Recurrence after transanal endoscopic microsurgery for large rectal adenomas

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Abstract
Background
Transanal endoscopic microsurgery (TEM) has revolutionized the technique and outcome of transanal surgery, becoming the standard of treatment for large sessile rectal adenomas. Nevertheless, only a few studies have evaluated the risk factors for local recurrence in order to recommend a "tailored" approach. The aim of this study was to identify predictor variables for recurrence after TEM to treat rectal adenoma.
Methods
This study is a retrospective analysis of a prospective database of patients treated for large sessile rectal adenomas by TEM at our institution, with a minimum follow-up of 12 months. Age, gender, tumor diameter, distance from the anal verge, degree of dysplasia, histology, and margin involvement were investigated.
Results
Between January 1993 and July 2010, 293 patients with a rectal adenoma ≥3 cm underwent TEM. Postoperative morbidity rate was 7.2 % (21/293) and there was no 30-day mortality. Over a median follow-up period of 110 (range = 12–216) months, 13 patients (5.6 %) were diagnosed with local recurrence. The median time to recurrence was 10 (range = 4–33) months, with 76.9 % of recurrences detected within 12 months after TEM. At univariate analysis, tumor diameter ($p = 0.007$), and positive margins ($p < 0.001$) were shown to be significant risk factors, while multivariate analysis indicated the presence of positive margins as the only independent predictor of recurrence ($p = 0.003$).
Conclusions
TEM provides excellent oncological outcomes in the treatment of large sessile benign rectal lesions, assuring a minimal risk of resection margin infiltration at pathology examination, which represents the only risk factor for recurrence.
Keywords
Transanal endoscopic microsurgery Rectal adenoma Recurrence Risk factors

Rectal cancer is a common disease in Western countries, with increased incidence in the elderly, males, and obese people [*1*, *2*]. Dysplasia precedes the occurrence of invasive rectal cancer [*3*, *4*]. Endoscopic detection and removal of rectal adenomas prevents the development of rectal cancer, significantly contributing to the "cure" of the disease [*5*, *6*]. Complete resection of the precancerous lesion is mandatory to prevent recurrence. However, for large sessile lesions, endoscopic mucosal resection (EMR) techniques may be inadequate to achieve a documented en bloc resection, and piecemeal resection has been reported to have a recurrence rate as high as 11.2 % [*7*]. On the other hand, endoscopic submucosal dissection (ESD) still remains a technical challenge without clear advantages compared to EMR in terms of achieving R0 resections [*8–11*]. Therefore, transanal surgery is mostly indicated.

While transanal local excision allows comfortable access only to the distal rectum, which explains in part the high rates of local recurrence [*12*, *13*], transanal endoscopic microsurgery (TEM), proposed almost 30 years ago by Buess [*14*, *15*], has the advantages of minimally invasive local treatment [*16*, *17*], allowing large full-thickness local resection under improved visualization conditions.
The aim of this study was to identify risk factors associated with local recurrence after TEM for treating large sessile rectal adenomas.

Materials and methods

This study was a retrospective analysis of a prospective database created in January 1993. All patients with a preoperative histological diagnosis of adenoma of the rectum, categorized as stage uT0 by preoperative transanal endoscopic ultrasound (EUS), who were treated by TEM between January 1993 and July 2010 were included.
All sessile lesions judged unsuitable for endoscopic removal and located within 12 cm from the anal verge on the anterior wall and 15 cm on the lateral and posterior walls, which corresponds to the estimated limits of the insertion of the peritoneum, were considered suitable for TEM. The distance from the anal verge and the location along the circumference were assessed by rigid endoscopy.
The preoperative workup included clinical evaluation, total colonoscopy to exclude further colonic polyps, EUS to assess the rectal wall grade of invasion, and tumor markers such as carcinoembryonic antigen (CEA) and cancer antigen 19–9. All patients ate a low-fiber diet the week before TEM and a rectal enema was performed 12 and 2 h preoperatively. Intravenous antibiotics such as second-generation cephalosporin and metronidazole were administered short-term before introduction of the rectoscope for prophylaxis.
The procedure was performed with the patient under general anesthesia in most cases, and spinal anesthesia was used when general anesthesia was contraindicated. Up to 2008 we routinely used the original Richard Wolf (Knittingen, Germany) TEM equipment; we then replaced it with the TEO (Transanal Endoscopic Operation) instrumentation by Karl Storz GmbH (Tuttlingen, Germany). Following the standard technique described by Buess [*14*], 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. Postoperative analgesia was intravenous paracetamol for 24 h. All patients had a urinary catheter in place at the time of surgery, which was removed 48 h after surgery for patients who had an anterior wall dissection, and 24 h after surgery for all other cases.
The TEM specimen was pinned to a corkboard before fixation in 10 % formal saline in order to preserve the margins of the normal mucosa surrounding the tumor. A single pathologist, who is expert in the field of colorectal tumors and TEM, evaluated all specimens. Tumor size was measured macroscopically and reported as the maximum diameter. Resection was considered complete when the specimen was in one piece and histological assessment confirmed clear margins (>1 mm). If the adenoma was excised intact but adenomatous tissue was found within 1 mm of the specimen's resection margin, the tumor was classified as macroscopically intact with microscopically involved resection margins.
We entered into the database and analyzed patient characteristics, lesion location, operative data, perioperative complications, definitive histology, and follow-up data. Patient characteristics included age, gender, and preoperative indication for TEM. Operative data examined included operating time and conversion rate to abdominal surgery. Pathological examination included histopathological definition, degree of dysplasia, and longitudinal and radial margins of excision. Short-term outcomes included postoperative morbidity, 30-day mortality, and length of hospital stay. Long-term outcome included local recurrence. Local recurrence was defined as any recurrence diagnosed endoscopically and confirmed by biopsy. Follow-up consisted of digital examination at

1 month and rigid rectoscopy every 3 months for the first year and then according to standard post-polypectomy policies.

Statistical analysis

Quantitative data are given as the median and range. χ^2 tests were used to compare proportions. Patients with a minimum follow-up of 12 months were included in the analysis of the long-term results. A level of 5 % was set as the criterion for statistical significance. A multinomial logistic regression analysis was performed to identify predictive factors of recurrence using both forward and backward stepwise selection. Recurrence-free survival was regarded as a continuous variable. Unifactorial Cox proportional hazards methodology identified single risk factors associated with recurrence. Patients' observations were censored on the date of the last examination. Explanatory variables with univariable $p \leq 0.200$ were included in a multivariable analysis. This significance level was chosen so as to incorporate all potentially important predictor variables in the final modeling process. All sets of variables were analyzed. Each single-outcome variable was analyzed using multinomial logistic regression to correlate it with the predictor variables. The predictor variables used were age, gender, tumor diameter, distance from the anal verge, degree of dysplasia, histology, and margins. The significant statistical correlation was expressed in terms of regression coefficient and relative p values. A level of 5 % was set as the criterion for statistical significance. The data were collected in an Excel spreadsheet (Microsoft Corp., Redmond, WA, USA). The statistical analysis was performed using Systat software (Systat Software, Inc., Chicago, IL, USA).

Results

Between January 1993 and July 2010, 293 patients [176 males and 117 females, median age = 68 (range = 30–88) years] with a large rectal adenoma, staged as uT0 by preoperative EUS, underwent TEM. Main symptoms at presentation were rectal bleeding in 177 (60.4 %) cases, tenesmus in 53 (18.1 %) cases, and mucorrhea in 24 (8.2 %) cases. In 39 (13.3 %) cases, diagnosis was achieved during a screening examination.

The distance between the lower edge of the neoplasm and the anal verge ranged between 3 and 15 (median = 7) cm. The neoplasm was located on the anterior wall of the rectum in 95 (32.4 %) patients, on the posterior wall in 102 (34.8 %), and on the lateral wall in 84 (28.7 %). It was semicircumferential or circumferential in 8 (2.7 %) and 4 (1.4 %) cases, respectively.

Intraoperative results

The median operation time was 60 (range = 15–240) minutes. Inadvertent opening of the peritoneum occurred in 15 (5.1 %) cases: 13 (86.7 %) were treated with direct suturing by TEM and two (13.3 %) required conversion to laparoscopic (one case) or laparotomic (one case) anterior resection at the beginning of our experience with performing TEM. The overall conversion rate to abdominal surgery was 0.7 %. No intraoperative blood transfusion was required.

Postoperative results

We observed a postoperative morbidity rate of 7.2 % (21/293), consisting of 11 cases of rectal bleeding, 5 cases of suture dehiscence, 3 rectovaginal fistulas, 1 rectovesical fistula, and 1 acute urinary retention. Rectal bleeding was treated with blood transfusion in nine cases, endoscopic hemostasis in one case, and transrectal packing in one case. Suture dehiscence was treated

conservatively (antibiotics and total parenteral nutrition) in all cases. A transvaginal surgical suture solved the three cases of rectovaginal fistula, while the patient with a rectovesical fistula required abdominal surgery consisting of abdominoperineal resection. A temporary urinary catheter was placed to solve the case of urinary retention. There was no 30-day mortality. The median length of hospital stay was 3.5 (range = 2–14) days.

Pathology results

The median diameter of the rectal lesion was 5 (range = 3–12) cm. Histological examination of the surgical specimens confirmed an adenoma in 233 (79.5 %) patients: 108 cases with low-grade dysplasia (LGD) and 125 with high-grade dysplasia (HGD). There were 48 tubular adenomas, 54 villous adenomas, and 131 tubulovillous adenomas. Invaded margins occurred in 26 (11.1 %) cases: 20.9 % (9/43) of the adenomas ≥ 5 cm versus 8.9 % (17/190) of the adenomas < 5 cm ($p = 0.047$). An invasive cancer was found in 60 (20.5 %) patients. Postoperative staging of resected adenocarcinomas was as follows: 43 pT1 (26 sm1, 9 sm2, and 8 sm3) and 17 pT2. Positive margins were detected in 4 (23.5 %) pT2 cases. In all cases the resection was judged full-thickness and no specimen fragmentation occurred.

Long-term results

Adenomas

Over a median follow-up period of 110 (range = 12–216) months, only one patient with rectal adenoma was lost to follow-up 12 months after surgery. A recurrence was diagnosed in 13 patients (5.6 %): in 6 (23.1 %) of the 26 patients with positive margins and 7 (3.4 %) of the 207 patients with negative margins ($p < 0.001$). The median time to recurrence was 10 (range = 4–33) months. Recurrence occurred in four cases within 6 months after TEM and in an additional six cases in the following 6 months. Therefore, 76.9 % of recurrences were detected within 12 months after TEM. Surgical treatment for local recurrence included TEM in ten cases, low anterior resection in two cases, and abdominoperineal resection in one case, which was an incontinent patient with rectovaginal fistula. No patient had a further recurrence during the follow-up.

Table 1 gives the univariate analysis for risk of recurrence. Of all the variables taken into consideration, only tumor diameter ($p = 0.007$) and positive margins ($p < 0.001$) demonstrated a statistically significant role. The multivariate analysis of the risk of recurrence is also given in Table 1 and shows the involvement of resection margins at pathology examination as the unique independent predictor of recurrence. HGD showed a statistical trend toward a higher risk of recurrence compared to LGD in both univariate and multivariate analyses ($p = 0.070$ and $p = 0.100$, respectively).

Table 1
Risk factors for local recurrence after transanal endoscopic microsurgery

Variable	**Univariate analysis**		**Multivariate analysis**	
	Hazard ratio	**p value**	**Hazard ratio**	**p value**
Age				
>68 years	1	0.143	1	0.232
≤68 years	2.698 (0.714–10.195)		2.415 (0.568–10.268)	
Gender				
Female	1	0.455		

Variable	Univariate analysis		Multivariate analysis	
	Hazard ratio	**p value**	**Hazard ratio**	**p value**
Male	1.450 (0.470 – 5.401)			
Tumor diameter				
<5 cm	1	0.007	1	0.062
≥5 cm	5.065 (1.556–16.489)		3.491 (0.941–12.960)	
Distance from the anal verge				
>7 cm	1	0.315		
≤7 cm	1.870 (0.552–6.338)			
Dysplasia				
LGD	1	0.070	1	0.100
HGD	3.425 (0.906–12.947)		3.350 (0.792–14.172)	
Histology				
Tubular	1	0.592		
Tubulovillous/villous	1.530 (0.323–7.259)			
Margins				
Negative	1	<0.001	1	0.003
Positive	10.909 (3.122–38.125)		7.739 (1.985 – 30.166)	

Values in parentheses are 95 % confidence intervals
LGD low-grade dysplasia, HGD high-grade dysplasia

Adenocarcinomas

During a median follow-up of 50 (range = 12–204) months, the overall recurrence rate was 4.6 % for the 43 pT1 patients: two pT1 sm2 patients developed local recurrence after 10 and 36 months, respectively. One patient underwent an additional TEM, while the other underwent laparoscopic total mesorectal excision (TME). Both are still alive disease-free at 25 and 150 months, respectively.

Among the 17 pT2 patients, 4 (23.5 %) underwent laparoscopic TME at 4, 5, 8, and 16 weeks after TEM. Residual tumor cells in the muscular layer were found in three cases, and perirectal lymph node metastasis was detected in one case. All patients are still alive and disease-free. Among the eight (47 %) patients who refused further surgery and underwent adjuvant radiotherapy, one patient showed a local recurrence after 33 months. He underwent laparotomic TME and is still alive and disease-free at 52 months after TEM. The remaining five patients refused any further treatment. One patient showed a local recurrence at 3 months, underwent laparoscopic TME, and is still alive and disease-free at 34 months; another patient presented with lung metastasis at 10 months and died of metastatic disease after 19 months. Therefore, the overall recurrence rate for pT2 patients was 17.6 % (3/17). Overall, only 1 of 60 (1.7 %) patients with rectal cancer died of the disease, with a disease-free rate at the completion of follow-up of 98 %.

Discussion

Endoscopic resection is the treatment of choice for premalignant lesions and noninvasive early cancers of the gastrointestinal tract. However, with large lesions conventional endoscopic mucosal resection (EMR) cannot be performed as an en bloc resection, and even with lesions smaller than 20 mm in diameter, incomplete resection or piecemeal resection often occurs. After piecemeal resections, histopathological assessment of complete resection is difficult and the risk of local recurrence is high. Iishi et al. [*18*] reported cure rates of 100 % after en bloc resection of rectal adenomas with a diameter of 2 cm or greater, whereas piecemeal resections needed additional endoscopic or surgical intervention in 55 % of cases, resulting in cure rates of 83 %.

In the last few years, ESD was introduced to overcome these difficulties and to allow resection of en bloc specimens, especially of lesions larger than 20 mm [*19*, *20*]. ESD has recently gained more support, mainly because of good clinical results in the treatment of esophageal and gastric neoplasms as reported in Japanese centers [*21*]. ESD has also been used to treat large colorectal adenomas, with recurrence rates of 0–9 % and complication rates of only 0–9 % [*11*, *22*, *23*]. However, compared to conventional EMR, the ESD technique is technically challenging and time consuming and requires a steep learning curve [*11*, *24*]. As a result, ESD has not gained wide acceptance in Western countries to date.

Transanal endoscopic microsurgery represents a valid surgical alternative to conventional transanal surgery in the treatment of large rectal adenomas. In fact, transanal surgery with retractors is associated with a consistent incidence of recurrence, especially for tumors of the upper and midrectum [*12*, *13*]. TEM combines a less invasive transanal approach with the benefits of better postoperative functional outcome and quality of life [*17*] and low recurrence rates for adenomas and selected early rectal cancers, thanks to enhanced visualization of the surgical field which allows more precise dissection [*25*].

No studies as of yet have compared piecemeal endoscopic techniques with TEM for large rectal adenomas. Recently, Barendse et al. [*7*] published a systematic review of the safety and effectiveness of EMR compared to TEM for large rectal adenomas, including 20 prospective and nonprospective case series in which the EMR technique was used and 48 in which the TEM technique was used with similar follow-up periods. Local recurrence rates were assessed in 3,890 patients (1,030 EMR and 2,860 TEM). The pooled estimate of the proportion of patients with early recurrence of adenoma in the EMR series was 11.2 % compared with 5.4 % in the TEM series ($p = 0.04$). Late recurrence rates were similar in both groups of patients: 1.5 % for EMR versus 3.0 % for TEM ($p = 0.29$). Because postoperative complication rates were 3.8 % for EMR and 13.0 % for TEM ($p < 0.001$), the authors concluded that EMR for large rectal adenomas was less effective but safer than TEM. However, this systematic review had some major limitations, as correctly stated by authors: First, only case series were available and were analyzed; second, there were some significant differences in terms of patient characteristics, including histology, location, and size of neoplasms between the two groups which can hardly be balanced by pooled analysis.

To our knowledge, our article presents the largest single-institution series of adenomas treated by TEM, with the longest follow-up period. In our series, over a median follow-up period of 110 (range = 12–216) months, the recurrence rate was 5.6 %. The median time to recurrence was 10 (range = 4–33) months. It is noteworthy that >75 % of recurrences were detected within 12 months after TEM. At multivariate analysis, a positive margin was the only factor statistically ($p = 0.003$) associated with early recurrence. Residual adenoma was found at the surgical margins in 23 (11.1 %) cases, in line with the published data [*26*]. Reviewing the published data on TEM, residual adenoma is detected in the surgical margins in 0–37 % of cases. However, the global recurrence rate is 0–16 % [*26*]. It is remarkable that although there are such high positive residual margin rates, reported recurrence rates are significantly lower. In our experience, only 6 (23 %) patients with positive margins relapsed and all within 12 months. This fact could be explained by the diathermic

damage to the remaining adenomatous tissue during dissection which causes the sterilization of the margins.

A further factor associated with risk of recurrence is the size of the adenoma, with increasing risk of recurrence over time for those who have large adenomas excised [*27–31*]. In our clinical practice, a full-thickness incision of the rectal wall is always initiated at a distance of approximately 5 mm around the tumor. Nevertheless, in our series 21 % of adenomas ≥5 cm were removed with positive margins compared with 9 % of adenomas <5 cm ($p = 0.047$). Furthermore, tumor diameter ≥5 cm was a predictive factor for recurrence ($p = 0.007$) at univariate analysis. Our results compare favorably with those reported by McCloud et al. [*31*] in their series of 75 patients who underwent TEM for adenoma with a follow-up period of 31 months. He found that larger polyps were incompletely excised, with 68.9 % of polyps ≤50 mm completely excised and only 33.3 % >50 mm completely excised ($p = 0.073$). Similarly, Ganai et al. [*28*] reported tumor size >4 cm to be an independent prognostic factor for local recurrence in 107 patients who had TEM for benign neoplasms.

The National Polyp Study [*32*] suggested HGD as a marker for potential malignancy in 1990. Recently, a systematic literature review by de Jonge et al. [*33*] confirmed that HGD is associated with an increased risk of recurrence of colorectal polyps. In our series, HGD showed a statistical trend toward a higher risk of recurrence compared to LGD in both univariate and multivariate analyses ($p = 0.070$, and $p = 0.100$, respectively). Similarly, multivariate analysis in the study by Ganai et al. [*28*] confirmed HGD as an independent predictor of local recurrence within a median follow-up period of 44 months.

TEM has now become an important therapeutic option in the treatment of recurrent adenoma. Six series have reported the use of TEM in the treatment of recurrent adenoma or residual disease without further recurrence [*31*, *34–38*]. In our series, there were ten recurrences after TEM, with no increased perioperative complication rates. Furthermore, no patient had a further recurrence during the follow-up. As more than 75 % of the recurrences occurred within 12 months in a well-determined subgroup of patients, we suggest an intensive follow-up protocol using rigid rectoscopy every 3 months for the first year and then every 6 months in case of positive margins at definitive histology, HGD adenomas, and adenomas ≥5 cm.

Even if EUS appears to be the most accurate preoperative diagnostic tool for investigating tumor invasion of the rectal wall, we report a 20.5 % discrepancy rate between preoperative EUS and histological staging of the tumors. This strengthens the idea that an appropriate full-thickness excision should be offered to all patients with rectal neoplasms, even in cases of benign preoperative histology, instead of a partial wall piecemeal endoscopic resection. In our series, 60 patients had a postoperative diagnosis of cancer: 43 pT1 and 17 pT2. Among pT1 patients, the local recurrence rate was 4.6 % (2 pT1 sm2). Both patients underwent surgical treatment of the recurrence and are still alive and disease-free at 25 and 150 months, respectively. Among pT2 patients, the overall recurrence rate was 17.6 %, but a multimodal approach based on immediate abdominal surgery or adjuvant radiotherapy made the mortality rate for cancer as low as 5.9 % (1/17).

The good oncologic results obtained in this series of patients are mostly due to the full-thickness excision that allowed a more accurate postoperative staging of the neoplasm and reduction of the rate of deep positive margins compared to endoscopic resection.

In conclusion, the present study shows that TEM provides excellent long-term outcomes in the treatment of benign rectal lesions and does not jeopardize the survival of patients with pT1 and pT2 rectal cancer detected at definitive histology. Close endoscopic follow-up is advisable for patients affected by HGD rectal lesions with a diameter ≥5 cm, and mostly for those with positive resection margins at definitive pathologic examination. Further prospective and eventually randomized clinical trials are needed to assess the role of TEM compared to EMR/ESD in the treatment of large rectal adenomas.

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