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SURGICAL ENDOSCOPY
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Transanal endoscopic vs total mesorectal laparoscopic resections of T_2–N_0 low rectal cancers after neoadjuvant treatment

A prospective randomized trial with a 3-year minimum follow-up period

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Abstract
Background: This study aimed to compare the results and the oncologic outcomes of transanal endoscopic microsurgery (TEM) with neoadjuvant radiochemotherapy and laparoscopic resection (LR), also with neoadjuvant radiochemotherapy, in the treatment of T_2–N_0 low rectal cancer.
Methods: The study enrolled 40 patients with T_2–N_0 rectal cancer, randomizing 20 to TEM (arm A) and 20 to LR (arm B).
Results: After neoadjuvant radiochemotherapy, tumor downstaging was observed for 13 patients (65%) in arm A (7 pT0 and 6 pT1) and in 11 patients (55%) in arm B (7 pT0 and 4 pT1). More than a 50% reduction of the tumor diameter was observed in four arm A cases and in six arm B cases. At a median follow-up period of 56 months (range, 44–67 months) in both arms, one local failure (5%) occurred after 6 months in arm A and one (5%) after 48 months in arm B. Distant metastases occurred in one arm A patient (5%) after 26 months of follow-up evaluation and in one arm B patient (5%) at 31 months. The probability of local or distant failure was 10% for TEM and 12% for laparoscopic resection, whereas the probability of survival was 95% for TEM and 83% for laparoscopic resection.
Conclusions: The findings show comparative results between the two study arms in terms of probability of failure and survival.

Key words: Rectal cancer — Radiochemotherapy — Transanal endoscopic microsurgery — Laparoscopic resection

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Over recent decades, the evolution in the treatment of rectal cancer has led to a drastic fall in the local recurrence rate, from 15–40% to 7–10%. This improvement resulted from the introduction of total mesorectal excision (TME).

The primary aims of surgery are the locoregional cure of the disease and increased survival, which are strictly related to the stage of the disease. For tumors located in the distal rectum, reaching these aims with surgical resection often has meant sacrificing the patient's quality of life in terms of sphincteric, urinary, and sexual functions. To reduce these complications, a number of sphincter-preserving procedures have been described. The impact of radiotherapy and chemoradiotherapy on surgical treatment also must be taken into account because these therapies currently are an integral part of the multidisciplinary approach to low rectal cancer treatment. Several studies report that tumor downstaging and lymph node sterilization have improved resectability after neoadjuvant therapy [5, 9, 16].

Most authors use chemoradiotherapy for T_3 and T_4 rectal cancer to reduce the tumor bulk, the degree of rectal wall invasion, and the lymph-nodal involvement. In our series of patients we have used neoadjuvant therapy also for T2 low rectal cancer to increase the possibility of sphincter-preserving surgical treatment, to improve local control, to improve survival, and potentially to provide a better quality of life.

The aim of our study was to compare the results of two minimally invasive procedures in a prospective, randomized trial. Local excision by transanal endoscopic microsurgery (TEM) was compared with laparoscopic low anterior resection or laparoscopic abdominoperineal resection of the rectum in the treatment of T_2–N_0 rectal cancer not larger than 3 cm in diameter. All the patients underwent preoperative high-dose radiotherapy and continuous infusion of 5-fluro-

uracil (5-FU). Our purpose was to evaluate whether local excision combined with preoperative chemoradiotherapy in selected patients with T_2 rectal cancer may be a possible alternative to more radical resections. In this preliminary study we report only cases with a minimum follow-up period of 3 years in a group of patients treated by the same surgical team.

Materials and methods

According to the protocol of the so-called "Urbino Trial," from April 1997 to April 2000, 40 patients were enrolled in the study. Before surgery, all the patients underwent neoadjuvant radiochemotherapy. After completion of the neoadjuvant treatment protocol, the patients were randomized to either TEM (arm A, 20 patients) or laparoscopic resection (low anterior or Miles' procedure) (arm B, 20 patients). The inclusion criteria specified low rectal cancer staged as T_2–N_0–G_{1-2}, tumor diameter up to 3 cm, and tumor location within 6 cm from the anal verge. The exclusion criteria for chemotheraphy specified G_3 tumor grading, evidence of distant metastases and presence of other malignancies in the patient's history, whereas the exclusion criteria for radiotherapy specified severe diverticular disease of the sigmoid colon and previous radiotherapy. Patients older than 70 years with compromised general conditions were excluded because they were not eligible for chemotherapy.

History, routine laboratory testing tumor markers, and accurate clinical examination, including digital examination to evaluate tumor fixation, were recorded for each patient in a database developed according to the prospective protocol.

Preoperative staging was evaluated on the basis of total colonoscopy, rigid rectoscopy, macrobiopsies of the tumor, and six to eight biopsies of normal mucosa at a distance of 1 cm around the tumor followed by india ink tattooing, endorectal ultrasound by means of a rotating 7-mHz probe, (B & K Company, Naerum, Denmark) multislice helical computed tomography (CT) scan and/or magnetic resonance imaging (MRI) of the abdomen and pelvis with 3-mm sections, chest radiography, and bone scan. Rigid rectoscopy was performed to measure the exact distance of the tumor from the anal verge, to evaluate the circumferential tumor extension, to select the position of the patient on the surgical table for TEM, and to obtain mandatory macrobiopsies of the tumor.

Each biopsy was examined in blind fashion by three morphologists to assess the grading. The parameters established for the grading were cellular differentiation (well, moderately well, or poor) and lymphatic, vessel, and neural infiltration.

All the patients included in the study underwent preoperative radiotherapy according to the technique described by Marks et al. [11] with an overall administration of 5,040 cGy in 28 fractions over 5 weeks. The irradiated areas were the anus, rectum, and mesorectum, as well as the regional and iliac lymph nodes. During radiotherapy, continuous intravenous infusion of 5-FU 200 mg/m^2/day was administered.

At 40 days after the end of neoadjuvant radiochemotherapy a second preoperative staging and evaluation of the lesion was performed by endoscopy to assess any variation in tumor diameter (using the tattoo spots as reference points), transanal ultrasound, CT scan, and/or MRI and digital examination.

The operation was performed 45 to 55 days after the completion of radiochemotherapy. Preoperative washout of the colon and short-term antibiotic prophylaxis were applied in all patients. The same surgical team performed all the surgical procedures.

The instrumentation described by Buess and Mentges [3] has been used for all patients randomized to TEM according to the technique that we have previously reported [8, 9]. A full-thickness excision of the tumor with negative margins was performed, including the adjacent perirectal fat. For anteriorly localized lesions, the plane of dissection was the vagina septum or the prostate capsule, whereas for posterior lesions it was the so-called "holy planed." Once the excision was completed, the shape of the specimen had the appearance of a "truncated pyramid" (Fig. 1).

In both laparoscopic low anterior resection and the Miles' procedure, all the established oncologic concepts of open surgery have been respected, such as high ligation of the inferior mesenteric vessels, lymphadenectomy, total mesorectal excision en bloc with the rectum, correct clearance of the specimen's margins, and integrity of the mesorectal fascia. Complete mobilization of the splenic flexure was mandatory, as well as suture of the pelvic peritoneum to exclude the anastomosis from the peritoneal cavity, as previously reported [10].

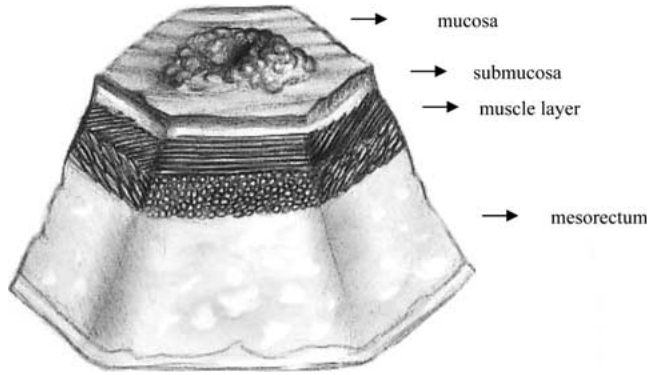

Fig. 1. Schematic representation of the removed specimen, which has the aspect of a truncated pyramid.

According to our protocol, the primary end points of this study were the probability of failure and the probability of survival at 3 and 5 years of follow-up evaluation. The secondary endpoints were morbidity and 30-day mortality, operative time, blood loss, analgesic use, and hospital stay.

All the patients were followed up prospectively by means of clinical examination, tumor markers, colonoscopy, endorectal ultrasound, liver ultrasonography every 6 months for the first 5 years as well as chest x-ray, and CT scan/MRI and bone scan once a year to evaluate local or systemic recurrence of the disease.

Statistical analysis

Each patient who met the inclusion criteria was consecutively assigned a progressive number from 1 to 40, and randomization of the patients in the two arms of the study was obtained through a random number generator table. Continuous data are presented as the median value with the 25th to 75th percentiles in parenthesis. The association between the characteristics of the patients (gender and age) and the procedure were investigated by means of the chi-square test and the Wilcoxon test. The patients' follow-up evaluation started on the date of the first treatment and ended on September 1, 2003. The cumulative probability of failure (local recurrence or distant metastases) and the probability of survival were estimated in both groups (laparoscopic resection and TEM) using the Kaplan–Meier method, and the relative risk of complications was estimated by the Cox regression model. The Long test was used to compare the survival curve and complications between the groups. A level of 5% was used to assess the statistical significance. The SAS System vs 8.2 (SAS Institute Inc., Cary, NC, USA) was used as the statistical software for all the analysis.

Results

Of the 40 consecutive patients staged as T_2–N_0–G_{1-2} and eligible for the current study, 20 were randomized to TEM (arm A) and 20 to the laparoscopic approach (arm B). The TEM group included 8 women and 12 men whose median age was 68 years (range, 64–70 years). The laparoscopic group included 7 women and 13 men with a median age of 67 years (range, 62–78 years). The anagraphic data and patients' distribution among American Society of Anesthesiology (ASA) classes were similar in the two groups.

Table 1. Main characteristics of the patients and results

	TEM Arm A	LR Arm B	*p* value
Male gender n (%)	12 (60)	13 (65)	0.744[a]
Age (years)			
Median (25th–75th% tile)	68 (64–70)	67 (62–68)	0.413[b]
Follow-up (months)			
Median (25th–75th% tile)	52 (43–58)	67 (53–72)	0.016[b]
Radiotherapy downstage n (%)			
pT0	7 (35)	7 (35)	0.723[a]
pT1	6 (30)	4 (20)	
pT2	7 (35)	9 (45)	
Intraoperative program change n (%)	0	2 (10)	0.244[c]
Conversions to open surgery n (%)	0	2 (10)	0.244[c]
Stoma n (%)			
None	20 (100)	12 (60)	0.016[c]
Temporary	0	4 (20)	
Definitive	0	4 (20)	
Operative time (min)			
Median (25th–75th% tile)	95 (90–150)	170 (155–194)	< 0.001[b]
Laparoscopic low anterior resection		165 (155–239)	
Laparoscopic Miles procedure		174 (150–194)	
Blood loss (ml)			
Median (25th–75th% tile)	50 (30–50)	200 (100–350)	< 0.001[b]
Transfusions n (%)	0	4 (20)	0.053[c]
Analgesic use n (%)	2 (10)	20 (100)	< 0.001[a]
Hospital stay (days)			
Median (25th–75th% tile)	4.5 (3–6)	7.5 (6–10)	< 0.001[b]
Postoperative complications n (%)			
None	17 (85)	17 (85)	0.203[c]
Minor	2 (10)	2 (10)	
Major	1 (5)	1 (5)	
Local recurrence n (%)	1 (5)	1 (5)[d]	0.513[c]
Distant metastases n (%)	1 (5)[d]	1 (5)[d]	0.513[c]

TEM, transanal endoscopic microsurgery; LR, laparascopic resection
[a] chi-square test
[b] Wilcoxon test
[c] Fisher exact test
[d] Died

After neoadjuvant radiochemotherapy, 13 patients (65%) in arm A were downstaged to pT0 in seven cases and to pT1 in six cases. In four of the remaining seven patients (20%), more than a 50% reduction in tumor diameter was observed (Table 1). Similarly, in arm B, 11 patients (55%) were downstaged to pT0 in seven cases and to pT1 in four cases. Of the remaining nine patients, six (30%) showed more than a 50% reduction in tumor diameter (Table. 1).

Chemoradiotherapy toxicity included anorectal mucosal irritation in 80% and diarrhea in 32% of the patients. These symptoms resolved with medical therapy, and they did not cause interruption of the treatment for any patient. Mortality was nil. In group A, no intraoperative complications or conversion to a different surgical procedure occurred. The median operative time was 95 min (range, 90–150 min). The median intraoperative blood loss was 50 ml (range, 30–50 ml), and no patient required intraoperative or postoperative blood transfusions. No protective ileostomy was performed. Postoperative pain was mild, and only two patients (10%) required a single dose of analgesic (ketorolac 30 mg) in the first 48 h. Patients were allowed to drink liquids on postoperative day 1, and were given a solid diet on the following day. The median postoperative hospital stay was 4.5 days (range, 3–6 days).

In arm B, 18 procedures (90%) were performed laparoscopically, and 2 (10%) were converted to open surgery. Both patients whose procedure was converted to open surgery were male patients with a narrow pelvis, which made distal rectum isolation more difficult. In four cases (20%), a laparoscopic Miles' operation was performed. In two of these cases, the scheduled operation was a low anterior resection, but we had to change the operative strategy because of inadequate free distal margins. Of the 16 patients treated with a low anterior resection, 4 (20%) underwent a protective ileostomy. The median operative time was 165 min (range, 150–194 min) for the laparoscopic low anterior resection and 174 min (range, 150–194 min) for the laparoscopic Miles' procedure. The median intraoperative blood loss was 200 ml (range, 100–350 ml), and four patients (20%) received postoperative blood transfusions. The nasogastric tube was removed at the end of the operation. All the patients required twice daily administration of an analgesic (ketorolac 30 mg) in the first 72 h, were allowed to drink liquids on postoperative day 1, and were given a solid diet on the postoperative day 3. The median postoperative hospital stay was 7.5 days (range, 6–10 days).

During the postoperative period minor complications occurred in two patients (10%) of Arm A related to partial

Table 2. Probability of complications (local and distant failure)

Type of procedure	Probability at the end of follow-up (77.6 months)	95% CI	*p* Value
LR	0.12	0.00–0.27	0.923
TEM	0.10	0.00–0.23	
Relative risk[a]	1.08	0.15–7.78	

CI, confidence interval; LR, laparoscopic resection; TEM, transanal endoscopic microsurgery
[a] Adjusted by age and gender

Table 3. Probability of survival

Type of procedure	Probability at the end of follow-up (77.6 months)	95% CI	*p* Value
LR	0.83	0.66–1.00	0.358
TEM	0.95	0.85–1.00	

CI, confidence interval; LR, laparoscopic resection; TEM, transanal endoscopic microsurgery

suture leakage that required local therapy (antibiotic and anesthetic enema) and parenteral nutrition for 6 days. One major complication (5%) was related to a perianal phlegmon, and it occurred in a 68-year-old, diabetic patient. In this case, no suture leakage was observed at postoperative endoscopy, and a laparoscopic ileostomy was performed after failure of antibiotic therapy.

In arm B, minor complications occurred in two patients (10%) from anastomosis leakage, which resolved with antibiotic therapy and parenteral nutrition. One major complication (5%) was related to pelvic peritonitis on postoperative day 2 from an anastomotic leakage, which was treated with laparoscopic ileostomy and peritoneal washing (Table 1).

At a median follow-up period of 56 months (range, 44–67 months), one local failure (5%) occurred in one arm A (pT2) patient at 6 months of follow-up evaluation, which was treated by laparoscopic abdominoperineal resection. At this writing the patient is still living and disease free after an additional 15 months of follow-up evaluation. Another (pT2) patient exhibited one liver metastasis at 26 months, which was treated by hepatic resection. The patient died 13 months later from systemic disease.

At a median follow-up period of 56 months (range 44–67 months), one arm B pT2 patient (5%) exhibited a local recurrence at 48 months and died 3 months later. Liver metastases developed in another pT2 patient and died after 31 months of follow-up evaluation. The probability of local and distant failure at the end of follow-up evaluation was, respectively, 10% for the TEM group and 12% for the laparoscopic resection group (relative risk, 1.08) (Table 2). The probability of survival at the end of follow-up evaluation was 95% for the TEM group and 83% for the LR group (Table 3).

Discussion

Low anterior resection, particularly in elderly, high-risk patients, may be associated with significant morbidity and mortality. Urinary and sexual dysfunction are reported in up to between 30% and 40% of patients [15], and anastomotic leakage occurs in 5% to 10% of patients, requiring a diverting ileostomy or colostomy. Further complications may arise from the perineal wound after abdominoperineal resection or from the stoma. Mortality rates of 2% to 6% are reported after radical rectal surgery, and this rate is even higher in elderly patients. Local recurrence rates of 7% to 14% are described at 3 years of follow-up evaluation for T_2 and T_3 rectal tumors. The 5-year survival rate after abdominoperineal resection is approximately 60% for all stages. After radical rectal cancer surgery, failure and death occur not only in advanced stages but also in earlier stage I (T_1–T_2) lesions [5, 15]. The high rate of complications and the poor quality of life associated with the sacrifice of the anal sphincter have led surgeons to reconsider local excision combined with neoadjuvant therapies in the treatment of distal rectal cancer to preserve anal continence as well as normal bladder and sexual functions. In fact, the main goal in the management of patients with rectal cancer is to provide the optimal chance for cure while trying to maintain the best quality of life.

Local excision of distal rectal cancer has long been used as an alternative surgical option for patients too unfit to undergo a major abdominal resection or unwilling to have a stoma. Currently, local excision for rectal cancer is accepted in the literature only for T_1 adenocarcinomas with favorable prognostic features: small size, mobility, moderately well to well differentiated histology without vascular, lymphatic or perineural invasion. In these patients, the risk of recurrence is low (3–5%), and it seems acceptable to spare the complications of a more radical operation [2, 5, 14, 15, 18]. Local excision of T_2 and T_3 rectal cancer without neoadjuvant radiotherapy has an unacceptably high local recurrence rate (17–50%) [4, 15, 18].

Adjuvant radiochemotherapy has recently become an integral part of the multidisciplinary approach to the management of rectal tumors in order to reduce the risk of local recurrence [9]. The Stockholm I and II randomized trials have demonstrated the advantages of preoperative radiotherapy in preventing local failure, and currently, there is a general agreement that preoperative radiochemotherapy does reduce the local recurrence rate [9, 12].

Neoadjuvant therapy for T_2–N_0–M_0 rectal cancer aims at reducing the tumor mass in order to perform a less invasive surgery with sphincter preservation and decreased morbidity. Other potential aims are to deliver radiation to well-oxygenated tissues and thereby to improve its efficacy, to eradicate locoregional micrometastatic disease, and to reduce the risk of intraoperative distant dissemination.

Preoperative radiochemotherapy was well tolerated by our patients, and it did not increase the technical difficulty during laparoscopic resection or the suture leakage rate after TEM, which occurred only when tension on the

suture line was present. It must be taken into account that high-dose radiotherapy initially causes tissue edema and subsequent sclerosis of the mesorectum. Because this phenomenon is time dependent, it is important to perform surgery 40 to 50 days after the completion of neoadjuvant radiotherapy. Concerning postoperative morbidity and quality of life, postoperative pain was lower and return to regular eating was faster in arm A. No patient treated with TEM required blood transfusions, and the postoperative hospital stay was shorter.

The results of the current study indicate that with T_2 rectal cancer, a wide local excision combined with preoperative high-dose radiotherapy and chemotherapy can achieve probabilities of local failure and survival that are comparable with those of laparoscopic resection. Clear tumor margins are mandatory. In our series of patients, a full-thickness excision, including at least 1 cm of normal mucosa around the lesion and the largest possible amount of local perirectal fat, was removed. In case of doubt, intraoperative histology by frozen section was performed to confirm complete tumor excision.

Several studies have recently demonstrated, a lower immunologic impairment in patients undergoing a minimally invasive procedure [1, 6, 10]. On the other hand, it is generally accepted that the factors responsible for depressing the immunologic system, such as blood transfusions, are associated with the worst survival rate for patients with colorectal cancer undergoing ''open'' resections. Several reports indicate that laparoscopic colorectal resection is less immunosuppressive than the open approach [1, 6]. Kirman et al. [6] reported that surgical trauma inhibits the immune function and compromises T-cell function in the peripheral tissues. T-cells, which express CD31+, are efficient tumor cell killers, and they decrease after open colorectal surgery, possibly in relation to a wider incision. Open colorectal resection also is associated with significant suppression of cell-mediated immune response, which is not reported after laparoscopic colorectal resection [7].

For these reasons, in the current study we decided to compare the short-term and the oncologic results of two minimally invasive approaches for patients with T_2–N_0–M_0–G_{1-2} low rectal cancer after neoadjuvant therapy. One arm of the study respected the ''classical'' concept of total mesorectal excision. The other arm of the study used a wide full-thickness local excision including only the local perirectal fat. To perform a local excision in T_2–N_0 rectal cancer, we consider it mandatory:

- to achieve a correct preoperative tumor and nodal staging. In recent years this has been made possible because of significant improvements in imaging techniques, namely transanal ultrasound, MRI and helical CT scan imaging.
- to obtain preradiotherapy morphology evaluation and grading of the tumors.
- to perform a complete full-thickness tumor ablation with 1 cm of surrounding free margin, removing also the largest amount of adjacent perirectal fat.
- to use the instrumentation introduced by Buess to achieve the necessary magnification, lighting, and excellent vision inside the rectal lumen.In conclusion the current study adds to a growing body of literature supporting local excision associated with preoperative radiochemotherapy for the management of selected patients with distal rectal cancer. To draw more conclusive scientific conclusions, we must wait to increase the number of cases submitted to this treatment protocol and to increase the duration of follow-up evaluation.

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