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Local excision of early rectal cancer: is transanal endoscopic microsurgery an alternative to radical surgery?

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ABSTRACT

Objective: transanal endoscopic microsurgery (TEM) allows locally complete excision of rectal neoplasms and provides an alternative to conventional surgery for benign tumours. However, its role in the curative treatment of invasive carcinoma is controversial. This paper examines the results of TEM compared with radical surgery (RS) for T1 rectal cancer.

Methods: 51 patients with T1 rectal tumours treated by RS, or local excision by means of TEM were included. The following parameters were evaluated: operating time, blood loss, hospital stay and complications, as well as local recurrence rate and survival.

Results: 17 patients were treated by RS and 34 by TEM. Operative time, blood loss, and duration of hospitalization were significantly lower in the TEM group compared with the RS group. In the RS group there were 4 patients with complications which required an operative revision (23.5%), compared to 1 reintervention (2.9%) in the TEM group. Local recurrence was 5.88% (n = 2) in the TEM group compared with none after RS (p = 0.547). The overall survival and disease-free survival showed not significant statistical differences between both groups (p = 0.59; p = 1.000, resp.).

Conclusions: although local recurrence was only observed after local excision, patients treated with TEM showed no significant differences in terms of overall survival and disease-free survival compared with patients who underwent RS. Inasmuch as local excision represents a minimally invasive technique in terms of morbidity, mortality and functional outcome, TEM should be offered as a valid option for well selected patients with early rectal cancer.

Key words: Local excision. Rectal cancer. Transanal endoscopic microsurgery.

RESUMEN

Objetivo: la cirugía transanal endoscópica (TEM) permite la resección completa de neoplasias de recto siendo una alternativa a la cirugía convencional para tumores benignos. Existe controversia sobre su papel en el tratamiento curativo del cáncer de recto. Esta publicación compara los resultados entre la resección radical (RS) y la exéresis local vía TEM del cáncer de recto en estadio precoz.

Métodos: se evaluaron 51 pacientes con neoplasia de recto cuya infiltración se limitaba a la submucosa (T1) y que fueron tratados mediante RS o TEM. Se evaluaron los siguientes parámetros: tiempo quirúrgico, pérdidas sanguíneas, estancia hospitalaria y complicaciones así como recidiva local y supervivencia.

Resultados: 17 pacientes fueron tratados mediante RS y 34 vía TEM. El tiempo quirúrgico, el posible sangrado y la estancia hospitalaria fueron significativamente menores en el grupo TEM. En el grupo RS, 4 pacientes presentaron complicaciones que obligaron a una revision quirúrgica (23,5%), comparado con sólo 1 reintervención (2,9%) en grupo TEM. La recidiva local sólo fue observada en dos pacientes (5,88%) del grupo TEM (p = 0,547). La supervivencia global y libre de enfermedad no mostró diferencias estadísticamente significativas entre ambos grupos (p = 0,59 y p = 1,000, respectivamente).

Conclusiones: si bien el grupo tratado con TEM advirtió dos recidivas locales, no se observaron diferencias en términos de supervivencia global y libre de enfermedad entre los dos grupos analizados. En tanto la resección local representa una técnica mínimamente invasiva en términos de morbilidad, mortalidad y resultados funcionales, la exéresis mediante TEM debe ser ofertada como una opción válida para pacientes muy bien seleccionados con carcinoma de recto en estadio precoz.

Palabras clave: Resección local. Cáncer de recto. Cirugía transanal endoscópica.

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INTRODUCTION

The standard treatment for early rectal cancer has been major surgery by anterior or abdominoperineal resection. After the introduction of total mesorectal excision, results regarding recurrence and survival rates have improved dramatically (1). However, mortality, morbidity, and functional disturbances after major surgery are considerable. Perioperative mortality rates are usually 2 to 3 percent, and overall morbidity 20 to 30 percent (2). Furthermore, anorectal, bladder, and sexual function may be compromised (3).

Given these side effects, there has been an increasing interest in the locoregional treatment of early rectal cancer. Nowadays local excision for selected rectal neoplasms is an accepted treatment worldwide (4). Compared to the gold standard of radical surgery, local procedures of strictly selected early rectal cancers should lead to identical oncological results and even better outcomes regarding morbidity, mortality, and quality of life (5).

Regardless of this trend, conventional transanal excision of rectal cancer has recently come under close scrutiny because of relatively high rates of local recurrence (6-10). In fact, skepticism has been expressed that such treatment is not in the patient's best interest.

Despite all these concerns transanal endoscopic microsurgery (TEM) has become the current standard procedure for the treatment of large rectal adenomas and early low-risk carcinomas with curative intent mostly in Europe (11-15). In contrast to conventional transanal excisions using anal retractors, TEM offers an exceptionally good overview of the whole rectum, allowing the precise removal of lesions not only in the lower and middle rectum but also in the upper region or even the retrorectal space, and obviates the need for major surgery (12,16,17).

Despite the limitations and the lack of power of clinical studies to detect differences in outcome such as survival and complication rates, TEM does appear to result in less local recurrence than other usual methods of local excision (14). Furthermore, after local excision of early rectal cancer by TEM recurrence and survival rates are comparable to those seen after major surgery, and complication rates and functional results are even superior to those seen after major surgery (18-22).

Since the introduction of TEM in our Division of Colon and Rectal Surgery a majority of patients with adenomas and T1 low-risk rectal cancer have been treated with local excision by this technique (23). The purpose of this single-center report was to evaluate the safety and oncological outcomes of TEM excision compared with radical surgery (RS) in the treatment of T1 low-risk rectal cancer.

PATIENTS AND METHODS

A retrospective analysis of prospectively collected data was performed to compare the outcomes of these two different surgical procedures (RS and TEM) in the treatment of rectal tumors. All 51 patients operated between August 1998 and January 2005 for early rectal, i.e. T1 low-risk carcinomas as described by the International Union against Cancer (24), were included in the study.

For all uT1N0 lesions with favorable histology (defined as well or moderately well differentiated lesions without lymphovascular or neuronal invasion) TEM was considered. Radical surgery was performed when these patients chose this option after giving their informed consent or because of improper preoperative staging. Furthermore, for three patients with tumors located ventrally and above the peritoneal reflection TEM was not recommended.

For tumor staging patients were examined prior to surgery using abdominal and endoluminal ultrasounds (Brüel & Kjaer Medical 6004 or 3535 with a rotating 7-MHz transducer), rectoscopy with biopsy, complete colonoscopy or barium enema, and abdominal-pelvic CT. Follow-up examinations included regular rectoscopy, rectal and abdominal ultrasounds, tumor marker profiles (carcinoembryonic antigen, cancer antigen 19-9), and if indicated CT scanning and/or biopsy.

Tumors were located by rectoscopy and endoluminal ultrasounds in the lithotomy position, and were classified according to location from the dentate line in centimeters (cm). Tumor size (cm^2) was assessed postoperatively according to the histo-pathological report.

Preoperative bowel cleansing included intestinal irrigation using 3-5 liters of polyethylene glycol (Oralav, Braun, Melsungen, Germany). Ten minutes before surgery all patients received a single shot of ceftriaxone and metronidazole. Surgery in both groups was performed under general anesthesia.

All tumors in this study were assessed by the same pathologist and staged according to the UICC classification (24). Only low-risk carcinomas (T1, G1/2 without lymphatic, vascular or neural invasion) were included in the analysis. All TEM-resected tumors were fixed to a corkboard for a specific evaluation of resection margins. The adequacy of resection was reported as "complete" (R0), "incomplete" (R1) or "doubtfully complete" (Rx).

In order to assess the safety of both procedures the following parameters were evaluated: operating time, blood loss, length of hospitalization, and incidence of complications. During follow-up visits recurrence and survival were assessed.

Radical surgery was performed after a midline incision and mobilization of the left colon including the splenic flexure, which was followed by central ligation of the inferior mesenteric artery and vein. For tumors located in the middle or lower rectum a total mesorectal excision was performed. An end-to-end anastomosis using a double-stapling technique was performed with a circular stapler *(Ethicon® or Surg Assist®);* in suitable cases a transverse coloplasty pouch was added. A distal tumor-free margin of 1.5 cm of the freshly resected, undistended specimen was considered to be oncologically safe.

Since the optics of the operative TEM rectoscope has an angle of 40°, the tumor should always be at a 6 o'clock lithotomy position on the operating table. Therefore, patients were positioned according to tumor location in a right lateral, left lateral, prone, or lithotomy position. After gentle extension of the sphincter the TEM equipment (Wolff, Knittlingen, Germany) was inserted. Under continuous distension of the rectal cavity by pressure-controlled CO_2 insufflation, lesions were resected as full-wall thickness excisions with an attempted macroscopically free margin of 1 cm, as described in the original publication (12). The defect of the rectal wall was always closed with a running suture.

Statistical computations were performed with the SAS system (release 8.02, SAS Institute Inc., Cary, NC, USA). If the data were normally distributed, mean values were compared using the two-sample t-test. If a normal distribution could not be assumed, U-tests by Mann-Whitney were performed.

RESULTS

Overall, 51 primary operations of low-risk T1 tumors were performed. The RS group (n = 17) included 10 low anterior resections with total mesorectal excision and creation of a protective loop-ileostomy except for a patient with preoperative fecal incontinence, in whom a Hartmann procedure was performed. In 7 patients an anterior resection was carried out. No abdominoperineal resection was performed. One patient with R1-resection after TEM underwent salvage therapy and was left in the TEM group. The TEM group included 34 operations. Five initial adenomas in the TEM group were classified as early rectal carcinoma upon postoperative pathological assessment.

Patient characteristics demonstrated no significant differences regarding age, sex, and comorbidity. Patients with hereditary non-polyposis colorectal cancer were not identified in any of the groups. Tumor characteristics showed no statistically significant differences in size, but tumors were found to be located significantly lower in the rectum in patients included in the TEM group (Table I).

Median follow-up was 93.0 months (48-108) in the RS group and 86.5 months (48-113) in the TEM group. These differences between RS and TEM were not statistically significant (U-Test by Mann-Whitney, p = 0.4593) (Table II). In the TEM group, four patients died during follow-up (9, 12, 15, 61 months after surgery) because of disease-unrelated causes. Three patients of the RS group died after 1 week (during hospital stay), 5 and 24 months. None of the other patients investigated in both groups were lost to follow-up.

Safety

Operating time

The duration of each procedure was measured from the first incision or insertion of the TEM rectoscope to the closure of the abdominal skin, or the removal of TEM instruments. The comparison of median operating time between RS and TEM showed a significant advantage for the local procedure (t-test, p < 0.0001) (Table I).

Blood loss

An analysis of the number of blood transfusions required showed that one or more transfusions were necessary in three (17.6%) of the patients during the operation in the RS group, in contrast to none in the TEM resection

Table I. Main characteristics of patients, tumors and intraoperative results

	RS (n = 17)	*TEM (n = 34)*	*p-value*
Patient age (years)	65.6 ± 9.7	68.4 ± 10.7	0.3694
Tumor size (cm^2)	5.5 ± 4.5	5.5 ± 5.3	0.7560
Distance from dentate line (cm)	10.9 ± 3.5	8.9 ± 3.2	0.045
Duration of hospitalization (d)	15 (10-55)	8 (4-49)	< 0.0001
Operation time (min)	200.0 (117-310)	77 (50-202)	< 0.0001
Blood loss (ml)	714.7 ± 857.1	94.1 ± 281.7	< 0.0001
Perioperative blood transfusions (patients)	3	0	0.0327
Perioperative blood transfusions (total number of units)	10	0	0.0327
Postoperative blood transfusions (patients)	3	1	0.1020
Postoperative blood transfusions (total numbers of units)	13	2	0.0558

group (p = 0.0327, Fisher's exact test). Furthermore, the mean amount of blood loss during the operation was significantly lower in the TEM group (t-test, p < 0.0001). The comparison between RS and TEM showed significant differences with respect to the number of blood transfusions not only during the operation but also in the postoperative period (Table I).

Time of hospitalization

The RS group showed a statistically significant longer duration of postoperative hospital stay when compared to the TEM group (t-test, p < 0.0001) (Table I).

Complications

There were eleven patients with a total of 12 surgical complications in the RS group (Table III). In 4 of these patients a total of 9 operative reinterventions were necessary due to anastomotic leakage with pelvic abscess (2 patients), fascial dehiscence after paralytic ileus (1 patient), and relevant anastomotic bleeding (1 patient).

The TEM group showed a total of 5 complications in 4 patients. Suture breakdown was found in four patients (11.8%). Whereas this was asymptomatic in 3 cases an operative revision was necessary in one case (protective ileostomy) (Table III). One case showed bleeding without suture breakdown and was treated conservatively. No adynamic ileus or suture-related strictures were observed in TEM-treated patients (Table III).

Mortality

One patient died (5.88%) due to pneumonia complicated with stroke in the fifth day after anterior resection in the RS group. No death occurred in the TEM group during hospital stay (Table III).

Oncological outcome

Residual tumor status

Regarding completeness of excision the RS group showed no R1 or Rx status of resection. In contrast there were two cases of Rx and one of R1 in the TEM group. Both patients with Rx received further treatment by means of radiotherapy after refusing salvage surgery. The patient with R1 was further treated with salvage low anterior resection and was included in the TEM group (Table II).

Recurrences

No recurrence was reported in the RS group. In the TEM group the overall recurrence rate was 5.88% (2 of

Table II. Oncological results

	RS (n = 17)	*TEM (n = 34)*	*p-value*
Rx status	0	5.88% (n = 2)	0.5467
R1 status	0	2.94% (n = 1)	1.000
Follow-up (months)	93.0 (48-108)	86.5 (48-113)	0.4593
Local recurrence	0	5.88 % (n = 2)	0.5467
Metastases	0	5.88 % (n = 2)	0.5467
Survival	82.35% (n = 14)	88.23 % (n = 30)	0.673
Disease-free survival	82.35% (n = 14)	82.35 % (n = 28)	1.000

Table III. Complications

	RS (n = 17)	*TEM (n = 34)*	*p-value*
Anastomotic dehiscence	11.76% (n = 2)	11.76% (n = 4)	1.0000
Pelvic abscess	11.76% (n = 2)	0	0.1067
Abdominal suture breakdown	5.88% (n = 1)	0	0.3333
Paralytic ileus	11.76% (n = 2)	0	0.1067
Postop. hemorrhage	11.76% (n = 2)	2.94% (n = 1)	0.3333
Pneumonia	11.76% (n = 2)	0	0.1067
Re-operations (patients)	23.53% (n = 4)	2.94% (n = 1)	0.0371
Re-operations (total number)	n = 9	n = 1	0.0233
In-hospital mortality	5.88% (n = 1)	0	0.3333
Anastomotic stricture	23.53% (n = 4)	0	0.0095

34 patients, after 9 and 24 months follow-up respectively). The first patient was treated with an abdominoperineal rectal resection after receiving preoperative radiochemotherapy. A pathology study of the resection piece showed an UICC yT2N0 stage. The same patient developed liver metastasis at a later stage necessitating right hemi-hepatectomy. The second patient showed local recurrence together with pulmonary metastases after 24 months, and underwent only palliative chemotherapy after refusing further surgery. The difference in recurrence rates within both groups revealed no statistical significance (Fisher's exact test, p = 0.5467) (Table II).

Adenomas at the site of local excision appeared during follow-up in two patients in the TEM group. In both cases adenomas were operated by means of TEM.

Survival

Overall survival and disease-free survival showed no statistical differences between both groups (p = 1.000; Fischer's exact test) (Table II).

DISCUSSION

Various surgical techniques are still under discussion for the treatment of early rectal carcinomas. The gold-standard procedures, such as anterior and abdominoperineal resection, show excellent results regarding local recurrence and survival rates (1), but are dearly paid for by a high incidence of complications (2) and impaired quality of life (anorectal, sexual, and urinary dysfunction) (3). Additionally, some of the patients require temporary diverting enterostomies, as 11 of our patients in the RS group did. On the other hand, there are conventional sphincter-preserving techniques, such as conventional transanal resection with Park's retractor (25), which are associated with an almost unacceptably high recurrence rate of up to 29% (7).

The primary factor limiting the effectiveness of local treatment for early rectal cancer is lymph node invasion. Depths of invasion into the rectal wall, grade or degree of differentiation, vascular, lymphatic and neural invasion are independent predictors of the risk of nodal metastasis. Since initial studies by Morson (26) and Hermanek (11) large series of resected rectal cancers have shown that well-differentiated tumors confined to the submucosa (T1) without vascular, lymphatic or neural invasion carry a 4% risk of nodal metastasis (27,28).

The inclusion criteria of the 51 patients incorporated in this study was the assessment of a moderately- to well-differentiated tumor confined to the submucosa (T1) without vascular, lymphatic or neural invasion, and no lymph node assessment (by means of endorectal ultrasounds or definitive pathology after radical abdominal resection). In this context, 2 patients with nodal positivity after RS were excluded from the study. It is of interest to note that a total of five patients were understaged as uT1 preoperatively and excluded from the study because of a definitive pT2 stage after local excision. All these cases were further treated by salvage therapy because of the high rate of recurrence after local excision (29).

Although the reported rate of recurrence for early rectal cancers (pT1) resected by TEM is between 4- and 14%, follow-up and differentiation between low- and high-risk features are variable among series reported (15,19-21,30-32). In fact, the only published prospective study comparing TEM with radical resection for T1 low-risk rectal cancer showed no statistical difference between local excision and radical resection regarding local recurrence and metastasis rate (18). These results are in accordance with our observations. We assessed two recurrences in the TEM group compared to none in the RS group. Local control is therefore undoubtedly better assessed after RS, but on the other hand it is interesting to underline that there was no statistically significant difference in overall survival and disease-free survival depending on the operation performed.

Although we assessed no existing differences concerning tumor size between the two groups, our study detected a significant variation in tumor site. Tumors treated with TEM were located significantly lower in the rectum than lesions in the RS group. This fact includes a possible selection bias in favor of the RS group, as the prognosis of lower rectal cancers tends to be poorer when compared to those located in the mid or upper rectum (8,22,27).

A second arguable selection bias could be tumor selection, adjuvant therapy, or salvage surgery. There were five lesions assessed as adenomas preoperatively that were eventually seen to be low-risk carcinomas upon pathological examination in the TEM group, compared to none in the RS group. These data could be interpreted as a selection of tumors with more favorable biology in the TEM group. Similarly it could be argued that the two patients showing Rx specimens after TEM and receiving adjuvant radiotherapy received better therapy than those with surgery alone. On the other hand the one patient undergoing salvage surgery due to an R1 status after TEM should have had a worse prognosis in terms of local recurrence.

Our study demonstrates that TEM is not only comparable in terms of survival but also superior in terms of safety as already reported in the literature (18,20,21). As a matter of fact, patients receiving a TEM procedure benefit from a minimal invasive procedure with comparable overall and disease-free survival. All parameters studied to assess safety between the two groups revealed a statistically significant difference favorable to the TEM group. Operating time, blood loss, duration of hospitalization and complications, including mortality, were more favorable in the TEM group compared to the RS group. Our results are in accordance with the literature regarding the safety of the TEM procedure as compared to RS (18,20,21).

In an outstanding systematic review published recently, both comparative and case-series studies were examined to assess evidence related to the safety and efficacy of TEM compared with radical resections and conventional local excisions (14). Despite limited evidence the authors pointed out the unequivocal tendency of TEM to achieve better results in well-selected cases than conventional local excision, without being less effective than radical resection. The question that arises is whether TEM represents the only adequate alternative to radical resection for early rectal cancer.

The reason for the superiority of TEM over other transanal conventional techniques is the use of an optical system with 3D-view, 6-fold magnification, and human-eye resolution; the creation of a stable pneumorectum, and specially designed instruments that allow full-thickness excision under excellent view conditions not only in the lower but also in the middle and upper parts of the rectum. Furthermore, full-thickness excision allows proper histological examination. Recently we showed the ability and advantages of this technique to approach tumors located in the retrorectal space (17).

The advantage of TEM has already been observed in the lower rate of recurrences for adenoma excision (up to 7%) when compared to recurrence rate after transanal conventional excision (up to 27.3%). Even for adenomas, completeness of excision is an important predictor for early recurrence (32). Furthermore, the literature reported a lower morbidity rate when using TEM for adenoma excision (7% complication rate compared to 14.5% for conventional transanal surgery) (32).

Surprisingly many publications still advocate for caution in the local excision of rectal cancer (6,8). However, these studies are questionable regarding selection criteria, use of endorectal ultrasounds preoperatively, proper *"in toto"* excision, and histological examination (R-Status, differentiation, and lymphovascular invasion). In addition, some data are compromised by mainly retrospective analyses over extended time periods, and by a lack of standardized pathology reports (7).

The main argument explaining the high rate of local recurrences after conventional local excision could be a technically inadequate operation in which margins are too small, inadequate depth of resection, or shedding and implantation of tumor cells into the surgical field. Moore et al. (33) compared 82 patients after TEM with another 89 after conventional transanal excision for rectal neoplasms. He found clear margins in 71 percent of specimens in the conventional group compared with 90% in the TEM group. Furthermore, non fragmented specimens were more likely to be found after TEM than after conventional surgery (94 *vs*. 65 percent). In our hands the rate of Rx and R1 after local excision was 5.88 and 2.94%, respectively.

We believe that strict patient selection criteria, together with full-thickness and margin-free excision is crucial for patient outcome (34). The strong correlation between incomplete tumor resection and poor outcome is widely accepted (14,35,36). In our experience, positive excision margins should not be regarded as a risk factor for recurrence but should be viewed as insufficient therapy requiring further treatment. Therefore, accurate pathological examination after corkboard fixation of the specimen, and intensive, close cooperation between surgeon and pathologist cannot be overemphasized.

Although local recurrence was only observed after local excision, patients treated with TEM showed in our study no significant differences in terms of overall survival and disease-free survival as compared to patients who underwent RS. Inasmuch as local excision represents a minimally invasive technique in terms of morbidity, mortality and functional outcome, TEM should be offered as a valid option for well-selected patients with early rectal cancer.

Despite the difficulty to perform further studies in the future comparing different methods of local excision with more radical procedures (37) and the possible combination of neoadjuvant chemoradiation for better local and distant control even for high risk tumors (4,38), our results add further evidence that TEM should be considered as best practice to perform a local excision of well selected cases of early rectal carcinoma.

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The first and second authors contributed equally to this paper.

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