Does peritoneal perforation affect short-and long term outcomes after transanal endoscopic microsurgery?

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Abstract
Background
Peritoneal perforation (PP) is frequently reported as a complication of transanal endoscopic microsurgery (TEM). Nevertheless, these concerns have only rarely been addressed in the literature, with no mention of the long-term oncologic consequences of PP.
Methods
A prospective database was analyzed with the intent to evaluate the influence of PP on the short- and long-term outcomes for patients undergoing TEM.
Results
Peritoneal perforation occurred in 28 (5.8 %) of 481 patients who underwent TEM for a rectal neoplasm. The conversion rate to abdominal surgery was 10.7 % (3/28). All the conversions occurred during the first 100 TEM procedures (3/100 vs 0/381; $p = 0.007$). The postoperative morbidity rate was 3.6 % (1/28), and the 30-day mortality was nil. Compared with the group of patients who had no peritoneal perforation, the PP group showed a significantly longer operating time (120 vs 60 min; $p < 0.001$) and a significantly longer hospital stay (6 vs 4 days; $p = 0.003$). Nevertheless, the global morbidity rate and the type of complications according to Dindo's classification were similar. In the multivariate analysis, the only independent predictor of PP was tumor distance from the anal verge ($p = 0.010$). During a median follow-up period of 48 months (range, 12–150 months), no liver or peritoneal metastases were detected in 13 patients with rectal cancer.
Conclusions
Peritoneal perforation does not seem to affect short-term or oncologic outcomes for patients submitted to TEM with full-thickness resection for upper rectum neoplasms. The use of TEM to resect rectal lesions involving the intraperitoneal rectum may therefore represent an intermediate step toward the development of transrectal natural orifice translumenal endoscopic surgery (NOTES) techniques.
Keywords
Full-thickness excision Morbidity Peritoneal perforation Rectal neoplasm Transanal endoscopic microsurgery

Routine excision of the intact mesorectum for cancer of the mid and low rectum has resulted in the lowest incidence of local recurrences ever reported [*1*]. Nevertheless, total mesorectal excision (TME) is associated with high rates of genitourinary dysfunctions [*2*–*5*], anastomotic leakage [*6*], and long-term functional bowel discomfort [*7*].

Proposed by Buess et al. [*8*, *9*] nearly 30 years ago, transanal endoscopic microsurgery (TEM) combines the advantages of minimally invasive local treatment with large full-thickness local resection and improved visualization. It rapidly became the standard of treatment for large rectal adenomas [*10*, *11*].

More recently, TEM has become a viable alternative in the management of selected early rectal cancer [*12*, *13*]. Combined with neoadjuvant treatment, TEM is progressively extending its indications because of its mild impact on patient recovery [*14*].

Originally, TEM was devised to remove extraperitoneal lesions. A peritoneal perforation (PP) was frequently reported as a complication of TEM, and tumors of the upper rectum, particularly when located on the anterior or lateral portion of the rectum, were considered a contraindication to TEM [*15–18*]. Peritoneal perforation makes it difficult or impossible to maintain a stable pneumorectum, often creating a formidable technical challenge for the surgeon. Furthermore, insufflation of carbon dioxide (CO_2) from the rectum into the peritoneum is considered a potential cause of clinical and oncologic complications. Nevertheless, these concerns have only rarely been addressed in the literature, with no mention of the long-term oncologic consequences of PP.

However, the recent introduction of natural orifice translumenal endoscopic surgery (NOTES) techniques as means of access to the peritoneum through the rectum has aroused controversy about the safety and efficacy of such a proposal [*19*]. We believe that with an analysis of the clinical consequences resulting from PP during TEM, some points in the debate could be clarified and that the current technical and clinical limitations of local excision of rectal neoplasms by TEM could be elucidated.

Thus, this study aimed to evaluate the influence of PP on the short- and long-term outcomes for patients undergoing TEM and to compare our results with evidence from the literature.

Material and methods

This study was a retrospective analysis of a prospective database created in January 1993. Patients in whom a PP occurred during a TEM procedure were identified from the data on the operative report. The indications for TEM were benign rectal lesions judged unsuitable for endoscopic removal, early rectal cancer, and invasive or metastatic rectal carcinoma treated with palliative intent.

A rigid rectoscopy was routinely performed to locate the lesion along the circumference and to measure its distance from the anal verge. The preoperative workup and surgical technique have been described previously [*20*].

The procedure was performed with the patient under general anesthesia in all cases. Until 2008, we routinely used Richard Wolf (Knittingen, Germany) TEM equipment conceived by Buess [*8*]. Afterward, we used transanal endoscopic operation (TEO) instrumentation (Karl Storz GmbH, Tuttlingen, Germany).

When the original Richard Wolf TEM equipment was used, patient positioning was varied to keep the lesion in the inferior part of the surgical field. Since we began to use the TEO instrumentarium, the patient ordinarily is placed supine due to the particular shape of the TEO rectoscope tip, which allows tissue handling over the entire surgical field, including its superior quadrant. Nevertheless, for treating lesions in the upper rectum and large neoplasms involving the anterior rectal wall, which are at risk for PP, the patient is placed prone to reduce gas losses and to help to maintain a stable pneumorectum if a PP occurs.

Since 2008, when we began to use the TEO, and with increasing surgical experience, a more liberal policy toward lesions located higher has been adopted. In all cases in this series, 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 dedicated silver clips (Richard Wolf). The same technique was used to close the peritoneum and to reconstruct the rectum if PP occurred.

We analyzed patient characteristics, operative data, and the short- and long-term outcomes of two groups: the no peritoneal perforation (NPP) group and the PP group. The patient characteristics were age, gender, and preoperative indication for TEM. The operative data included length of the operative procedure and rate of conversion to abdominal surgery. The short-term outcomes were defined as postoperative morbidity according to Dindo's classification [*21*], 30-day mortality, and length of hospital stay. The long-term outcomes were defined as the local tumor recurrence rate and the incidence of distant metastases.

Follow-up assessment involved digital examination, rectoscopy, and tumor marker testing (in case of malignant lesions) every 3 months for the first 2 years, then every 6 months thereafter. A full colonoscopy was performed at 12, 36, and 60 months. In case of malignancy in NPP group and in all cases of PP, abdominal and pelvic computed tomography (CT) scans also were obtained at 6, 12, and 24 months for early detection of peritoneal seeding (of adenomatous or cancer tissue) and liver metastases.

Quantitative data are given as median and range. Chi-square tests were used to compare proportions. The Student's t-test was used to compare normally distributed variables.

A stepwise logistic regression analysis was performed to identify factors predictive of PP. The variables potentially related to PP with a p value of 0.200 or less in the univariate analysis were entered into a multivariate analysis. The predictor variables used were patient age, gender, tumor diameter, tumor distance from the anal verge, and tumor localization on the rectal wall. A level of 5 % was set as the criterion for statistical significance. The data were entered on an Excel spreadsheet. The statistical analysis was performed using SPSS Software (SPSS Inc., Chicago, IL, USA).

Results

Between January 1993 and December 2010, 481 patients (289 males and 192 females; median age, 68 years; range, 13–94 years) underwent TEM. Perforation of the peritoneum occurred in 28 cases (5.8 %, PP group), with 14 cases (50 %) involving men (median age, 70.5 years; range, 41–94 years). Peritoneal perforation was experienced by 15 (8.5 %) of 177 patients who had surgery in the preceding 4 years versus 13 of 304 patients (4.3 %) who underwent surgery earlier (p = 0.090). Table 1 reports the patients' characteristics and perioperative data.

Table 1

Patient characteristics

	PP (n = 28)	**NPP (n = 453)**	**p value**
Male gender: n (%)	14 (50)	275 (60.7)	0.356
Median age: years (range)	70.5 (41–94)	67 (13–91)	0.366
Median distance from anal verge: cm (range)	9 (6–13)	7 (2–15)	<0.001
Median tumor diameter: cm (range)	5 (3–10)	4 (3–12)	0.372
Median operative time: min (range)	120 (35–320)	60 (15–235)	<0.001
	120 (35–240)[a]		<0.001
Postoperative complications: n (%)	1 (3.6)	28 (6.2)	0.879
Median hospital stay: days (range)	6 (4–14)	4 (2–20)	0.003

PP peritoneal perforation group, NPP no peritoneal perforation group

[a]Three cases of conversion to abdominal surgery were excluded

The preoperative indications were 23 adenomas and 5 carcinomas (4 uT1N0 and 1 uT2N0). The median diameter of the rectal lesion was 5 cm (range, 3–10 cm). The distance between the lower edge of the neoplasm and the anal verge ranged between 6 and 13 cm (median, 9 cm).

In the PP group, the neoplasm was located on the anterior wall in ten patients (35.7 %), the lateral wall in nine patients (32.1 %), and the posterior wall in four patients (14.3 %). It was circumferential in five patients (17.9 %).

In 25 cases (89.3 %), the PP was sutured by TEM. In 3 cases (10.7 %), PP necessitated conversion to laparoscopic (2 cases) or open (1 case) anterior resection. All conversions occurred during the first 100 TEM procedures (3/100 vs 0/381; p = 0.007). The median operating time was 120 min (range, 35–320 min). Excluding the 3 cases converted to abdominal surgery, the operating time ranged from 35 to 240 min (median, 120 min). No intraoperative blood transfusions were required.

We observed one case of postoperative complications (3.6 %) involving a rectovesical fistula that required subsequent abdominoperineal resection. No 30-day mortality was observed. The median hospital stay was 6 days (range, 4–14 days).

Compared with the NPP group, the PP patients showed a significantly longer operating time (120 vs 60 min; $p < 0.001$) and a significantly longer hospital stay (6 vs 4 days; $p = 0.003$). Nevertheless, the global morbidity rate and type of complications were similar in the two groups (Tables 1, 2). Histologic examination of the surgical specimens confirmed an adenoma in 15 cases (53.6 %), with invaded margins in 3 cases (20 %). The rate of margin invasion was higher than that of the 246 patients with adenoma in the NPP group, but the difference was not significant (20 vs 10.2 %; $p = 0.444$). A rectal cancer was diagnosed in the remaining 13 patients (46.4 %): 7 pT1, 5 pT2, and 1 pT3. Histology detected no margin invasion in this group. In two cases, the margin clearance was less than 1 mm. The resection was judged to be full thickness in all cases, and no specimen fragmentation occurred.

Table 2

Postoperative morbidity according to Dindo's classification

	PP (n = 28)	**NPP (n = 453)**	**p value**
	n (%)	**n (%)**	
Postoperative complications	1 (3.6)	28 (6.2)	0.879
Grade 1	0	6 (1.3)	0.781
Grade 2	0	9 (1.9)	0.999
Grade 3	1 (3.6)	13 (2.9)	0.716
3a	0	6 (1.3)	0.781
3b	1 (3.6)	7 (1.5)	0.934
Grade 4	0	0	
Grade 5	0	0	

PP peritoneal perforation group, NPP no peritoneal perforation group

Table 3 shows the univariate analysis for risk of PP. Of all the variables taken into consideration, tumor distance from the anal verge ($p = 0.005$), tumor diameter ($p = 0.038$), and tumor location on the entire circumference ($p < 0.001$) demonstrated a statistically significant role. The multivariate analysis of the risk for PP, also shown in Table 3, indicates tumor distance from the anal verge as a unique independent predictor ($p = 0.010$).

Table 3

Risk factors for peritoneal perforation

Variable	**n = 481**	**Univariate analysis**		**Multivariate analysis**	
		OR (95% CI)	**p value[a]**	**OR (95% CI)**	**P value[a]**
Age (years)					
<68	240	1	0.538		
≥68	241	1.371 (0.637–2.944)			
Gender					
Female	192	1	0.356		
Male	289	1.544 (0.717–3.305)			
Tumor diameter (cm)					
<4	271	1	0.038	1	0.235
≥4	210	2.446 (1.106–5.423)		1.835 (0.801–3.276)	

Variable	n = 481	Univariate analysis		Multivariate analysis	
		OR (95% CI)	p value[a]	OR (95% CI)	P value[a]
Distance from the anal verge (cm)					
<7	198	1	0.005	1	0.010
≥7	283	4.494 (1.532–13.151)		4.276 (1.488–12.266)	
Rectal wall					
Posterior	181	1		1	
Lateral	119	2.766 (0.792–9.663)	0.180	1.833 (0.668–8.011)	0.254
Anterior	169	3.382 (0.987–10.699)	0.053	2.108 (0.880–9.049)	0.105
Circumferential	12	31.607 (14.131–70.668)	<0.001	20.014 (0.910–55.467)	0.082

OR odds ratio, CI confidence interval

[a]Stepwise logistic regression analysis

During a median follow-up period of 72 months (range, 12–216 months), no patient with adenoma was lost to follow-up evaluation. At this writing, all patients are disease free with no sign of local recurrence or intraperitoneal seeding of adenomatous tissue.

During a median follow-up period of 48 months (range, 12–150 months), no patient with rectal cancer was lost to follow-up evaluation. The follow-up period was longer than 3 years for 69% (9/13) of the patients, and longer than 4 years for 46.1 % (6/13) of the patients. At this writing, all the patients with a pT1 rectal cancer are disease free. Among the pT2 patients, two patients underwent postoperative chemoradiotherapy, two patients had abdominal surgery (laparoscopic TME), and all are disease free at this writing. Neither patient submitted to TME had any intraoperative evidence of liver metastases or peritoneal carcinomatosis. Their postoperative course was uneventful. One pT2 patient refused any treatment after TEM, had a local recurrence after 13 months, underwent chemoradiotherapy, and died of lung metastases 42 months after TEM. The uT2 patient who underwent TEM with palliative intent because of severe cardiac comorbidities and had a postoperative diagnosis of pT3 rectal cancer locally relapsed after 4 months, refused further treatment, and died of lung metastases 12 months after TEM. During the follow-up period, no liver or peritoneal metastases were detected in any of the patients who had neoplasms treated with radical intent in the PP group (Table 4).

Table 4

Oncologic results in patients with peritoneal perforation (PP)

	Adenoma (n = 15)	Carcinoma (n = 13)	
		pT1 (n = 7)	pT2–3 (n = 6)
Median follow-up: months (range)	72 (12–216)	48 (12–150)	
Local recurrence: n (%)	0	0	2 (33)
Peritoneal seeding: n (%)	0	0	0
Liver/peritoneal metastases: n (%)	NA	0	0
Lung metastases: n (%)	NA	0	2 (33)

NA not applicable

Discussion

Although PP is frequently considered a complication of TEM [*18*, *22–34*], few studies have addressed this concern specifically to date [*35–37*]. With a view to clarify the short- and long-term

implications of PP during TEM, we analyzed our series of 28 PP cases and compared the results with the published data.

Globally, 17 studies [*18*, *22–37*] have reported the number of PP occurrences during TEM, showing a mean PP rate of 4.8 % (148/3100) (Table 5). The reported rate of PP varies widely between 0 and 32.3 %, reflecting the fact that a submucosal dissection may be preferred over a full-thickness excision in cases at risk for PP. However, due to the discrepancy existing between pre- and postoperative histology and staging, our policy is to offer an appropriate full-thickness excision, even in the case of anterior wall lesions, to obtain a complete specimen and to allow a correct pT staging.

Table 5

Peritoneal perforation during transanal endoscopic microsurgery (TEM): review of the literature

Author (year)	**No. of TEMs**	**No. of PPs (%)**	**No. of conversions (%)**	**No. of stomas (%)**	**Postoperative morbidity (%)**	**Median postoperative stay (days)**	**Local recurrence (%)**	**Distant metastasis (%)**
Demartines et al [*18*]	50	2 (4)	1 (50)	1 (50)	NA	NA	NA	NA
Cocilovo et al [*22*]	56	1 (1.8)	1 (100)	0	NA	NA	NA	NA
Dafnis et al [*23*]	58	1 (1.7)	1 (100)	0	NA	NA	NA	NA
Meng et al [*24*]	31	2 (6.5)	0	0	0	NA	NA	NA
Palma et al [*25*]	100	8 (8)	1 (12.5)	0	0	NA	NA	NA
Platell et al (2004) [*26*]	113	3 (2.7)	0	0	0	NA	NA	NA
Whitehouse et al [*27*]	146	20 (13.6)	0	6 (30)	0	4.5	NA	NA
Ganai et al (2006) [*28*]	144	9 (6)	0	0	NA	NA	NA	NA
Zacharakis et al [*29*]	76	3 (3.9)	2 (66.6)	1 (33.3)	NA	NA	NA	NA
Serra-Aracil et al [*30*]	96	1 (1)	0	0	0	NA	NA	NA
Ramirez et al [*31*]	173	7 (4)	1 (14.3)	0	NA	NA	NA	NA
de Graaf et al [*32*]	353	28 (8.7)	0	0	0	NA	NA	NA
Guerrieri et al [*33*]	402	13 (3.2)	0	0	NA	NA	NA	NA
Léonard et al [*34*]	123	2 (1.6)	1 (0.8)	0	0	NA	NA	NA
Gavagan et al [*35*]	34	11 (32.3)	0	0	45	NA	NA	NA

Author (year)	No. of TEMs	No. of PPs (%)	No. of conversions (%)	No. of stomas (%)	Postoperative morbidity (%)	Median postoperative stay (days)	Local recurrence (%)	Distant metastasis (%)
Ramwell et al [*36*]	257	15 (5.8)	5 (33.3)	6 (40)	27	8	NA	NA
Baatrup et al [*37*]	888	22 (2.5)	0	0	4.5	7	10	14
Global	3100	148 (4.8)	13 (8.8)	14 (9.4)				
Current series	481	28 (5.8)	3 (10.7)	1 (3.6)	3.6	6	7	0

PP peritoneal perforation, NA not available

To date, no study has assessed the risk factors for PP. In our series, in the multivariate analysis, a tumor distance of 7 cm or more from the anal verge was the unique independent predictor of PP, whereas the tumor location on the anterior rectal wall or on the entire circumference showed a statistical trend toward an increased risk for PP ($p = 0.105$ and $p = 0.082$, respectively).

We observed a trend toward a higher rate of PP in our series over the last 4 years compared with the preceding period (8.5 vs 4.3 %, $p = 0.090$), reflecting the extension of indications to larger and more proximal lesions. The extension of indications for TEM in our series derived not only from increased surgical experience and dexterity but also from the use of the TEO instrument (Karl Storz GmbH), which allows manipulation and suturing of the rectal wall on a 360° surface, thanks to the particular shape of the rectoscope tip.

Concerning intraoperative outcomes, we found that PP was associated with a significantly longer operative time, mainly related to the proximal location of the lesion and closure of the defect, which are technically challenging, rather than to the learning curve of the surgeon. The learning curve and the case volume of the surgical centre are two main factors that can influence the treatment strategy to be adopted when PP occurs. It is noteworthy that conversion to laparotomy was reported in 50–100 % of PP cases only in a series with fewer than 100 patients, whereas it ranged between 0 and 40 % in larger series (Table 5).

These data confirm the results obtained by Salm et al. [*38*] in a survey of 1,900 TEM procedures performed in Germany in 1994. They reported that the rate of conversion to laparotomy during TEM for all causes, including inadvertent transrectal opening of the peritoneal cavity, decreased with experience from 11.6 % (1 to 10 TEM procedures) to 1.2 % (>100 TEM procedures). In our series, three conversions were performed during the first 100 TEMs compared with 0/381 in more recent years ($p = 0.007$), confirming the crucial role that experience plays in the management of PP.

Only a few studies [*24–27*, *30*, *32*, *34–37*] have reported a specific postoperative morbidity rate (range, 0–27 %). No cases of pelvic sepsis or infectious complications after PP have been reported. In our series, we observed no statistically significant difference in the overall complication rate (3.6 vs 6.2 %) or the degree of severity according to Dindo's classification between the PP and NPP groups (3.6 % of grade 3b complications in the PP group vs 1.5 % in the NPP group). A longer hospital stay (6 vs 4 days) was observed for the PP patients, mainly due to a more conservative postoperative management.

This study had some limitations, including the retrospective design and the relatively small sample size of the PP group.

However, according to the results of our series, TEM seems not to be associated with a higher risk for pelvic infections or other complications when a PP occurs. Furthermore, the low morbidity rate and the absence of pelvic infectious complications in our series demonstrate that a nonfunctioning stoma generally is not necessary in high-volume institutions (Table 5).

To our knowledge, the only study to evaluate the oncologic results of patients undergoing TEM with an inadvertent PP was that by Baatrup et al. [*37*], who reported 22 perforations into the peritoneal cavity during a total of 888 TEM procedures for rectal cancer performed at four European centers. During a median follow-up period of 36 months (range, 3–164 months), local recurrence developed in one pT1 patient (7 %) and in one pT2 patient (25 %), whereas distant metastases were detected in three patients.

In our series, at this writing, during a median follow-up period longer than 4 years, all the patients who experienced a PP during TEM for adenoma or pT1 rectal cancer are disease free, with no sign of intraperitoneal seeding of adenomatous or cancer tissue. Four pT2 patients who underwent laparoscopic TME or chemoradiotherapy and remain disease free. Local recurrence developed only in the pT2 and pT3 patients who did not receive further treatment after TEM. No patient with PP has experienced liver or peritoneal metastases. Therefore, although a limited number of patients were evaluated and in a retrospective way, PP does not seem to correlate with an increased risk of local recurrence or liver/peritoneal metastasis.

In the NOTES era, transrectal access to the peritoneal cavity has been variously described [*39–42*], taking into consideration feasibility and risk for fecal contamination of the abdomen. In an experimental trial, Denk et al. [*43*] demonstrated the feasibility of some transrectal NOTES procedures (diagnostic peritoneoscopy, liver biopsy, sigmoid resection) using TEM instrumentation, suggesting TEM as a portal for NOTES.

The experience gained in handling PP with TEM and the good results of the current series could enhance confidence in the management of such situations. The use of TEM to resect rectal lesions involving the intraperitoneal rectum may therefore represent an intermediate step toward the development of transrectal NOTES techniques [*19*]. However, we believe that the application of the transanal approach to NOTES may be limited in the future to selected centers with tremendous experience in TEM to minimize the risks of conversion to abdominal surgery, stoma, and perioperative complications. From analysis of the published data, we found that a stoma was more frequently performed (30–50 %) in series with fewer than 100 TEM procedures [*18*, *29*] or by surgeons not particularly skilled in endoscopic closure of the peritoneal defect [*36*] (Table 5).

In our series, no stoma was performed intraoperatively for PP. Only one patient (3.6 %) had a stoma for treatment of a postoperative rectovesical fistula after a TEM procedure for a lesion on the anterior rectal wall.

In conclusion, evidence from the literature and our personal experience suggest that when TEM is performed at expert centers, indications for TEM can be safely extended to selected lesions in the upper rectum with no further risk of conversion to abdominal surgery or a nonfunctioning stoma and with good early and late oncologic results.

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