

Randomized clinical trial of endoluminal locoregional resection versus laparoscopic total mesorectal excision for T2 rectal cancer after neoadjuvant therapy

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Background: In selected patients with early low rectal cancer, locoregional excision combined with neoadjuvant therapy may be an alternative treatment option to total mesorectal excision (TME).

Methods: This prospective randomized trial compared endoluminal locoregional resection (ELRR) by transanal endoscopic microsurgery versus laparoscopic TME in the treatment of patients with small non-advanced low rectal cancer. Patients with rectal cancer staged clinically as cT2 N0 M0, histological grade G1–2, with a tumour less than 3 cm in diameter, within 6 cm of the anal verge, were randomized to ELRR or TME. All patients underwent long-course neoadjuvant chemoradiotherapy.

Results: Fifty patients in each group were analysed. Overall tumour downstaging and downsizing rates after neoadjuvant chemoradiotherapy were 51 and 26 per cent respectively, and were similar in both groups. All patients had R0 resection with tumour-free resection margins. At long-term follow-up, local recurrence had developed in four patients (8 per cent) after ELRR and three (6 per cent) after TME. Distant metastases were observed in two patients (4 per cent) in each group. There was no statistically significant difference in disease-free survival ($P = 0.686$).

Conclusion: In selected patients, ELRR had similar oncological results to TME. Unique Protocol ID: URBINO-LEZ-1995; registration number: NCT01609504 (<http://www.clinicaltrials.gov>).

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Introduction

Transanal endoscopic microsurgery (TEM) for T1 rectal cancer has gained acceptance as a valid alternative to radical surgery¹. Most surgeons, however, are concerned about extending this to T2 rectal cancer. Without adjuvant treatment, recurrence rates range from 28 to 47 per cent^{2–7}. It is important to note that most published reports do not provide enough detail concerning the extent of local excision. Neoadjuvant treatment may lead to tumour downstaging, possibly allowing higher rates of sphincter-saving operations and better local control of the disease^{8–11}. The present study was designed to assess the oncological results, in terms of local recurrence and distant metastases, of endoluminal locoregional resection (ELRR) performed by TEM compared with laparoscopic

total mesorectal excision (TME), after neoadjuvant chemoradiotherapy in patients with clinical stage cT2 N0 M0, histological grade G1–2 rectal cancer.

Methods

The present protocol was defined during an international expert meeting in Urbino, Italy in 1995, and was approved by the ethics committee. Patients were enrolled between April 1997 and April 2004 in the Department of General Surgery at the University of Ancona and the Department of General Surgery, Surgical Specialities and Organ Transplantation 'Paride Stefanini' at the University of Rome 'La Sapienza'. This randomized clinical trial included selected patients with low rectal tumour limited to the muscularis propria of the rectal wall, without

lymphadenopathy or metastatic disease (clinical (c) T2 N0 M0) on staging according to the National Comprehensive Cancer Network¹². After neoadjuvant treatment, the patients underwent repeat staging to evaluate tumour response and were subsequently randomized to ELRR performed by TEM or to laparoscopic TME.

Inclusion criteria were: American Society of Anesthesiologists (ASA) fitness grade I–II; superior margin of the tumour located within 6 cm of anal verge; histologically confirmed well (G1) or moderately well (G2) differentiated adenocarcinoma with a diameter no larger than 3 cm. Higher-risk patients (ASA III–IV) with more proximally located tumours, poorly differentiated (G3) or undifferentiated (G4) tumours, and tumours with lymphovascular or perineural invasion, were excluded.

Assessment and tumour staging on enrolment

History, clinical evaluation, routine laboratory tests including tumour markers, digital examination to evaluate tumour fixation and sphincter tone were recorded for each patient in a database (Microsoft® Excel; Microsoft, Redmond, Washington, USA).

At admission, staging included: endorectal ultrasonography (EUS) (7-MHz rotating probe; Brüel & Kjaer, Naerum, Denmark); rigid sigmoidoscopy and tumour biopsies; total colonoscopy with vital dye staining of the rectum, taking six to eight standard biopsies of normal mucosa approximately 1 cm around the tumour (with indian ink tattooing of biopsy sites); helical whole-body computed tomography (CT); and pelvic magnetic resonance imaging (MRI). Rigid sigmoidoscopy was performed in order to measure the exact distance of the tumour from the anal verge, and to select the most appropriate patient position on the operating table for TEM surgery.

Each biopsy was examined blindly by three pathologists to assess histological grade, according to cellular differentiation (G1, well differentiated; G2, moderately well differentiated; G3, poorly differentiated; G4, undifferentiated), and lymphatic, vessel and neural infiltration.

Positive lymph node status at imaging was established according to the following criteria: at EUS, diameter more than 0.8 cm, circular or irregular shape, hypervascularization on colour Doppler imaging and hypoechogenicity¹³; and at CT and MRI, diameter over 0.8 cm, circular or irregular shape. All patients with suspicious nodes or inconsistent findings at EUS, CT or MRI tumour staging were excluded from the study. EUS was carried out by expert operators with minimum of 5 years' experience. Each image was analysed by two to three senior radiologists.

Neoadjuvant therapy

All patients underwent long-course three-dimensional four-field chemoradiotherapy in the prone position, with bladder preparation and use of intravenous contrast¹⁴. The total dose given was 50.4 Gy in 28 fractions over 5 weeks. The irradiated areas were: anus, rectum, mesorectum, and regional and iliac lymph nodes. The superior limit was L5–S1 and the inferior limit around 3–5 cm under the ischiopubic ramus. A continuous infusion of 5-fluorouracil 200 mg per m² per day was administered during radiotherapy treatment.

Preoperative staging

Forty days after the end of neoadjuvant therapy, staging was repeated as described above, apart from total colonoscopy. The same surgical and radiological team re-evaluated the tumour to determine whether downsizing or downstaging had occurred. Based on downsizing, patients were classified into responders (tumour mass reduction at least 50 per cent) and low or non-responders (tumour mass reduction less than 50 per cent). Patients with disease progression were excluded.

Patient randomization

Randomization was performed on the day before operation. Patients were allocated randomly in equal numbers to the two arms of the study, ELRR by TEM or laparoscopic TME, by means of sealed opaque envelopes containing computer-generated random numbers. Recruitment stopped when 100 patients had undergone operation.

Surgical treatment

Surgery was performed between 45 and 55 days after the end of chemoradiotherapy. Preoperative washout of the colon with polyethylene glycol was carried out, and short-term antibiotic prophylaxis (metronidazole and second-generation cephalosporin) was administered to all patients. All surgery was performed by two surgeons, both expert in open rectal surgery and skilled in both laparoscopic and TEM procedures. In accordance with the protocol, each surgeon had done at least 80 laparoscopic rectal resections for malignancy and 100 TEM procedures. The laparoscopic surgical techniques were low anterior or abdominoperineal resection with TME. These procedures have been described in detail previously¹⁵.

ELRR by TEM was performed with Wolf (Tuttlingen, Germany) instrumentation, as follows. Mucosal incision included all the tattoo spots marked at admission staging,

in order to excise a minimum of 1 cm of normal mucosa around the tumour, according to its diameter before neoadjuvant therapy. Starting from the mucosal incision the dissection was continued deeply to remove all the mesorectum adjacent to the tumour, following a cutting line with an angle of approximately 120–135° with respect to the mucosal plane. For posterior and lateral lesions, the deep dissection plane was carried down to the 'holy plane', and for anterior lesions to the level of the vaginal septum or the prostatic capsule. For tumour with a distal limit at the level of the anal canal, the incision included the dentate line and the internal sphincter fibres were partially removed. The defect was closed by multiple running sutures according to the technique described by Buess and Mentges¹⁶.

Endpoints and follow-up

The primary endpoint of the study was the oncological result in terms of local recurrence or distant metastases, with minimum follow-up of 5 years. Secondary endpoints were: cancer-related mortality, duration of operation, blood loss, analgesic use, morbidity, hospital stay and 30-day mortality. Major morbidity was defined as complications requiring surgical treatment. To evaluate local and/or systemic recurrence, all patients were followed up prospectively by clinical examination, measurement of tumour markers and sigmoidoscopy every 3 months for the first 3 years, and every 6 months thereafter. Whole-body CT and pelvic MRI were repeated every 6 months for the first 5 years. No adjuvant therapy was administered after curative resection of pathological (p) T2 N0 rectal cancer, in accordance with published guidelines¹².

Statistical analysis

Using a one-sided log rank test, it was calculated that an overall sample size of 100 subjects (50 in each group) would be needed to achieve about 80 per cent power at a 0.05 significance level to detect a difference of 0.20 between groups in the probability of developing recurrence or metastases at 5 years of follow-up (based on a probability of 0.10 in the ELRR group and 0.30 in the TME group).

A non-parametric approach was used to analyse quantitative variables as their distribution was not normal. Quantitative variables are presented as median (interquartile range) unless indicated otherwise. The Wilcoxon rank sum test was used to evaluate differences in continuous data between the two surgical procedures. Qualitative data were analysed by means of χ^2 test or Fisher's exact test (if expected frequencies were lower than 5).

Survival analysis was applied for estimating the cumulative probability of developing recurrence or metastases, as well as overall and cancer-related survival. The Kaplan–Meier method was used to estimate the cumulative probabilities according to surgical procedure and the log rank test to compare the resulting curves. Cox regression analysis was performed to evaluate the effect of prognostic factors on the probability of developing the above events.

A level of probability of 0.05 was chosen to assess statistical significance and 95 per cent confidence intervals (c.i.) were estimated to give a measure of precision.

All statistical analyses were performed using SAS[®] version 9.1 (SAS Institute, Cary, North Carolina, USA).

Results

Between April 1997 and April 2004, from a cohort of 1125 patients with colorectal cancer, 283 patients presented with low rectal cancer (tumour distance within 6 cm of anal verge) and no contraindication to anaesthesia (ASA I–II), and were thus eligible for staging as described above. The other 842 patients were excluded (tumour distance from anal verge more than 6 cm, 716; ASA III–IV, 87; refused to enter study, 32; reason unknown, 7). Some 178 patients with low rectal cancer did not meet the eligibility criteria, leaving 105 with cT2 N0 M0 disease eligible for inclusion. During preoperative staging three patients refused the protocol and decided to have surgery elsewhere. Two other patients, who initially agreed to be included in the trial and had been randomized to laparoscopic TME, asked to have open surgery instead. Finally there were 50 patients in each group (*Fig. 1*). Patients in the two groups were similar in terms of demographic features and response to neoadjuvant treatment (*Table 1*).

Toxicity from chemoradiotherapy included anorectal mucosal irritation, which occurred in 31 and nine patients in the ELRR and TME groups respectively, and diarrhoea in 29 and 11 respectively. These resolved with medical therapy and did not lead to interruption of neoadjuvant therapy.

The overall downstaging and downsizing rates achieved by neoadjuvant therapy were 51 and 26 per cent respectively. Tumours were downstaged in 26 patients in the ELRR group (14 to pT0, 12 to pT1) and 25 in the TME group (13 to pT0, 12 to pT1). Of the remaining 49 patients, 26 (13 in each group) had a reduction in tumour diameter of more than 50 per cent. In the remaining patients a reduction in tumour diameter of less than 50 per cent was observed. All enrolled patients completed

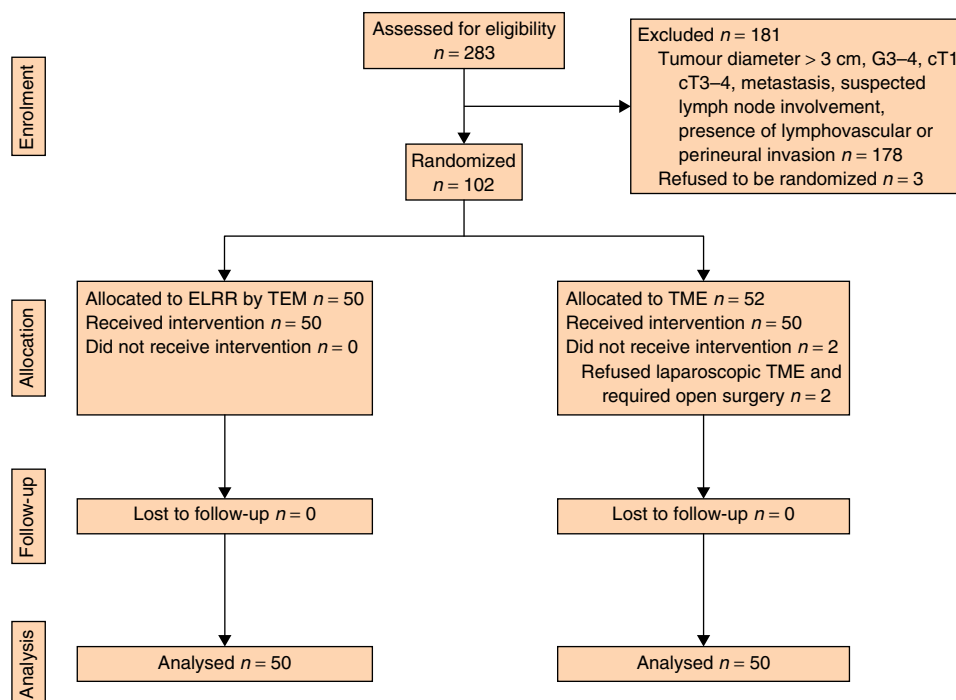


Fig. 1 Flow diagram for the study. cT, clinical tumour category; G, histological grade; ELRR, endoluminal locoregional resection; TEM, transanal endoscopic microsurgery; TME, total mesorectal excision

Table 1 Main characteristics of the patients

	ELRR (n = 50)	TME (n = 50)	P‡
Age (years)*	66 (58–70)	66 (60–69)	0.899§
Sex ratio (M:F)	30:20	34:16	0.405
Distance of lower tumour margin from anal verge (cm)†	4.92 (3–6)	5.00 (3–6)	0.716§
Follow-up (years)*	9.6 (8.5–11.1)	9.6 (7.4–11.9)	0.764§
Alive at follow-up	40	43	
Neoadjuvant treatment			
Downstaging			0.972
pT0	14 (28)	13 (26)	
pT1	12 (24)	12 (24)	
pT2	24 (48)	25 (50)	
Downsizing in pT2 (%)			0.879
≥ 50	13 (26)	13 (26)	
< 50	11 (22)	12 (24)	

Values in parentheses are percentages unless indicated otherwise; values are *median (interquartile range) and †median (range). ELRR, endoluminal locoregional resection; TME, total mesorectal excision; pT, pathological tumour category. ‡ χ^2 test, except §Wilcoxon rank sum test.

neoadjuvant therapy and no patient had disease progression after preoperative staging.

Intraoperative and postoperative data are shown in Table 2. The 30-day mortality rate was zero in both

groups. No patient treated with ELRR experienced an operative programme change, conversion to open surgery or stoma. In the TME group, six patients (12 per cent) had a change in the operative programme during the operation ($P = 0.013$); the procedure was converted to open surgery in five patients (10 per cent) ($P = 0.028$). A total of 23 patients in this group required a stoma, which was temporary in 11 patients (22 per cent) to protect the anastomosis after very low anterior resection, and definitive in 12 (24 per cent) who underwent abdominoperineal resection.

The ELRR group had a significantly shorter operating time (median 90 *versus* 174 min; $P < 0.001$) and less blood loss (45 *versus* 200 ml; $P < 0.001$). No patient in this group received blood transfusions, whereas ten (20 per cent) in the TME group had blood transfusions ($P < 0.001$). Analgesics were administered to all patients in the TME group but to only seven (14 per cent) in the ELRR group ($P < 0.001$).

Patients were allowed to drink liquids and start a semisolid diet on the day after ELRR. In the TME group, the nasogastric tube was removed at the end of the operation and patients were allowed to drink liquids on day 1 or 2 after surgery, as tolerated, and a semisolid diet

Table 2 Main intraoperative and postoperative features according to surgical procedure

	ELRR (n = 50)	TME (n = 50)	P†
Intraoperative programme change	0 (0)	6 (12)	0.013‡
Conversion to open surgery	0 (0)	5 (10)	0.028‡
Stoma			
Temporary	0 (0)	11 (22)	< 0.001
Definitive	0 (0)	12 (24)	< 0.001
Duration of operation (min)*	90 (90–100)	174 (160–190)	< 0.001§
Blood loss (ml)*	45 (45–45)	200 (100–350)	< 0.001§
No. of patients receiving transfusion	0 (0)	10 (20)	< 0.001
No. of patients receiving analgesia	7 (14)	50 (100)	< 0.001
Hospital stay (days)*	3 (3–4)	6 (5–7)	< 0.001§
Postoperative complications			
Minor	6 (12)	7 (14)	0.766
Major	1 (2)	3 (6)	0.250‡

Values in parentheses are percentages unless indicated otherwise; *values are median (interquartile range). ELRR, endoluminal locoregional resection; TME, total mesorectal excision. † χ^2 test, except ‡Fisher's exact test and §Wilcoxon rank sum test.

on day 3. Median postoperative hospital stay was 3 (3–4) days after ELRR and 6 (5–7) days after TME ($P < 0.001$).

There were no statistically significant differences between the groups in minor or major postoperative complications. In the ELRR group, six patients (12 per cent) had suture-line leakage that resolved with local therapy (antibiotics and local anaesthetic enema) and parenteral nutrition for 6 days. One major complication, a perianal phlegmon, occurred in a 68-year-old diabetic patient; no suture-line leakage was shown at postoperative colonoscopy and a laparoscopic ileostomy was performed after failure of antibiotic therapy. In the TME group, five (13 per cent) of 38 patients had minor anastomotic leakage that resolved with antibiotics and parenteral nutrition, and two (4 per cent) had postoperative haemorrhage requiring blood transfusions. Three major complications (8 per cent of 38 patients) related to pelvic peritonitis from anastomotic leakage were treated with peritoneal irrigation and laparoscopic ileostomy. The median duration of follow-up was 9.6 years for both groups (range 5.5–12.4 years in ELRR group and 4.7–12.3 years in TME group).

All patients had R0 resection with tumour-free resection margins. At definitive histology no positive lymph nodes were observed. The median number of lymph nodes removed with the specimen was 1 (0–3) in the ELRR group and 11 (10–14) in the TME group ($P < 0.001$). This is in accordance with the number of lymph nodes identified in

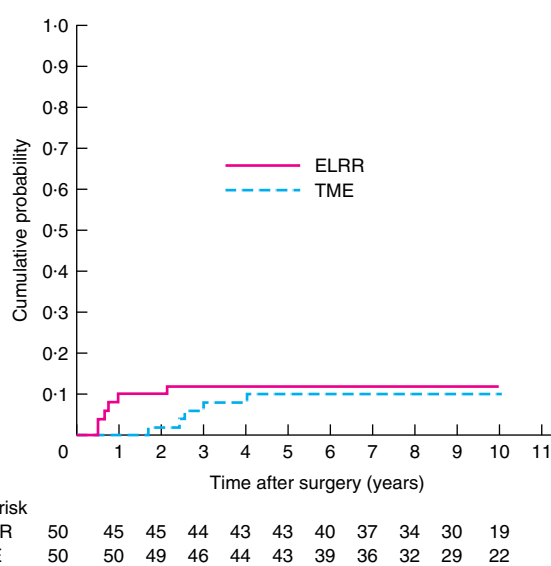


Fig. 2 Cumulative probability of developing recurrence or metastases according to type of operation. ELRR, endoluminal locoregional resection; TME, total mesorectal excision. $P = 0.686$ (log rank test)

the specimen after neoadjuvant therapy, which is usually significantly lower than in patients who did not receive such therapy¹⁷.

During follow-up, six patients developed recurrence or metastases after ELRR (4 local recurrence, 2 metastasis) and five after TME (3 local recurrence, 2 distant metastasis). In both groups, local recurrence or distant metastasis occurred only in low or non-responders to neoadjuvant therapy. Fig. 2 shows the cumulative probability of developing recurrence or metastases according to the surgical procedure. The probability of developing recurrence or metastases at the end of follow-up was 12 (95 per cent c.i. 6 to 25) per cent after ELRR and 10 (4 to 22) per cent after TME ($P = 0.686$).

Ten patients in the ELRR group and seven in the TME group died during follow-up. Of these, four and three patients respectively died from cancer-related causes. The cancer-related survival rate at the end of follow-up was 89 (70 to 96) per cent for those who underwent ELRR and 94 (82 to 98) per cent for patients who underwent TME ($P = 0.687$) (Fig. 3). Overall survival rates at the end of follow-up were 72 (51 to 86) and 80 (62 to 90) per cent respectively ($P = 0.609$).

Cox regression analysis was used to estimate the relative risk (RR) of failure (developing recurrence, metastases and/or death) according to the main prognostic factors. Variables included in the analysis were: type of procedure (ELRR versus TME), duration of operation, blood loss

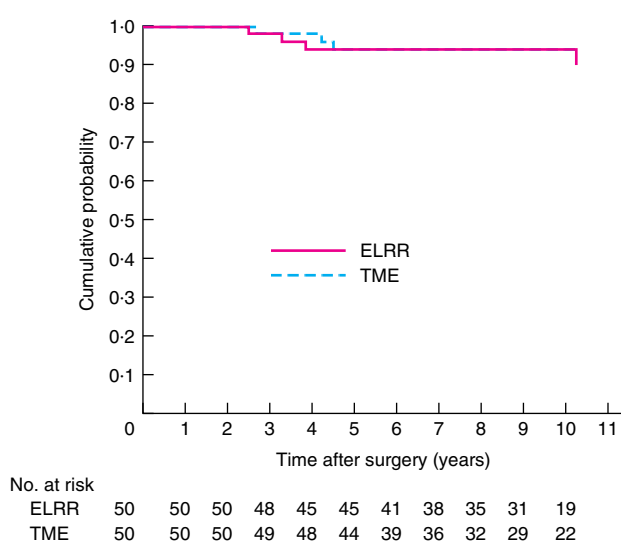


Fig. 3 Cumulative probability of cancer-related survival according to type of operation. ELRR, endoluminal locoregional resection; TME, total mesorectal excision. $P = 0.687$ (log rank test)

and hospital stay. In the final model, type of procedure (RR 14.24, 95 per cent c.i. 1.36 to 149.16; $P = 0.027$) and blood loss (RR 1.01, 1.00 to 1.01; $P < 0.001$) were the only variables with a significant effect on the development of recurrence or metastases. Even if the RR estimate had a very low level of precision because of few events in both groups (as shown by the width of the confidence interval), ELRR played a significant role in the development of local recurrence or distant metastasis compared with TME. The significantly higher risk could be explained by the earlier occurrence of events in that group, as illustrated in Fig. 2. When the RR of death was evaluated, no variable significantly affected the probability of failure.

Discussion

According to the literature^{1,18} local excision is curative in patients with primary tumour limited to the mucosa or invading, but not extending beyond, the submucosa of the rectum with no high-risk features (poorly differentiated, lymphovascular and neural invasion, presence of mucinous histology and tumour ulceration), as also clearly stated in the guidelines for treatment of rectal cancer of the National Comprehensive Cancer Network¹².

A few studies have reported experience of local excision by TEM in the management of T2 rectal cancer, but these were not randomized and long-term results are not yet available^{1,7,19}. Some authors have also reported acceptable oncological results in patients with T3 rectal

cancer who responded to neoadjuvant chemoradiotherapy and were treated with transanal excision^{8,9}. This approach may have an equivalent outcome to radical surgery in patients with a complete response to neoadjuvant chemoradiotherapy²⁰. Patients with residual mucosal abnormalities after chemoradiotherapy have a low risk of nodal metastases and may be suitable for local excision²¹. A recent review demonstrated that pathological complete response correlates with excellent long-term survival, as well as low local recurrence and distant metastasis rates²². Proctectomy with intersphincteric resection and local excision is an alternative to abdominoperineal resection that has shown acceptable oncological results with better functional outcome than radical surgery²³, although not always satisfactory.

The authors have described ELRR, an original surgical technique with *en bloc* resection of the rectal wall including the locoregional mesorectal fat and its fascia. The present study was designed as a prospective randomized trial comparing the short- and long-term outcomes (minimum follow-up 5 years) of two minimally invasive surgical procedures (ELRR by TEM *versus* laparoscopic TME with low anterior resection or abdominoperineal resection) for small cT2 N0 M0, G1–2 rectal cancer previously treated with long-course chemoradiotherapy.

Close follow-up is essential to verify whether salvage surgery is required. For low rectal cancer, local recurrence after TME is the major problem and carries a poor prognosis²⁴. Curative treatment with sphincter preservation is rarely possible. In contrast mucosal local recurrence developing after ELRR by TEM can be treated by salvage TME²⁵.

Neoadjuvant therapy may downstage or downsize the tumour, reduce the local recurrence rate and increase the rate of sphincter preservation^{11,26}. Preoperative chemoradiotherapy was well tolerated by the patients and in the authors' experience did not significantly increase either the technical difficulty of the operation or the risk of suture dehiscence during laparoscopic resection or TEM. The main criticism of local excision is that it does not remove the draining lymph nodes. Correct staging by imaging before neoadjuvant therapy is crucial to define patient eligibility for ELRR. In the present study, all patients underwent pelvic MRI and whole-body CT before surgery, evaluated by two to three different operators, and EUS in order to confirm T category, evaluate lymph node status and identify metastatic disease.

The majority of published studies on local excision did not specify the surgical technique well enough to evaluate whether the local excision performed was adequate in terms of circumferential margin and radial clearance from

the tumour, as well as depth of mesorectal fat excision. In a multicentre study on local excision by TEM in 847 patients, a local recurrence rate of 29.3 per cent was reported²⁷. There are multiple reasons for these unfavourable results: a limited number of patients enrolled by each centre, inadequate preoperative staging (in 31 per cent of patients the lesion was considered benign) and surgical technique (R1 rate 22 per cent). Moreover only 34.3 per cent of TEM resections adhered to guidelines for local excision. The extent of mesorectum removal *en bloc* with the rectal wall is the most relevant surgical innovation that differentiates the technique employed in the present study from that of other authors¹⁶.

The oncological results of the present study showed that the probability of developing recurrence or metastases was similar in both groups. Similarly, the cancer-related survival rate at the end of follow-up was not different. The short-term results, on the other hand, significantly favoured ELRR by TEM in terms of operating time, stoma rate, blood loss and transfusions, need for analgesia and hospital stay. There was no significant difference in morbidity rates, although more minor and major complications such as pelvic peritonitis and haemorrhage were observed after TME. In contrast, no life-threatening complication occurred after ELRR by TEM, and no suture-line leakage was demonstrated in the only patient who underwent ileostomy, who had diabetes.

In a previous paper, the authors reported that histological grade, a traditionally valid prognostic factor, seemed less reliable in predicting the results after neoadjuvant therapy²⁶. On this basis, a longer duration of follow-up is recommended, as reported in the present study.

ELRR by TEM may be used to treat patients with cT2N0M0 small rectal cancer after neoadjuvant chemotherapy. Patient selection is a crucial factor and requires a dedicated multidisciplinary team. The technical accuracy of ELRR, which can be achieved only by TEM carried out by well trained surgeons, provides a curative treatment that avoids the risks of major surgery, with more favourable short-term results and similar long-term oncological outcomes to those of TME.

Disclosure

The authors declare no conflict of interest.

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