognosis. [26] Literature on salvage surgery for local recurrence after local excision is limited. Most series lack both an adequate number of patients undergoing salvage procedures and adequate follow-up to allow proper analysis. It only concerns local recurrences following TE as technique used. [27, 28] Disease free survival rates following salvage procedures range between 30-58%. Moreover, to obtain a R0 resection, extended resections are required, often involving multivisceral excision. Results after salvage surgery are worse compared to after immediate salvage surgery in case of adverse histopathologic features. [10, 24, 29] Salvage surgery in case of a local recurrence following TEM seems amenable to most patients, with often a possible R0 resection. In this study, of 15 local recurrences 12 were amenable to salvage surgery (80%), of which in 11 (92%) a R0 resection could be obtained by performing a TME. Maybe the elegant and precise technique of TEM is the key element for these results. Or perhaps it was the early detection due to the intensive follow-up. About 90 per cent of recurrences were diagnosed within 18 months. Moreover, about 25% of the local recurrences were diagnosed only with endorectal ultrasound as described by others. [30]

In conclusion, TEM is a safer procedure than TME for T1 rectal adenocarcinomas. Despite obtaining a negative excision margin status, local recurrence rate is still unacceptably high and efforts should be made to investigate prognostic factors. Survival rates are comparable after TEM and TME, although long-term results have to be awaited. Salvage surgery for local recurrences is possible, however future studies are needed to spare as many patients as possible from the adverse effects of TME.

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