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ScienceDirect

EJSO 43 (2017) 1488–1493

EJSO the Journal of Cancer Surgery

www.ejso.com

Transanal endoscopic microsurgery after neoadjuvant radiochemotherapy for locally advanced extraperitoneal rectal cancer

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Accepted 11 May 2017

Available online 25 May 2017

Abstract

Purpose: The aim of this study is to provide a prospective analysis of post-operative and oncological outcomes in patients affected by locally advanced rectal cancer (LARC), who obtained a major/complete clinical response after pre-operative radio-chemotherapy (RCT) and were treated with local excision (LE) by trans-anal endoscopic microsurgery (TEM) to confirm a pathological complete response (pCR) after to neo-adjuvant RCT.

Methods: All patients with LARC treated by pre-operative RCT and full-thickness LE by TEM (2000–2014) were included in the study. If the pathological analysis confirmed near complete or pCR, intensive follow up was proposed. If the pathological response was incomplete, a radical resection with TME was proposed. Post-operative (according to Clavien's classification), functional and long-term oncological outcome were analyzed.

Results: 36 patients were treated by TEM. The median post-operative hospital stay was 5 days. The post-operative morbidity was 41.6% (no grade ≥3). At pathological analysis, 23 specimens were ypT0 TRG1, and 4 were ypT1 TRG2. In 9 cases (ypT>1 and/or TRG>2), radical surgery with TME was proposed but 3 refused it. Median follow-up was 68 months. One local recurrence and 4 distant metastases occurred. The 5-yr actuarial local control, overall survival and disease-free survival were 96.0%, 92.0% and 82.8%.

Conclusions: In case of major or complete clinical response of LARC after pre-operative RCT, LE by TEM can be used to confirm the pathological response. This avoids the necessity of radical surgery and, in our experience, this approach seems to guarantee oncological safety with the functional advantages of an organ-sparing procedure.

Keywords: Rectal cancer; Radiochemotherapy; Transanal endoscopic microsurgery; Complete pathological response; Organ-sparing; Tailored treatments

Introduction

Neo-adjuvant pre-operative radiotherapy (RT) or radio-chemotherapy (RCT) followed by radical surgical resection with total mesolectal excision (TME) represents the gold standard of treatment for locally advanced extra-peritoneal rectal cancer. Several trials have demonstrated the efficacy of pre-operative RCT in reducing the rate of local recurrence.[1,2] Neo-adjuvant RCT is also associated with a significant rate (8–30%) of pathological complete responses (pCR).[3] From an oncological perspective, pCR represents an extremely favorable prognostic factor, with disease-free and overall survival rates of approximately 90%.[4] In view of these results, in this selected group of rectal cancer patients, radical surgery with TME can be considered over-treatment due to the related risk of short- and long-term

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http://dx.doi.org/10.1016/j.ejso.2017.05.011

post-operative complications, especially in terms of functional outcomes.[5] For these reasons, a rectum-preserving policy called "watch and wait," based on clinical observation without any type of surgery, has been suggested for those patients who have obtained a clinical complete response (cCR) of the tumor after RCT. Oncological outcomes similar to those of patients treated with radical surgery with TME have been reported.[6,7] The major criticisms to the "watch and wait" approach are based on the different correlation rates reported between cCR and pCR (ranging between 25 and 75%)[8–10] and the significant rate of local regrowth during the first year of observation. Local excision by trans-anal endoscopic microsurgery (TEM) has been proposed in rectal cancer patients who were pre-operatively treated with RCT to obtain a surgical specimen to be analyzed. Since its introduction in our institution, the full-thickness excision by TEM of the rectal wall disk containing the residual scar of rectal cancer after pre-operative RCT is considered the most effective diagnostic tool for identifying a pCR after neoadjuvant RCT. In this context, two multicenter studies evaluated the role of local excision after CRT in major responder patients and reported promising oncological results.[11,12] The aim of this study was to provide a prospective institutional analysis of complications, oncological outcomes and functional results in patients who were treated with long-course RCT for locally advanced extra-peritoneal rectal cancer and obtained a major or complete clinical response and were subsequently treated by TEM.

Materials and methods

From 2000 to 2014, all patients who were affected by no-metastatic extra-peritoneal rectal cancer (up to 12 cm from the anal margin) were enrolled in a pre-treatment workup that included a digital examination, colonoscopy with biopsy, chest and abdominal computed tomography scan, pelvic magnetic resonance imaging (MRI) and positron emission tomography (PET). Patients with early (cT1-2 N0 M0) extra-peritoneal rectal cancer were directly submitted to surgery (TME or TEM in selected low-risk cT1 cases). If pre-treatment workup staged the cancer as non-metastatic locally advanced (T3-4 N0 M0/any T N + M0), the patients were treated with neo-adjuvant long-term RCT. Patients with low-lying stage T2 tumors, who were candidates for abdominoperineal resection, were also considered eligible for neo-adjuvant RCT. The radiation therapy consisted of 50.4 Gy of external-beam radiation therapy to the pelvis. During the study, different protocols of chemotherapy were adopted: cisplatin and 5-Fluouracil (5-FU PVI protocol),[13] raltitrexed and oxaliplatin (TOMOX protocol)[14] or oxaliplatin and capecitabine (CAPOX and XELOX protocols).[15,16] Six weeks after the end of RCT, re-staging exams were performed to estimate the tumor response to RCT. The clinical response to RCT was assessed according to the World Health Organization score.[17,18] A clinical major or complete response (cCR) was established if the following was observed:

- At digital examination and endoscopy: no mucosal abnormality, a residual scar or a superficial ulcer less than 1 cm;
- At MRI: absence of cancer in the rectum and absence of positive regional lymph node;
- At PET: absence of pelvic signal-uptake.

A local excision by TEM was proposed to patients with a major or cCR to assess the pathological response of primary tumor. Pre-operatively, all patients signed an informed consent form that was approved by the Ethics Committee. TEM was performed under general anesthesia, using Richard Wolf's (Knittlingen, Germany) TEM equipment, according to the standard technique described by Buess et al.[19] Only one surgeon (C.C.) performed TEM. In all patients, a full-thickness excision was performed, and the wound was closed with one or more running sutures and secured with silver clips. All patients had a urinary catheter in place at the time of surgery, which was removed 24 h after operation. All patients were given antibiotics with gram-negative, aerobic and anaerobic coverage, e.v. Narcotics were prescribed on demand. The specimens were staged according to the TNM system.[20] Tumor response to RCT was evaluated according to Mandard's tumor regression grade.[21] When specimen examination confirmed a complete (ypT0 and TRG1) or nearly complete (ypT1 and TRG2) pathological response with margins free of tumors (tumor was >1 mm from the border of resection), no adjunctive radical surgery or RCT was proposed to the patient. In all other cases (ypT>1 or ypT1 TRG>2), immediate (within 1 month) radical surgery with TME was suggested. Short-term (within 30 days) post-operative morbidity and mortality after TEM were recorded, and complications were graded according to the classification proposed by Clavien and colleagues.[22] Patients received a follow-up every 3 months in the first 2 years and then every 6 months during years 3–5. At each visit, digital rectal examination, carcinoembryonic antigen measurement and proctoscopy were performed. Pelvic MRI, CT scan were scheduled every 6 months in the first 2 years and annually during years 2–5. Colonoscopy was performed yearly in the first 5 years. Local recurrence (LR) was defined as the presence of tumor in the pelvis, perineum or intraluminal as diagnosed by histological, radiological, or clinical examination. Distant metastasis was defined as evidence of a tumor in any other organ or body site. The probabilities of overall survival (OS), disease-free survival (DFS) and local control (LC) were calculated using the product limit method of Kaplan–Meier. Survival was calculated from the day of surgery by TEM. The functional results after TEM were evaluated at a follow-up visit one year after surgery. Patients who had undergone to TEM after RCT were asked to answer questions to evaluate the