Endoluminal locoregional resection versus laparoscopic total mesorectal excision for t2 rectal cancer after neoadjuvant therapy: a randomized clinical trial

Alessandro Maria Paganini1
Mario Guerrieri2
Giovanni Lezoche2
Andrea Balla1
Daniele Scoglio1
Silvia Quaresima1
Gianfrancesco Intini1
Maria Vittoria Antonica1
Emanuele Lezoche1

1Department of Surgery “Paride Stefanini”, Endolaparoscopic Surgery and Advanced Technology Unit, Policlinico “Umberto I”, Rome, Italy
2Clinic of General Surgery and Surgery Methodology, Polytechnic University of Marche, Ancona, Italy

Corresponding Author:
Andrea Balla
Department of Surgery “Paride Stefanini”, Endolaparoscopic Surgery and Advanced Technology Unit, (Director Prof. E. Lezoche), Policlinico “Umberto I”, Rome, Italy
E-mail: andrea.balla@gmail.com

Summary

Background: locoregional excision combined with neoadjuvant therapy may be an alternative treatment option to total mesorectal excision (TME) in selected patients with early low rectal cancer. Methods: endoluminal locoregional resection (EL-RR) by transanal endoscopic microsurgery and laparoscopic TME were compared in a prospective randomized trial. Patients with rectal cancer staged clinically as cT2 N0 M0, histological grade G1-2, tumour less than 3 cm in diameter, within 6 cm from the anal verge were randomized to ELRR or TME after longcourse neoadjuvant chemoradiotherapy. All statistical analyses were performed using SAS®version 9.1 (SAS Institute, Cary, North Carolina, USA). 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 χ² test or Fisher’s exact test (if expected frequencies were lower than 5). 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.

Results: there were 50 patients in each group. Tumour downstaging and downsizing rates after neoadjuvant chemoradiotherapy were 51 and 26% 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%) after ELRR and three (6%) after TME. Distant metastases occurred in two patients (4%) 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.

KEY WORDS: rectal cancer, neoadjuvant radiochemotherapy, TEM, TME, ELRR.

Introduction

Transanal endoscopic microsurgery (TEM) for T1 rectal cancer is accepted as a valid alternative to radical surgery (1). Most surgeons, however, are concerned about extending this to T2 rectal cancer. Without adjuvant treatment, recurrence rates range from 28 to 47% (2-7). Most published reports, however, do not provide enough detail on the extent of local excision. Neoadjuvant treatment may lead to tumour downstaging, possibly allowing higher rates of sphincter-saving operations and better local tumour control (8-11). The 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 protocol was defined during an international expert meeting in Urbino, Italy in 1995, and was approved by the ethics committee. Patients enrollment occurred between April 1997 and April 2004 in the Department of General Surgery at the University of Ancona and the Department of General Surgery, Surgical Specialties and Organ Transplantation “Paride Stefanini” at the “Sapienza” University of Rome, Italy. This randomized clinical trial (RCT) included selected patients with low rectal cancer confined to the muscularis propria, without lym-
Patient assessment and tumour staging

History, clinical evaluation, 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; Bruel & 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 hypoechogenicity (13); 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. 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 contrast (14). 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. Intravenous 5-fluorouracil (200 mg per m² per day) continuous infusion was administered during radiotherapy.

Preoperative staging

Staging was repeated as described above (except total colonoscopy) 40 days after the end of neoadjuvant therapy. The tumour was again evaluated by the same surgical and radiological team to determine whether downsizing or downstaging had occurred. Based on tumour response, patients were classified into responders (tumour mass reduction at least 50%) and low or non-responders (tumour mass reduction less than 50%). Patients with disease progression were excluded.

Patient randomization

Randomization took place on the day prior to surgery. Patients were randomly allocated 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, 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 hypoechogenicity (13); 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. Each image was analysed by two to three senior radiologists.

Endpoints and follow-up

The primary endpoint of the study was the oncological result in terms of local recurrence or distant metas-
tases, 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 (12).

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% 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 χ² 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% 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, 283 patients presented with low rectal cancer (tumour distance within 6 cm of anal verge) from a cohort of 1125 patients with colorectal cancer, and no contraindication to anaesthesia (ASA I-II), and were thus eligible for staging as described above. The remaining 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 patients 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. In the end, 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 (Tab. 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% 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%. In the remaining patients a reduction in tumour diameter of less than 50% was observed. All enrolled patients completed neoadjuvant therapy and no patient had disease progression after preoperative staging. Intraoperative and postoperative data are shown in Table 2. Mortality was nil 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%) had a change in the operative programme during the operation (P = 0.013); the procedure was converted to open surgery in five patients (10%) (P = 0.028). A total of 23 patients in this group required a stoma, which was temporary in 11 patients (22%) to protect the anastomosis after very low anterior resection, and definitive in 12 (24%) 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%) in the TME group had blood transfusions (P < 0.001). Analgesics were administered to all patients in the TME group and to seven (14%) 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 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 two groups in minor or major postoperative complications. In the ELRR group, six patients (12%) 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 demonstrated at postoperative colonoscopy and a laparoscopic ileostomy was performed after failure of antibiotic therapy. In the TME group, five (13%) of 38 patients had minor anastomotic leakage that resolved with antibiotics and parenteral nutrition, and two (4%) had postoperative haemorrhage requiring blood transfusions. Three major complications (8% of 38 patients) related to pelvic peritonitis from anastomotic leakage were treated with peritoneal irrigation and laparoscopic ileostomy. The median follow-up duration was 6-9 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 the specimen after neoadjuvant therapy, which is usually significantly lower than in patients who did not receive such therapy (17). Six patients developed recurrence or metastases after ELRR (4 local recurrence, 2 metastasis) and five after TME (3 local recurrence, 2 distant metastasis) during follow-up. In both groups, local recurrence or distant metastasis occurred only in low or non-responders to neoadjuvant therapy. Figure 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% c.i. 6 to 25) % after ELRR and 10 (4 to 22) % 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
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), EL-RR 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 Figure 2. When the RR of death was evaluated, no variable significantly affected the probability of failure.

**Discussion and Conclusions**

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) (1, 18), as also stated in the NCCN guidelines for treatment of rectal cancer (12). Few studies have reported the results 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 chemoradiotherapy (20). Patients with residual mucosal abnormalities after chemoradiotherapy have a low risk of nodal metastases and may be suitable for local excision (21). A recent review demonstrated that pathological complete response correlates with excellent long-term survival, as well as low local recurrence and distant metastasis rates (22). Proctectomy with intersphincteric resection and local excision is an alternative to abdominopерineal resection with acceptable oncological results and better functional outcome as compared to radical surgery (23), 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 abdomino-perineal resection) for small cT2 N0 M0, G1-2 rectal cancer after long-course chemoradiotherapy. Close follow-up is essential to verify whether salvage surgery is required. For low rectal cancer, local recurrence after TEM is the major problem and carries a poor prognosis (24). Curative treatment with sphincter preservation is rarely possible. In contrast, mucosal local recurrence developing after ELRR by TEM can be treated by salvage TME (25). Neoadjuvant therapy may downstage or downsize the tumour, reduce the local recurrence rate and increase the sphincter preservation rate (11, 26). Preoperative chemoradiotherapy was well tolerated by the patients in the present series and in the
Disclosure

The authors declare no conflict of interest.

References

19. Lezoche G, Guerrieri M, Baldarelli M, et al. Transanal endoscopic microsurgery for 135 patients with small non ad-

A.M. Paganini et al.