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Risk factors for recurrence after transanal endoscopic microsurgery for rectal malignant neoplasm

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Abstract

Background

Indications and results of local excision of rectal lesions are currently under debate. Transanal endoscopic microsurgery (TEM), allowing a precise, full-thickness excision, could improve oncological results in early rectal tumors.

Methods

A prospective database was analyzed with the intent to identify risk factors for recurrence after TEM.

Results

Among 355 patients subjected to TEM, 107 had an adenocarcinoma: 48 pT1, 43 pT2, and 16 pT3. Comparing pre- and postoperative data, histological discrepancy was 20% and staging discrepancy was 34%. Mortality was nil, morbidity was 9%. Mean follow-up was 54.2 months (range = 12–164), follow-up rate was 100%. The 5-year disease-free survival rate was 85.9, 78.4, and 49.4% for pT1, pT2, and pT3, respectively ($p = 0.006$). Recurrence rate was 0% (0/26) in pT1sm1 cancers and 22.7% (5/22) in sm2-3 ($p < 0.05$). A submucosal infiltration represented a significant risk factor for recurrences: 0% sm1, 16.7% sm2, and 30% sm3. Recurrence in pT2 was 0% in patients who had neoadjuvant therapy and 26% in the others. At univariate analysis, diameter, sm stage, pT stage, tumor grading, margin infiltration, and lymphovascular invasion demonstrated statistical significance. Multivariate analysis indicated sm stage, pT stage, and tumor grading as independent predictors of recurrence.

Conclusions

TEM represents an effective curative treatment for pT1 sm1 rectal malignancies. pT1 sm2-3 patients should be considered high-risk cases if treated only by TEM. A consistent improvement in the preoperative assessment of the risk factors identified by the present study will be a crucial development for optimal treatment of early rectal cancers.

Keywords

Transanal endoscopic microsurgery Malignant rectal neoplasm Recurrence Risk factors

The goal of oncological surgery is to achieve the best cancer control with preservation of function and quality of life. In the field of malignant rectal neoplasms, radical resection, consisting of anterior resection with total mesorectal excision (TME) when feasible and abdominoperineal resection (APR) when mandatory, represents the best curative treatment. Nevertheless, these procedures are burdened with a consistent morbidity rate, including genitourinary and sexual dysfunction (30–40%) [1–4], anastomotic leakage (5–17%) [5], and long-term functional bowel disturbance [6]. Up to 40% of patients experience perineal wound complications and long-term discomfort following APR, while stoma and stoma appliance-related complications occur in up to 66%. There is also significant psychological morbidity associated with change in body image and depression in 30% [7].

A transanal approach to rectal malignant neoplasms, if suitable, would lower risks and improve functional results. Unfortunately, the conventional transanal excision is characterized by a high incidence of remnant disease or early recurrence [8, 9]. For more than 25 years, transanal endoscopic microsurgery (TEM) had revolutionized the technique and outcome of transanal surgery, becoming the standard of treatment for large rectal adenomas [10–12], then offering a possibly curative treatment for early rectal cancer [13, 14], and, finally, generating discussion on the potential role in the treatment of more invasive cancer in combination with neoadjuvant treatments [15–18].

The aim of this study was to identify risk factors associated with local recurrence after TEM and consequently to improve selection criteria for TEM.

Materials and methods

This study is a retrospective analysis of a prospective database created in January 1993. 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. Inclusion criteria depended on anatomic restrictions assessed by rigid rectoscopy to locate the lesion along the circumference and to measure its distance from the anal verge. Lesions were considered suitable for TEM only when located within 10 cm from the anal verge on the anterior wall, 12 cm on the lateral walls, and 15 cm on the posterior wall, these being the limits of the insertion of the peritoneum on the rectal wall.

The preoperative work-up included clinical evaluation, total colonoscopy, upper abdominal ultrasound, endoscopic ultrasound, and pelvic computed tomography until 2003, then pelvic magnetic resonance imaging (MRI) was included. The procedure was performed under general anesthesia in all cases, with the original Richard Wolf (Knittlingen, Germany) TEM equipment, according to the standard technique described by Buess [10]. 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. Postoperatively, all patients had a urinary catheter placed at the time of surgery, which was removed 48 h after surgery in all anterior wall dissections and 24 h after surgery in all other cases.

Only patients with a histopathological diagnosis of malignancy based on examination of the TEM specimen were enrolled in this study. The specimen was pinned to a corkboard before fixation in 10% formal saline in order to preserve the margin of normal mucosa surrounding the tumor. Depth of neoplastic invasion was reported according to TNM guidelines [19]. pT1 cancers were classified using the Paris endoscopic classification of superficial neoplastic lesions and its revision [20,21].

The pathologist evaluated the resection margins, defining three groups: incomplete resection when the tumor reached resection margins, <1000 μm , or >1000 mm depending on the presence of foci of invasive tumor cells within 1 mm of the deep or peripheral surgical resection margin. Tumor grade, intramural lymphatics, and blood vessel invasion were recorded. Tumor size was measured macroscopically and reported as the maximum diameter. To achieve standardization of staging, all the histological diagnoses were reviewed by a single pathologist expert in the field of colorectal tumors, unaware of the follow-up of the patients included in the series.

Only patients with a minimum follow-up of 12 months were included. We entered into the database information about patient characteristics, preoperative assessment, lesion location and histology, perioperative complications, and follow-up data. Follow-up consisted of digital examination, rectoscopy, and tumor markers every 3 months for the first 2 years, then every 6 months. A full colonoscopy was performed at 12 months and then every 3 years. An abdominal and pelvic CT scan was performed at 6, 12, and 24 months. Local recurrence was defined as any recurrence diagnosed endoscopically or radiologically and confirmed by biopsy. Distant recurrence was defined by radiological evidence of tumor spread.

Values of different parameters are given as absolute values, percentage, and 95% confidence limits. 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 last examination. Explanatory variables with univariable $p \leq 0.200$ were included in a multivariable analysis. This significance level was chosen 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 gender, distance from the anal verge, anterior/posterior/lateral site, intraoperative complications, diameter (≤ 3 cm or >3 cm), stage according to pT and sm classification, tumor grade, margins (involvement/ <1 mm/ ≥ 1 mm), lymphovascular infiltration, and postoperative complications.

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. The statistical analysis was performed using Stata Software (Stata Corp., College Station, TX, USA).

Results

Between January 1993 and January 2009, 825 patients were treated at our department for mid- and low-rectal neoplasms. Of these, 337 were treated laparoscopically, 133 with an open technique, and 355 by TEM according to previously described inclusion criteria. Among those treated by TEM, 110 patients were diagnosed as being affected by rectal malignancy at pathology examination of the specimen and therefore were included in the present study. Thirty-four were females and 76 were males. Fifty-four patients (49.1%) had a preoperative benign histology, while 56 (50.9%) were already histologically diagnosed as malignant, of whom 3 had a carcinoid tumor.

Among 107 TEM procedures for adenocarcinoma, the age of the patients ranged from 34 to 94 years (mean = 68.4, median = 71), and the median distance of the neoplasm from the anal verge was 7 cm (range = 3–12). The lesion was located mainly on the anterior wall in 19 (17.8%), on the posterior wall in 43 (40.2%), and on lateral walls in 45 (42.0%) cases. The diameter of the tumor ranged between 1 and 7 cm (mean = 2.89, median = 3), with an area between 2 and 38 cm² (mean = 12.8, median = 13).

The median operation time was 60 min (mean = 72.6, range = 15–240). In 10 cases (9%), an inadvertent peritoneal opening occurred which was treated under TEM conditions in 9 cases; in 1 case, at the beginning of our experience, an open anterior resection was performed. No patient required an intraoperative blood transfusion. We observed postoperative morbidity in 10 cases (9%), consisting of rectal bleeding in 6, suture dehiscence in 2, rectovaginal fistula in 1, and rectovesical fistula in 1. Rectal bleeding was treated with blood transfusion in 4 cases, endoscopic hemostasis in 1 case, and transrectal packing in 1 case. Suture dehiscences were treated conservatively (antibiotics and total parenteral nutrition) in both cases. A transvaginal surgical suture solved the case of rectovaginal fistula, while the patient with a rectovesical fistula required abdominal surgery consisting of a definitive stoma. Mortality was nil. The hospital stay ranged between 2 and 15 days (mean = 5.3, median = 5).

Pathology results and staging

Histological staging of resected adenocarcinomas was 48 pT1, 43 pT2, and 16 pT3. Twenty-six of the pT1 cancers resulted sm1, 12 sm2, and 10 sm3, according to the Paris endoscopic classification of superficial neoplastic lesions and its revised classification [20,21].

The results of preoperative endorectal ultrasound staging are presented in Table 1, matched with postoperative histological tumor stage. A precise T staging by EUS was possible in 60% of pT1 and 50% of pT2. We observed a consistent improvement in EUS results during the study period: at the beginning of our series, understaging occurred in 13/26 (50%) and overstaging in 5/26 (19.2%), decreasing, respectively, to 9/26 (34.6%) and 3/26 (11.5%) in the middle period, and to 5/26 (19.2%) and 1/26 (3.8%) recently. Twenty uT2 and 5 uT3 lesions were treated by TEM for different reasons: 6 had a preoperative benign histology at biopsy sampling, 16 were judged unfit for abdominal resection due to general conditions or refused the risk of a temporary/definitive stoma (5 received neoadjuvant radiotherapy), and 3 had synchronous liver metastases and were treated with palliative intent.

Table 1

Preoperative endorectal ultrasound vs. histological staging in 107 adenocarcinomas

T stage	pT1	pT2	pT3	Total
uT0-1	32 (60.4%)	17	4	53
uT2	5	10 (50%)	6	21
uT3	1	3	1	5
No EUS	10	13	5	28
Total	48	43	16	107

In all cases the resection was judged full-thickness. Invaded resection margins occurred in 2.1, 18.6, and 50% of patients with pT1, pT2, and pT3 carcinoma, respectively ($p < 0.05$), while free margins of < 1 mm were detected in 6.3, 20.9, and 75%, respectively ($p < 0.05$).

Oncologic outcomes

Among pT1 patients, during a mean follow-up of 54.2 ± 42.1 months (median = 39.5, range = 12-164), the overall recurrence rate was 10.4% (5/48). Local recurrence was observed at 6, 12, 18, 36, and 48 months, respectively. All patients underwent laparoscopic TME and are currently alive, three disease-free and two with liver metastasis (Fig. 1A). According to sm classification, there was a trend toward a higher recurrence rate as the sm grading increased (sm1 = 0%, sm2 = 16.7%, sm3 = 30%, $p = 0.12$). Comparing sm1 lesions with sm2 and sm3 lesions, we found no recurrence among 26 patients versus 5 (22.7%) recurrences among 22 patients ($p = 0.036$).

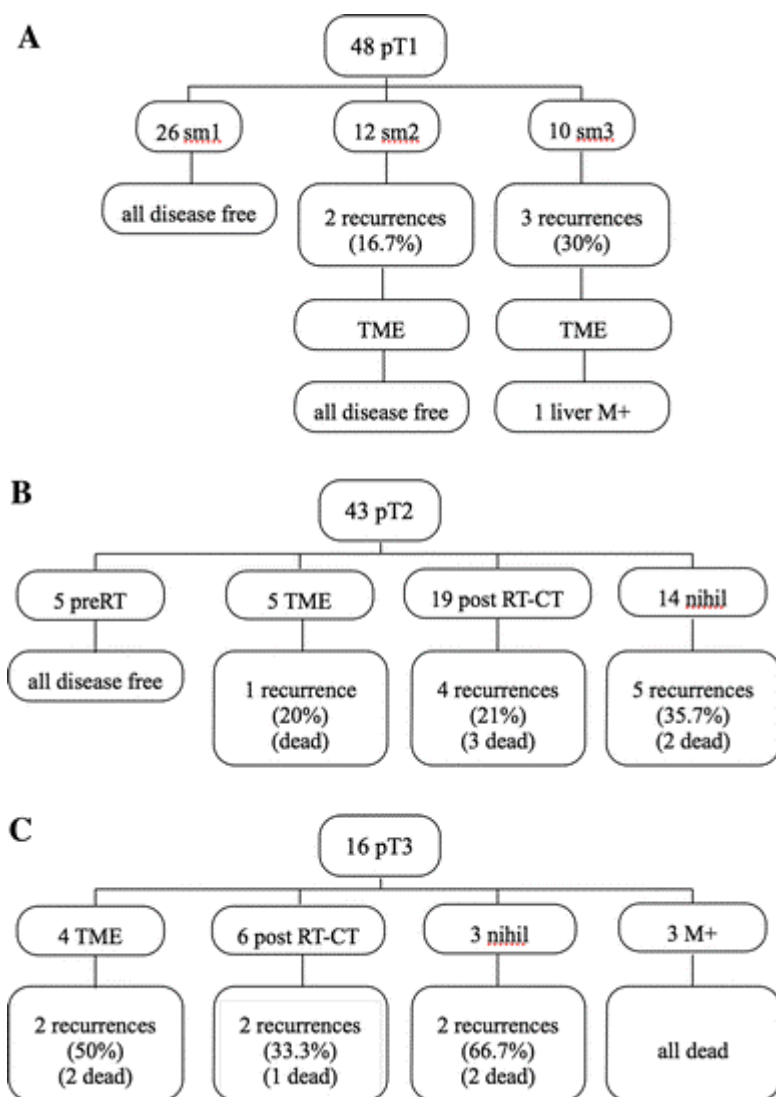


Fig. 1

Diagram of oncological results of (A) pT1, (B) pT2, and (C) pT3 patients. TME total mesorectal excision, M+ metastasis, pre RT neoadjuvant radiotherapy, post RT-CT adjuvant chemoradiotherapy

Among pT2 patients (Fig. 1B), the overall recurrence rate was 23.2% (10/43). All five patients who underwent neoadjuvant treatment are all disease-free at 13, 27, 57, 74, and 138 months from TEM, respectively. Of the other 38 pT2 patients, 5 (13.1%) accepted further surgical treatment consisting in all cases of laparoscopic TME at 4, 6, 8, 9, and 16 weeks from TEM, respectively. In all cases, no residual tumor and no lymph node involvement was found in the further resected specimen. Nevertheless, we observed 1 (20%) recurrence at 15 months which was treated by APR and adjuvant chemotherapy but the patient died of the disease. Nineteen (44%) pT2 patients refused further surgery and preferred adjuvant chemoradiotherapy; 4 (21%) showed a local recurrence at 10, 12, 12, and 70 months, respectively. One patient underwent further surgery and is disease-free, while the other three did not undergo any further treatment and died of spread disease. The remaining 14 patients refused any further treatment, but 5 (35.7%) of them showed local recurrence at 6, 10, 12, 12, and 13 months, respectively, which was treated by anterior resection in 2 cases (one patient is alive and disease free at 62 months while the other died of the disease), APR in 1 case (alive and disease free at 46 months), and radiotherapy in 2 cases (one dead of the disease). The differences observed in terms of local recurrence among these three groups of patients (surgery, adjuvant treatment, observation) were not statistically significant ($p = 0.518$).

Among the 16 pT3 patients (Fig. 1C), 3 had synchronous liver metastases and were treated with palliative intent and were excluded from the following data analysis. Of the remaining 13 pT3

patients, 4 underwent radical surgery consisting of TME. Nevertheless, 2 (50%) experienced local recurrence at 6 and 20 months, respectively, were treated by chemoradiotherapy, and died of the disease. Six patients with pT3 lesions accepted only postoperative radiotherapy, in which 2 (33%) cases developed a local recurrence at 13 and 14 months, respectively, which were treated by additional radiotherapy in one case and APR in the other; the first patient died of the disease and the other is still alive and disease-free. Three patients were not suitable for any further treatment due to comorbidities and 2 relapsed at 4 and 12 months and died of the disease. Therefore, the overall recurrence rate was 46.1% (6/13).

The stage-by-stage overall survival and disease-free log-rank curves are shown in Fig. 2. Overall survival rate at 60 months was 100, 80.2, and 62.9% for pT1, pT2, and pT3, respectively ($p < 0.001$). Disease-free survival rate at 60 months was 85.9, 78.4, and 49.4% for pT1, pT2, and pT3, respectively ($p = 0.006$). Disease-free log-rank curves for pT1 cancers divided into sm1, sm2, and sm3 stages are represented in Fig. 3. Sm1 lesions showed a 100% disease-free rate at 60 months, while sm2 and sm3 had rates of 66.7 and 63.0%, respectively, although there was no statistical significance among the groups ($p = 0.122$).

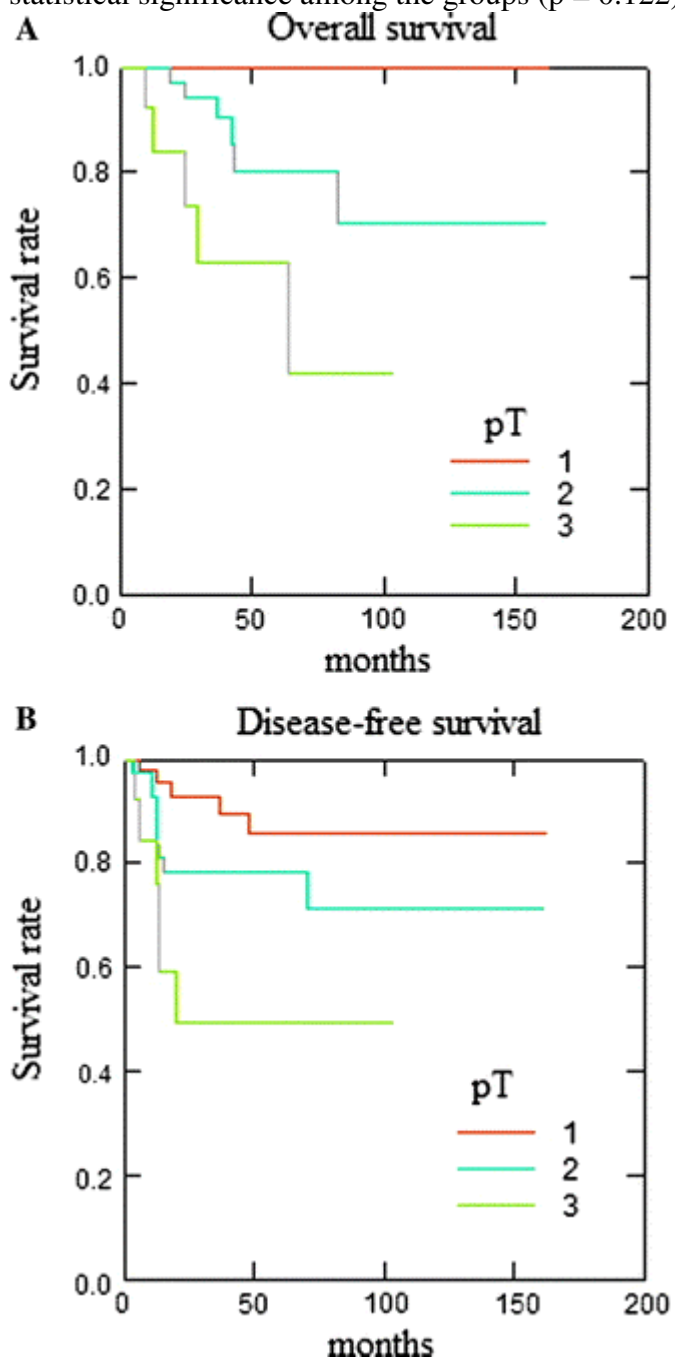


Fig. 2

Overall (A) and disease-free (B) survival rate of cancer patients stratified by tumor stage, including data of patients with additional treatments such as chemoradiotherapy and salvage surgery. $p < 0.001$ and $p = 0.006$, respectively, log rank test. pT pathological tumor stage

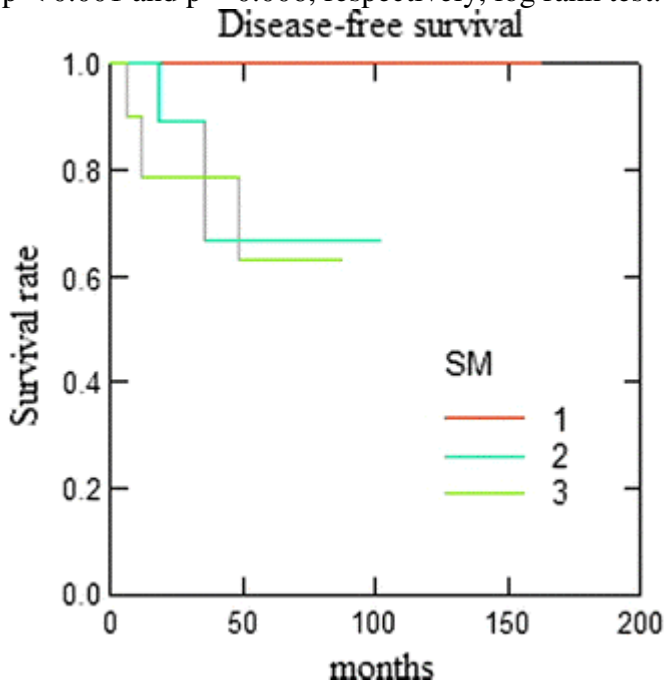


Fig. 3

Disease-free survival rate of pT1 cancer patients stratified by sm classification. $p = 0.122$, log rank test

The univariate analysis for risk of recurrence (Table 2) showed no statistical significance for gender, distance from the anal verge, site, intraoperative complications, free margins <1 mm, and postoperative complications, while diameter, sm stage, pT stage, tumor grading, margin infiltration, and lymphovascular invasion demonstrated a statistically significant role. The multivariate analysis for risk of recurrence (Table 3) indicated pT stage, sm stage, and tumor grading as independent predictors of recurrence.

Table 2

Univariate analysis of predictors of local recurrence after transanal endoscopic microsurgery

Variable	Hazard ratio	CI 95%	p
Gender			
M	1		
F	1.13	±0.8366	0.386
Distance from the anal verge			
<5 cm	1		0.301
5–10 cm	0.67	±0.3845	0.207
>10 cm	0.89	±0.5221	0.301
Site			
Anterior	1		0.225
Posterior	0.68	±0.5612	0.483
Lateral	0.36	±0.3284	0.101
Intraoperative complications			
Present	1		
Absent	1.05	±1.2950	0.467
Diameter			
≤3 cm	1		
>3 cm	1.35	±0.6930	0.031
sm			
sm1	Unavailable		
sm2	1		
sm3	2.05	±0.3428	0.035
pT			
pT1	1		
pT2	2.73	±0.8677	0.041
pT3	4.47	±1.7071	0.034
Tumor grading			
G1-2	1		
G3	2.68	±1.1481	0.033
Margin infiltration			
Absent	1		
Present	2.54	±1.1653	0.008
Free margin			
≥1 mm	1		
<1 mm	2.07	±1.5411	0.093
Lymphovascular infiltration			
Absent	1		
Present	1.20	±1.1544	0.048
Postoperative complications			
Absent	1		
Present	1.05	±0.7847	0.467

Table 3

Multivariate analysis of predictors of local recurrence after transanal endoscopic microsurgery

Variable	Hazard ratio	CI 95%	p
sm			
sm1	1		
sm2	1.33	±0.7397	0.041
sm3	1.67	±0.7448	0.035
pT			
pT1	1		
pT2	1.62	±0.7728	0.047
pT3	2.23	±0.7484	0.031
Tumor grading			
G1-2	1		
G3	3.33	±0.7977	0.029
Margin infiltration			
Absent	1		
Present	2.46	±0.8580	0.024
Lymphovascular infiltration			
Absent	1		
Present	1.77	±0.7617	0.048

None of the three patients affected by a carcinoid tumor showed recurrence at follow-up.

Discussion

Abdominal surgery has long been considered the appropriate surgical treatment for rectal neoplasms. Nevertheless, anterior rectal resection and total mesorectal excision are burdened with high morbidity and mortality rates [5], including urogenital dysfunctions [1]. Transanal surgery with retractors, although less invasive, is associated with a consistent incidence of recurrence, especially for tumors of the upper and medium rectum [22-25].

Twenty-five years ago, the introduction of transanal endoscopic microsurgery (TEM) afforded the advantage of combining a less invasive transanal approach with low recurrence rates thanks to enhanced visualization of the surgical field which allowed more precise dissection. Initially proposed as a technique for excision of benign rectal neoplasms, TEM indications were extended to include "low-risk" pT1 rectal adenocarcinomas [26] with curative intent [27] and more invasive rectal adenocarcinomas with palliative intent.

In order to contribute to the settlement of clear indications for TEM in malignant lesions, we analyzed our series aiming to identify potential risk factors for recurrence. A lesion diameter of >3 cm, pT staging, depth of submucosal invasion for pT1 cancers, poorly differentiated tumor grading, positive resection margins, and the presence of lymphovascular infiltration were identified as negative prognostic factors at univariate analysis. When investigating the independence of these parameters, we could confirm that pT staging, submucosal invasion for pT1, and tumor grading were the only statistically significant factors influencing the risk of recurrence. As a consequence, it appears that an adequate preoperative staging of these parameters would certainly help define correct indications for TEM. In particular, a precise evaluation of the depth of tumor invasion and lymph node metastasis is crucial for the appropriate selection of the patient. Even if EUS appears to

be the most accurate preoperative diagnostic tool for investigating tumor invasion of the rectal wall, we could ascertain, as already indicated by others [28-32], a consistent discrepancy between preoperative EUS and histology staging of the tumors, with 27/78 (34.6%) understaged and 9/78 (11.5%) overstaged lesions. The high incidence of lesions that were considered benign at preoperative biopsies but were shown to be malignant after excision led us not to take into consideration the preoperative histology when benign. This strengthens the idea that an appropriate full-thickness excision should be offered to these patients instead of a partial wall piecemeal resection as flexible endoscopy does. Despite its evident limitations, it is indeed more valuable to consider EUS staging as it can provide information on wall infiltration by which to choose a local or a radical excision. It is difficult to objectively define preoperatively which lesion would better be removed by TEM instead of transabdominal surgery, or even if it would benefit from neoadjuvant therapy, which, associated with TEM, in uT2 lesions was reported to be as effective as abdominal radical surgery [15-18].

Nevertheless, it must be remembered that our series extended over 15 years and was affected by a great evolution in technology, such as the introduction of EUS 360° probes, an improvement in image definition, and the introduction of high-definition EUS 20-MHz through-the-channel miniprbes [33]. These innovations came together with a growing experience in the EUS technique. In fact, if we differentiate the discrepancy rate between preoperative and postoperative staging during the entire study period among three consecutive homogeneous groups, we observe a consistent improvement in EUS results from a 50% understaging and a 19% overstaging rate in the first period to 19% and 3%, respectively, in the more recent group of patients. This improvement in rates probably might not be considered adequate, but it clearly shows a trend that looks promising. Furthermore, the introduction of pelvic MRI in clinical practice since 2003 has contributed to the amelioration of these results, reducing the understaging rate and allowing a better selection of patients.

A further step toward more accurate preoperative staging would be to use TEM as a macrobiopsy with curative potential if submucosal infiltration and tumor grading are not unfavorable. A better 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, the results of which are occasionally disappointing. In our series, the cases in which abdominal surgery was not contraindicated were promptly referred for total mesorectal excision. Of the 9 patients who underwent immediate further abdominal surgery, 3 (33%) died of the disease, in line with that reported elsewhere [9,12,14,34]. On the other hand, in a recent multicenter study, when TME followed TEM, the odds of recurrence were reduced 15-fold [30]. The main concern when performing a TME after a full-thickness TEM is that the perirectal fat might be compromised by tumor implantation or would be affected by a fibrotic scar, making dissection of the correct planes more challenging.

One of the key factors in avoiding local recurrence after removal of rectal adenocarcinomas is complete excision with sufficient tumor-free margins. Even if TEM allows better exposure, a constant view of the margin, and reduction of the risk of piecemeal tumor excision, the risk of invaded margins increases with a more advanced tumor stage, as demonstrated in our series. Therefore, a precise preoperative T staging is crucial from a technical point of view since margin invasion in pT1 cancers occurs occasionally (2%). We consider a rectal lesion with a preoperative benign histology but suspect for a deeper invasion on EUS as malignant. In this case, TEM with a full-thickness excision allows a more precise postoperative staging, reducing the rate of positive deep margins. Furthermore, an effort to increase the rate of free margins must be made to allow a radical local excision in case of more advanced rectal cancers. Lezoche [16] has recently proposed a tattooing of the lesion margins at the moment of diagnosis followed by neoadjuvant chemoradiotherapy in T2 neoplasms. We did not experience any recurrence in T2 patients treated by neoadjuvant chemoradiotherapy in our series, confirming the efficacy of this therapeutic strategy. Furthermore, on the basis of our results, we believe that the protocol proposed by Lezoche

[16] should be extended in the future to T1 sm2 and sm3. At present, unfortunately, we are not able to correctly identify this group of patients.

Nevertheless, the recent introduction of high-definition 20-MHz through-the-channel miniprbes seems to be a step toward the possibility of preoperatively identifying not only the T stage but also the depth of submucosal invasion [33]. The present series shows a significant difference in recurrence rate between pT1 sm1 (0%) and sm2-3 (22.7%). Therefore, we need in the future to preoperatively discriminate between these two groups of patients.

Finally, TEM also plays an undisputed role as a tool for palliation. We have used the TEM technique with palliative intent in patients with T3 tumors and significant comorbidities, as it is often the case in elderly patients. In this case, oncological results are poor, also related to a very high incidence of insufficient free resection margins, but the local disease control looks adequate, as others reported [30].

In conclusion, the present study shows that TEM gives excellent clinical and oncological results in pT1 sm1, while pT1 sm2 and sm3 patients should be considered high-risk cases if treated only by TEM. A precise preoperative definition of risk factors such as T stage, sm classification, and tumor grading is the key point for a “tailored” therapeutic approach to rectal cancer. New developments in preoperative staging techniques will be crucial to improve patient selection and consequently clinical outcomes.

Disclosures

Mario Morino, Marco Ettore Allaix, Mario Caldart, Gitana Scozzari, and Alberto Arezzo have no conflicts of interest or financial ties to disclose.

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