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DOI:10.1007/s00464-013-2911-x

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UNIVERSITÀ DEGLI STUDI DI TORINO

DOI 10.1007/S00464-013-2911-x

Previous transanal endoscopic microsurgery for rectal cancer represents a risk factor for an increased abdominoperineal resection rate

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Abstract
Background
Transanal endoscopic microsurgery (TEM) represents a surgical option in the treatment of selected early rectal cancers. However, when definitive histopathology shows negative prognostic factors, rectal resection with total mesorectal excision (TME) is recommended to reduce the risk of recurrence. No studies have yet analyzed the impact of previous TEM on the perioperative outcomes of immediate laparoscopic TME (LTME) for rectal cancer. The aim of this study was to evaluate the perioperative outcomes of LTME after TEM for rectal cancer.
Methods
This study was a retrospective analysis of a prospective database. All patients undergoing LTME within 8 weeks after full-thickness TEM for rectal cancer between January 2001 and December 2011 were included. Each patient was matched on the basis of demographic and clinical characteristics with two patients undergoing primary LTME for rectal cancer during the same period. Age, gender, body mass index, tumor distance from the anal verge, tumor size, neoadjuvant chemoradiation, previous TEM, rectal wall defect size created during TEM, and intraoperative complications were included in a multivariate analysis to identify risk factors for abdominoperineal resection (APR).
Results
A total of 17 patients undergoing TEM followed by LTME were compared to 34 patients undergoing primary LTME. Mean operative time of LTME after TEM was significantly higher (206 vs. 188 min, P = 0.025). APR was more frequently performed after TEM [odds ratio (OR) 5.25, P = 0.028] and in male patients (OR 9.04, P = 0.034). On multivariate analysis, a previous TEM was the only independent predictor of APR (OR 4.13, P = 0.046). The incidence and severity of postoperative complications were similar in both groups. Mesorectum integrity was complete in all cases.
Conclusions
LTME after TEM is a challenging procedure, with a significantly higher risk of APR compared to primary LTME. Future improvements in preoperative patient selection for TEM are needed to reduce this risk.
Keywords
Abdominoperineal resection Coloanal anastomosis Laparoscopy Rectal cancer Total mesorectal excision Transanal endoscopic microsurgery

Rectal resection combined with total mesorectal excision (TME) [*1*] is the gold standard in the surgical treatment of rectal cancer [*2*]. However, TME is associated with significant postoperative mortality and morbidity [*3*], including sexual and urinary dysfunction [*4–7*] and stoma-related complications [*8*, *9*]. A temporary diverting stoma is created in 50–100 % of sphincter-saving procedures [*10*], while an abdominoperineal resection (APR) is still performed in up to 30 % of cases [*11*].

Conceived almost 30 years ago by Buess et al. [*12*] as a technique for full-thickness excision of large rectal adenomas [*13*], transanal endoscopic microsurgery (TEM) has been more recently proposed for treatment of selected early rectal cancer [*14*, *15*]. Compared to abdominal surgery, TEM offers the advantage of combining a minimally invasive approach with the evident benefits in terms of postoperative morbidity and recovery, long-term functional outcomes, and quality of life [*16*].

When unfavorable pathologic features, including depth of tumor invasion beyond pT1 sm1, poorly differentiated tumor grading, lymphovascular invasion, or positive resection margins, are found in the TEM specimen, rectal resection with TME is recommended in order to minimize the risk of recurrence [*14*, *17–23*].

Although several series have looked at the oncologic results of rectal resection combined with TME after TEM [*15*, *17–23*], only few studies have focused on the short-term outcomes, reporting disappointing results in terms of morbidity [*24*] as well as high APR rates [*18*, *20*, *25*]. However, potential risk factors for APR after a full-thickness TEM for rectal cancer have never been investigated.

The aim of this study was to evaluate the influence of a previous TEM on the short-term outcomes of immediate laparoscopic TME (LTME) for rectal cancer.

Materials and methods

All patients undergoing LTME within 8 weeks after a full-thickness TEM between January 2001 and December 2011 were included in the study (TEM group).

Indications for TEM were lesions located in the mid and lower rectum with a preoperative histologic diagnosis of adenoma, staged uT0 at the preoperative transanal endoscopic ultrasound (EUS), and judged unsuitable for endoscopic removal, as well as malignant rectal lesions staged uT1N0 at the EUS. Rectal cancers staged uT2N0 were considered for TEM only in patients who refused abdominal surgery or who were medically unfit for major surgery because of severe comorbidities.

The preoperative patient assessment before TEM has been previously described [*15*].

The procedure was performed with the patient under general anesthesia in all cases. Before 2008 we routinely used the original Richard Wolf (Knittlingen, Germany) TEM equipment. Afterward, we performed TEM with transanal endoscopic operation instrumentation (Karl Storz GmbH, Tuttlingen, Germany). In all cases a full-thickness excision was made on the rectal wall to the perirectal fatty tissue, and the wound was closed with one or more running sutures secured with silver clips, according to previously described standard techniques [*12*, *26*].

The decision to carry out a LTME after TEM was taken by a multidisciplinary setting including the surgeon, medical oncologist, radiotherapist, and patient, on the basis of the following histologic criteria: depth of tumor invasion >T1sm1, lymphovascular or perineural invasion, poor differentiation, mucinous type disease, or incomplete resection.

The preoperative assessment before TME included a computed tomographic scan of the chest and upper abdomen, and pelvic magnetic resonance imaging.

Each patient in the TEM group was matched on the basis of gender, age, American Society of Anesthesiologists (ASA) score, body mass index (BMI), tumor size, and tumor distance from the anal verge, with two similar patients who underwent primary LTME for rectal cancer during the same period (no-TEM group) at our institution.

All patients in both groups were preoperatively considered for a sphincter-saving procedure.

All laparoscopic procedures were performed with the patient under general anesthesia, following the same oncologic principles as described by MacFarlane et al. [*1*] Our technique of LTME has been previously described [*27*]. In case of a sphincter-saving procedure, the anastomosis was usually fashioned with a mechanical circular stapler. When the distal clearance of the inferior margin of the tumor was at the level of the surgical anal canal, or in a narrow pelvis where a transverse stapled section was sometimes impossible, the technique of choice was a hand-sewn transanal coloanal anastomosis. An ileostomy was performed in all cases.

The decision to perform a laparoscopic APR was made on the basis of intraoperative findings precluding a safe and radical dissection, such as large amount of fibrotic tissue involving the surgical planes at the level of the pelvic floor in the TEM group, or when the neoplasm involved the anatomic anal canal or was fixed to the pelvic floor in the no-TEM group.
Clinical analyzed parameters included patient characteristics (age, gender, BMI, ASA score, distance of the tumor from the anal verge, neoadjuvant chemoradiation), operative variables, and short-term outcomes. Operative variables examined included duration of surgery (from skin incision to the application of dressings), estimated blood loss, intraoperative complication, conversion rate to open surgery, and type of procedure performed. Short-term outcomes included postoperative morbidity according to the Dindo classification [*28*], 30-day mortality, and length of hospital stay.
Quantitative data are provided as mean and standard deviation. Proportions were compared by the χ^2 test or Fisher's exact test, where appropriate. Student's t test was used to compare normally distributed variables. The following variables were analyzed as risk factors for APR: age, gender, BMI, tumor distance from the anal verge, size of the tumor, neoadjuvant chemoradiation, previous TEM, size of the wall defect created during TEM, and intraoperative complications. Statistical analysis of the risk factors was carried out by univariate and multivariate regression. A level of 5 % was set as the criterion for statistical significance. The variables potentially related to the risk of APR with $P \leq 0.200$ in the univariate analysis were entered into a multivariate analysis. The data were collected in an Excel spreadsheet. The statistical analysis was performed by SPSS software, version 19 (SPSS, Chicago, IL, USA).

Results

Between January 2001 and December 2011, a total of 350 patients underwent TEM. Among them, 17 patients underwent LTME within 8 weeks after the TEM procedure (TEM group).
Preoperative indication for TEM was a large sessile adenoma with high grade dysplasia in 7 cases, and an adenocarcinoma in 10 cases, 6 staged uT1 N0, and 4 uT2 N0 in patients who initially refused abdominal surgery (Table 1).
Table 1
Agreement between pre- and postoperative T staging in patients undergoing transanal endoscopic microsurgery

Histology	**Preoperative stage by EUS**	**Postoperative pathologic stage[a]**				
		pT1 sm2	**pT1 sm3**	**pT2**	**pT3**	**Total**
Adenoma	uT0–T1		1	6		7
Carcinoma	uT1	1	1	3		5
	uT2			1	4	5
Total		1	2	10[b]	4[c]	17

EUS endoscopic ultrasound
[a]pT1 sm1 not included because it was not present
[b]Two with lateral positive margins
[c]One with positive deep margin
Intraoperative peritoneal opening during TEM occurred in 2 cases (11.8 %), both sutured by TEM technique.
The incidence of 30-day postoperative morbidity was 11.8 %: 1 case of suture dehiscence with rectal abscess and 1 case of rectal bleeding, both conservatively managed.
Table 1 summarizes the pathologic evaluation of the TEM specimens.
No suspected lymph node involvement or distant metastases were recorded at the staging evaluation before LTME that was performed at a median time of 40 (range 20–56) days from TEM.
The clinical features of the 34 no-TEM patients are reported in Table 2.

Table 2

Patient characteristics

Characteristic	TEM (n = 17)	No TEM (n = 34)	P
Male gender n (%)	11 (64.7)	20 (58.8)	0.918
Age (years): mean ± SD	61.1 ± 11.1	62.6 ± 11.6	0.661
BMI (kg/m^2): mean ± SD	24.8 ± 4.3	24.1 ± 3.4	0.529
ASA score n (%)			
I	5 (29.4)	8 (47.1)	0.363
II	6 (47.1)	21 (41.2)	0.919
III	4 (23.5)	5 (11.7)	0.493
IV	0	0	
Tumor size (cm): mean ± SD	3.7 ± 1.2	4.2 ± 1.8	0.332
Distance from anal verge (cm): mean ± SD	5.4 ± 2.2	5.5 ± 1.9	0.867
≤5 cm from anal verge n (%)	10 (58.8)	19 (55.9)	0.920
Preoperative chemoradiotherapy n (%)	0	4 (11.8)	0.288
Rectal wall defect size (cm^2): mean ± SD	26.6 ± 10.7	NA	

TEM transanal endoscopic microsurgery, BMI body mass index, ASA American Society of Anesthesiologists, NA not applicable

The mean operative time was significantly higher in the TEM group compared to the no-TEM group (206 vs. 188 min, P = 0.025). No statistically significant differences were observed in terms of operative time between the TEM patients who underwent LTME within (7 cases) or over (10 cases) 30 days (217 ± 33.8 vs. 200 ± 55.9 min, P = 0.486).

Intraoperative complications occurred in 1 case (5.9 %) in the TEM group and in 3 cases (8.8 %) in the no-TEM group (P = 0.854). Interestingly, no intraoperative complications occurred in both patients who experienced a surgical complication after the previous TEM.

Conversion rate to open surgery was 5.9 % in both groups (P = 0.528).

A significantly higher rate of APR was observed in the TEM group (41.2 vs. 11.7 %, P = 0.028) (Table 3), with no statistically significant differences among the subgroup of patients treated within 30 days (3 of 7, 42.9 %) or more than 30 days after TEM (4 of 10, 40 %) (P = 0.702).

Table 3

Operative results

Characteristic	TEM (n = 17)	No TEM (n = 34)	P
Type of procedure			
APR n (%)	7 (41.2)	4 (11.7)	0.028
SSP n (%)	10 (58.8)	30 (88.3)	
AR	7	22	
CAA	3	8	
Loop ileostomy n (%)	10 (100)	30 (100)	1
Operative time (min): mean ± SD	206 ± 42.0	188.1 ± 12.6	0.025
Intraoperative blood loss (ml): mean ± SD	328.1 ± 643.9	163.4 ± 92.8	0.146

Characteristic	TEM	No TEM	P
	(n = 17)	(n = 34)	
Intraoperative blood transfusion n (%)	1 (5.9)	0	0.718
Intraoperative complications n (%)	1 (5.9)	3 (8.8)	0.854
Bleeding	1	2	
Stapler misfiring	–	1	
Conversion to open surgery n (%)	1 (5.9)	2 (5.9)	0.528
Obesity	1	–	
Bleeding	–	1	
Stapler misfiring	–	1	

TEM transanal endoscopic microsurgery, APR abdominoperineal resection, SSP sphincter-saving procedure, AR anterior resection, CAA coloanal anastomosis

Severe local inflammation and tissue retraction precluding a safe distal dissection from the abdomen were the reasons for APR in 5 patients in the TEM group. In addition, 2 patients who had previously undergone a TEM procedure for uT2 rectal cancer located close to the sphincter had a APR because of positive margins detected at the pathologic evaluation of the TEM specimen.

Table 4 shows the univariate analysis for risk of APR. Of all the variables taken into consideration, a previous TEM ($P = 0.028$) and gender ($P = 0.034$) demonstrated statistical significance, while tumor distance from the anal verge and BMI showed a statistical trend ($P = 0.088$, and $P = 0.165$, respectively). The multivariate analysis of the risk of APR is also shown in Table 4 and indicates a previous TEM to be the only independent predictor ($P = 0.046$).

Table 4

Risk factors for abdominoperineal resection

Variable	n	Univariate		Multivariate	
		OR (95 % CI)	P	OR (95 % CI)	P
Age					
≤63 years	26	1	0.451		
>63 years	25	2.14 (0.54–8.48)			
Gender					
Female	20	1	0.034	1	0.108
Male	31	9.04 (1.05–77.46)		8.12 (0.88–69.11)	
BMI					
<25 kg/m^2	30	1	0.165	1	0.254
≥25 kg/m^2	21	3.25 (0.81–13.04)		2.57 (0.70–11.86)	
Distance from anal verge					
>5 cm	22	1	0.088	1	0.116
≤5 cm	29	4.50 (0.86–23.49)		3.89 (0.81–20.23)	
Tumor size					
<4 cm	23	1	0.734		
≥4 cm	28	1.58 (0.40–6.27)			
Neoadjuvant chemoradiation					

Variable	n	Univariate		Multivariate	
		OR (95 % CI)	P	OR (95 % CI)	P
Yes	4	1	0.646		
No	47	1.23 (0.12–13.14)			
Previous TEM					
No	34	1	0.028	1	0.046
Yes	17	5.25 (1.26–21.75)		4.13 (1.09–15.55)	
Wall defect size created during TEM					
<28 cm^2	8	1	0.839		
≥28 cm^2	9	1.33 (0.19–9.31)			
Intraoperative complications					
No	47	1	0.646		
Yes	4	1.23 (0.12–13.14)			

OR odds ratio, CI confidence interval, BMI body mass index, TEM transanal endoscopic microsurgery

Incidence (11.8 vs. 23.5 %, P = 0.463) and severity of postoperative complications were similar in both groups (Table 5). In the TEM group, further surgery was required in 1 case for ileostomy stricture. In the no-TEM group, an ileostomy revision was performed to treat an ileostomy stricture, while a percutaneous drainage of a pelvic collection was necessary in 3 patients. There was no postoperative 30-day mortality in both groups.

Table 5

Short-term outcomes

Characteristic	TEM (n = 17)	No TEM (n = 34)	P
30-day morbidity[a] n (%)	2 (11.8)	8 (23.5)	0.463
Grade			
I	0	0	
II	1	4	0.654
III	1	4	0.654
IIIa	–	3	
IIIb	1	1	
IV	0	0	
V	0	0	
30-day mortality n (%)	0	0	1
Hospital stay (days): mean ± SD	10.9 ± 4.9	11.1 ± 4.6	0.887
Readmission n (%)	0	0	1

SD standard deviation, TEM transanal endoscopic microsurgery

[a]According to Dindo classification

In the TEM group, the histologic examination of the surgical specimen revealed scattered cancer cells in the muscular layer in 3 cases (3 pT2 N0) and in the perirectal fat in 1 case (1 pT3 N0), whereas lymph node metastases were observed in 4 cases (1 pT0 N1, 2 pT2 N1, 1 pT3 N1). No residual neoplasm was observed in the remnant 9 cases (52.9 %).

The pathologic findings in both groups are listed in Table 6.
Table 6
Pathologic findings

Characteristic	**TEM**	**No TEM**	**P**
	(n = 17)	**(n = 34)**	
Tumor stage n (%)			
No residual cancer	9 (52.9)	2 (5.9)	<0.001
I	3 (17.6)	12 (35.3)	0.328
II	1 (5.9)	8 (23.5)	0.241
III	4 (23.6)	12 (35.3)	0.594
Mesorectum integrity n (%)	17 (100)	34 (100	1
Length of specimen (cm): mean ± SD	25.8 ± 12.5	26.3 ± 7.2	0.857
No. of lymph nodes: mean ± SD	10.8 ± 5.4	12.4 ± 4.7	0.281
Distal/circumferential margin involvement n (%)	0	0	1

SD standard deviation, TEM transanal endoscopic microsurgery

Discussion

The depth of submucosal invasion represents one of the most important risk factors for local recurrence and poor survival in patients undergoing transanal excision for early rectal cancer [*14*, *15*]. Even though EUS appears to be the most accurate preoperative diagnostic tool for investigating tumor invasion of the rectal wall, the discrepancy between preoperative EUS and definitive pathologic tumor staging is high [*29–31*]. In addition, rectal lesions diagnosed as benign at the preoperative biopsy harbor cancer cells in 10–20 % of cases [*32–34*]. This high histologic discrepancy rate led us to not take into consideration the preoperative histology when performing a TEM, instead offering to all patients an appropriate full-thickness excision instead of a partial-wall piecemeal resection as performed by flexible endoscopy and conventional transanal excision [*26*].
An accurate selection of patients who could be considered cured by the precise local excision that TEM offers would avoid the need to resort to further abdominal surgery to accomplish treatment. Although long-term outcomes of immediate rectal resection with TME after transanal excision are documented, only few authors have addressed the impact of full-thickness transanal excision on TME for rectal cancer [*18*, *20*, *24*, *25*] in terms of intraoperative and early postoperative outcomes.
Hahnloser et al. [*18*] reported a retrospective review of 52 locally excised rectal cancers that were followed by radical open surgery (24 APR and 28 low anterior resections) within 29 days. The overall morbidity rate after open surgery was 13.5 %. The median hospitalization was 12 (range 4–48) days. The authors concluded that local excision of rectal tumors followed by radical surgery within 30 days does not compromise short-term outcomes compared to primary radical surgery.
Piessen et al. [*24*] published a case-matched study on 14 patients undergoing full-thickness transanal excision with the use of long retractors followed by open TME within 4 months compared to 25 patients who had undergone primary open TME for lower rectal cancer. The operative time did not significantly differ between the two groups. No differences were reported in terms of type of procedures, with an APR performed in 4 patients (28.6 %) after transanal excision and in 7 patients (28 %) of the control group.
To our knowledge, the only study that specifically compared the short-term outcomes of early TME after TME versus primary TME was the case-matched study by Levic et al. [*25*]. They compared 25 patients who underwent TME after TEM (sTME group) to 25 patients who were treated by primary TME (pTME group). A full-thickness TEM was performed in all but 3 patients (88.9 %). The

median time from TEM to sTME was 37 (range 14–90) days. Six patients (24 %) in the sTME group and 2 (8.3 %) in the pTME group underwent a laparoscopic TME. No significant differences were reported in terms of intraoperative outcomes. The APR rate was 44 % in both groups. The 30-day mortality rate was similar between the two groups (8 vs. 0 %, P = 0.49). On the basis of these results, the authors concluded that no differences were found in short-term outcome between the two groups. However, the interpretation of these results may be biased by the fact that (1) patients in the two groups were matched according to several variables, including the type of surgical procedure performed, (2) some patients had undergone previous partial thickness excision, (3) some patients underwent laparoscopic TME while other underwent open TME, and (4) no details were provided regarding the management of the rectal wall defect during the TEM procedure.

In order to better clarify the impact of full-thickness TEM on short-term outcomes of LTME, we compared 17 patients treated by LTME after a full-thickness TEM to 34 well-matched patients who underwent primary LTME for extraperitoneal rectal cancer. Although operative time was significantly longer after a previous TEM, LTME after TEM was demonstrated to be a safe procedure, with similar intraoperative complication rates, the same conversion rate to open surgery, and a postoperative morbidity rate that compared favorably with primary TME.

Nevertheless, the present study shows a severe drawback of LTME after TEM: a significant increase in the APR rate (41.2 vs. 11.7 %, P = 0.028). Our results are consistent with those published by Hahnloser et al. [*18*], Levic et al. [*25*], who reported a 46 and 44 % rate of APR after full-thickness transanal excision, respectively.

Unlike the above-mentioned studies, we investigated several variables as potential risk factors for APR. A previous TEM (P = 0.028) and male gender (P = 0.034) demonstrated a statistically significant role, while tumor distance from the anal verge and BMI showed a statistical trend (P = 0.088, and P = 0.165, respectively) at the univariate analysis. By multivariate analysis, a previous TEM was the only independent predictor for APR (P = 0.046).

In our opinion, the main concern when performing a TME after a full-thickness TEM is that the rectal wall and perirectal fat might be affected by a fibrotic scar, making dissection of the correct planes down to the pelvic floor much more challenging even under a clear and magnified laparoscopic view, and sometimes making a low colorectal or a transanal coloanal anastomosis technically impossible.

Concerning the most appropriate timing for a TME after transanal local excision, limited data are available in the literature. The median time between full-thickness excision and TME ranges between 7 and 37 days [*18*, *25*]. In our series, patients underwent LTME after a median time of 40 days, and no differences were observed in terms of intraoperative and postoperative outcomes between the group of patients operated within or over 30 days. More recently, rectal resection combined with TME within a week after local excision has been proposed. However, the results of large studies are needed to draw any definitive conclusion regarding the influence of local inflammation on surgical outcomes in this subgroup of patients.

One controversial technical aspect of full-thickness TEM concerns the management of the rectal wall defect. Even though no strong evidence from the literature supports the closure of the defect, the suture of the wall may represent one of the technical advantages of TEM compared to classical transanal excision and could be key to reducing the risks of local infection and sepsis, even in case of later TME.

Significantly lower rates of complete mesorectal excision after full-thickness excision have been reported [*24*]. The potential mechanisms of damage to the mesorectum include the traction on the rectum during the mobilization by open surgery that may cause a tear in those patients undergoing previous full-thickness excision. We did not find significant differences between the two groups in terms of mesorectal excision quality. This is probably due to the clearer visualization achieved with laparoscopy compared to open surgery and the reduced risk of adhesions resulting from inflammation and infection that may occur outside the mesorectum when the rectal wall defect is sutured.

Finally, more than 50 % of patients undergoing TME after TEM were overtreated in our series because no residual cancer cells in the rectal wall and in the perirectal lymph nodes were found. On the other hand, the remaining patients had definitive correct staging of the disease after TME. These results reflect the still relatively low accuracy of EUS and magnetic resonance imaging in the evaluation of the rectal wall invasion and lymph node involvement before and after local excision, even in high-volume centers. Studies that investigate other staging modalities, such as positron emission tomography and sentinel node biopsy, are awaited to better identify the subgroup of patients that could avoid an unnecessary TME after TEM, with the increased risk of an APR.
In conclusion the present study demonstrated that LTME after full-thickness TEM is a challenging procedure, even though it is not associated with increased morbidity, increased mortality, or poor quality of mesorectal excision. However, a previous TEM represents a risk factor for an increased rate of APR. These conclusions may be biased by the small numbers and the retrospective design of the study and should be therefore be considered with caution. However, we think that this study clearly demonstrates the need for an accurate selection of patients before TEM.

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