

Non-inferiority multicenter prospective randomized controlled study of rectal cancer T₂–T_{3s} (superficial) N₀, M₀ undergoing neoadjuvant treatment and local excision (TEM) vs total mesorectal excision (TME)

X. Serra-Aracil¹ · C. Pericay² · T. Golda³ · L. Mora¹ · E. Targarona⁴ · S. Delgado⁵ · A. Reina⁶ · F. Vallribera⁷ · J. M. Enriquez-Navascues⁸ · S. Serra-Pla¹ · J. C. Garcia-Pacheco¹ · On behalf of TAU-TEM study group

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Abstract

Purpose The standard treatment of rectal adenocarcinoma is total mesorectal excision (TME), in many cases requires a temporary or permanent stoma. TME is associated with high morbidity and genitourinary alterations. Transanal endoscopic microsurgery (TEM) allows access to tumors up to 20 cm from the anal verge, achieves minimal postoperative morbidity and mortality rates, and does not require an ostomy. The treatment of T₂, N₀, and M₀ cancers remains controversial. Preoperative chemoradiotherapy (CRT) in association with TEM reduces local recurrence and increases survival. The

TAU-TEM study aims to demonstrate the non-inferiority of the oncological outcomes and the improvement in morbidity and quality of life achieved with TEM compared with TME. **Methods** Prospective, multicenter, randomized controlled non-inferiority trial includes patients with rectal adenocarcinoma less than 10 cm from the anal verge and up to 4 cm in size, staged as T₂ or T₃-superficial N₀-M₀. Patients will be randomized to two areas: CRT plus TEM or radical surgery (TME). Postoperative morbidity and mortality will be recorded and patients will complete the quality of life questionnaires before the start of treatment, after CRT in the CRT/TEM arm, and 6 months after surgery in both arms. The estimated sample size for the study is 173 patients. Patients will attend follow-up controls for local and systemic relapse.

Conclusions This study aims to demonstrate the preservation of the rectum after preoperative CRT and TEM in rectal cancer stages T₂–T_{3s}, N₀, M₀ and to determine the ability of this strategy to avoid the need for radical surgery (TME).

Trial registration [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01308190) identifier: NCT01308190. Número de registro del Comité de Ética e Investigación Clínica (CEIC) del Hospital universitario Parc Taulí: TAU-TEM-2009-01.

Keywords Rectal cancer · Neoadjuvant treatment and rectal cancer · Local excision and rectal cancer · Transanal endoscopic microsurgery (TEM) · Total mesorectal excision (TME)

Background

Local surgery for superficial T₂–T₃, N₀, M₀ rectal cancer is limited by node involvement, which reaches rates of between

✉ X. Serra-Aracil
xserraa@gmail.com; jserraa@tauli.cat

¹ Coloproctology Unit, General and Digestive Surgery Department, Parc Tauli University Hospital, Universitat Autònoma de Barcelona, Parc Tauli s/n. 08208, Sabadell, Spain

² Medical Oncology Department, Parc Tauli University Hospital, Universitat Autònoma de Barcelona, Sabadell, Spain

³ Coloproctology Unit, General and Digestive Surgery Department, Bellvitge University Hospital, Barcelona, Spain

⁴ General and Digestive Surgery Department, Santa Creu and Sant Pau University Hospital, Barcelona, Spain

⁵ General and Digestive Surgery Department, Clinic University Hospital, Barcelona, Spain

⁶ Coloproctology Unit, General and Digestive Surgery Department, Torrecardenas University Hospital, Almeria, Spain

⁷ Coloproctology Unit, General and Digestive Surgery Department, Vall d'Hebron University Hospital, Barcelona, Spain

⁸ General and Digestive Surgery Department, Donostia University Hospital, Donostia, Spain

12 and 28% [1]. Recurrence after local excision is higher than 20%, a figure considered unacceptable. Recent meta-analyses of local surgery followed by adjuvant therapy in these tumors have not reported any great improvements, with rates between 11 and 19% [2]. Therefore, the treatment of choice for T2–3s, N0, M0 rectal cancer in the middle and lower third is total mesorectal excision (TME), which achieves local recurrence rates of between 2 and 11% and systemic recurrence between 2 and 13%; however, the morbidity and mortality rates associated with TME are high, at 30–40 and 2%, respectively [3]. TME patients usually require temporary or permanent ostomies and the genitourinary and sexual dysfunction alterations reach non-negligible rates of between 20 and 30% [4, 5]. These circumstances directly compromise the quality of life of these patients.

To a large extent, transanal endoscopic microsurgery (TEM) is able to correct these problems. First described by Buess [6], TEM is an endoscopic procedure that preserves the sphincter apparatus and allows access to rectal tumors located up to 20 cm from the anal verge. Postoperative morbidity rates are below 10% and mortality is close to 0%, and no genitourinary alterations or sexual dysfunctions have been reported [7, 8].

Attempting to preserve the rectum, the combination of preoperative chemoradiotherapy (CRT) and local excision has been proposed as a less aggressive alternative to TME, since it appears to obtain similar results [9, 10]. The main objective of neoadjuvant treatment is to achieve the highest percentage of pathological complete response (pCR) and thus to obtain the best oncological results. The pCR values published in the literature for locally advanced rectal cancer range from 15 to 27% [11]. In T2 and T3, they vary widely, between 11.7 and 73% [12]; a recent study by the group leading the present study found a rate of 37.5% [13].

In order to address the issues of local and systemic disease and quality of life, since 2010, our group has led a randomized, controlled, prospective, multicenter clinical trial of T2–T3 (superficial) N0, M0 rectal cancer, comparing the combination of neoadjuvant treatment (CRT) plus TEM with standard TME.

Hypothesis and objectives

Hypothesis

In patients with rectal adenocarcinoma (ADK) located less than 10 cm from the anal verge and with a size of 4 cm or less, staged as T2-N0-M0 and superficial T3-N0-M0 by endorectal ultrasound (ERUS) and magnetic resonance imaging (MRI), who undergo preoperative CRT and subsequent local surgery (TEM), the efficacy results will be similar to those obtained radical surgery (TME) in terms of local

recurrence and tolerance; in addition, quality of life will be improved.

Objectives

The primary objective is to compare local recurrence at 2 years in patients treated with preoperative CRT and TEM and in patients undergoing conventional radical TME surgery.

The secondary objectives are to compare the 3-year survival results in patients treated with preoperative CRT and TEM or with conventional radical TME surgery and to evaluate postoperative morbidity and mortality and quality of life in patients undergoing one or other treatment, both before and after the procedure. The following measures will be taken:

- Study of postoperative morbidity and mortality in the groups assessed, using the Dindo-Clavien classification [14] and the Comprehensive Complication Index (CCI) [15].
- Comparison of specific elements with a bearing on quality of life; bladder, urinary, and sexual dysfunction, and the need for an ostomy in the two groups.
- Assessment of quality of life and morbidity associated with preoperative CRT in the local surgery group.
- Study of the clinical and histological response of patients undergoing preoperative CRT and subsequent local surgery (TEM).

Methods/design

Study design

Prospective, multicenter, randomized controlled non-inferiority trial of the treatment of T2–T3 (superficial) N0, M0 cancer with preoperative CRT and TEM versus TME.

Recruitment and scope of the study

To achieve the predetermined sample size and to increase the external validity of the study, a multicenter design will be used.

Spanish hospitals with specialized colorectal surgery, radiodiagnosis, oncology, and radiotherapy units will be enlisted. The hospitals included are Hospital Universitario Parc Tauli de Sabadell, Hospital Clínic de Barcelona, Hospital de Sant Pau de Barcelona, Hospital de Bellvitge, Hospital de la Vall d'Hebron de Barcelona, Hospital General Universitario de Valencia, Hospital La Paz de Madrid, Hospital de Getafé de Madrid, Hospital Marqués de Valdecillas, Hospital Torrecardenas de Almería, Hospital del Mar, Hospital Fundación Jiménez Díaz, Hospital Reina Sofía de Córdoba,

Hospital de Sagunto, Hospital Cabueñes de Gijón, Hospital Universitario de Donostia, Hospital General Universitario de Elche, and Hospital Universitario Joan XXIII de Tarragona.

Patients: definition of the study population

All patients diagnosed with a rectal tumor will undergo a complete colonoscopy with multifocal biopsy to indicate the tumor's distance from the anal verge and its size. Endorectal ultrasound (ERUS), pelvic magnetic resonance imaging (MRI), and abdominal computed tomography (CT) will be performed. Tumor markers CEA and CA 19.9 will be determined preoperatively. Preoperative staging with ERUS will apply the criteria described by Hildebrandt [16], and staging with pelvic MRI the criteria described by Brown [17, 18]. T3 tumors will be subdivided into two groups: superficial, when tumor invasion of the mesorectum is less than 4 mm, and deep when invasion is 4 mm or more [19].

The maximum diameter of the tumor will be measured in order to apply the RECIST (Response Evaluation Criteria In Solid Tumors) [20] criteria and thus assess the response of patients to neoadjuvant treatment.

Inclusion criteria

Inclusion criteria are as follows: rectal ADK located within 10 cm of the anal verge, measured by rigid rectoscopy at the time of ERUS; preoperative staging of T2 N0 by ERUS and pelvic MRI; in the case of disparity, the more advanced staging will be considered as definitive diagnosis; superficial T3, N0 by MRI, when the tumor invasion of the mesorectum is less than 4 mm; tumors with a maximum diameter of 4 cm or less as measured by MRI; ASA Index III or less; the absence of distant metastases on abdominal CT and chest X-ray (if not conclusive, chest CT); pathological variables in the TME specimen (distal margin more than 2 cm, circumferential margin more than 1 mm, the presence of more than 12 nodes in the specimen); TEM pathology specimen with full thickness excision and minimal distance of 1 mm between the tumor and the lateral and deep resection margin.

Exclusion criteria

Exclusion criteria are as follows: preoperative staging by ERUS or pelvic MRI of T1, deep T3–T4 or N1–2; the presence of distant metastases; synchronicity with other colorectal ADKs; radiotherapy; failure to sign informed consent.

Patients who meet these exclusion criteria will be assigned to the conventional cancer protocol.

All patients who meet the inclusion criteria will complete two quality of life questionnaires validated by the EORTC (European Organization for Research and Treatment of Cancer) [21]. A general questionnaire, the EORTC QLQ-

C30 (version 2) [22], and the specific module for colorectal cancer, EORTC QLQ-CR38 [23], and also the Karnofsky Scale to measure general QoL [24]. Figure 1 shows the outline of the study protocol.

Informed consent and legal considerations

Patients who meet the inclusion criteria and provide signed informed consent will enter the randomization process.

The study protocol, patient information, and informed consent documents have been approved by the Clinical Research Ethics Committees of all participating testing centers, in accordance with Spanish Royal Decree 1090/2015. The Ethics Committee of the Parc Taulí University Hospital is the reference (ID: TAU-TEM-2009-01). The trial has been recorded in the ClinicalTrials.gov database (ID: NCT01308190) and in the EU Clinical Trials Registry database (EudraCT number: 2009-014310-94). Prior to randomization, all patients must give signed informed consent to participate in the clinical trial.

This test is carried out in accordance with the 7th revision of the Declaration of Helsinki [25], the SPIRIT 2013 Standard Protocol Articles for Clinical Trials [26], and the Spanish laws and regulations for biomedical research, with the authorization of the Spanish Agency of Medicines and Medical Products.

Description of randomization

Patients will be randomly assigned to one or other group: CRT/TEM or TME (1:1) using a computer-generated list of random numbers centralized by the Contract Research Company (CRO) “Efficie Servicios para la Investigación SL.”

Procedure

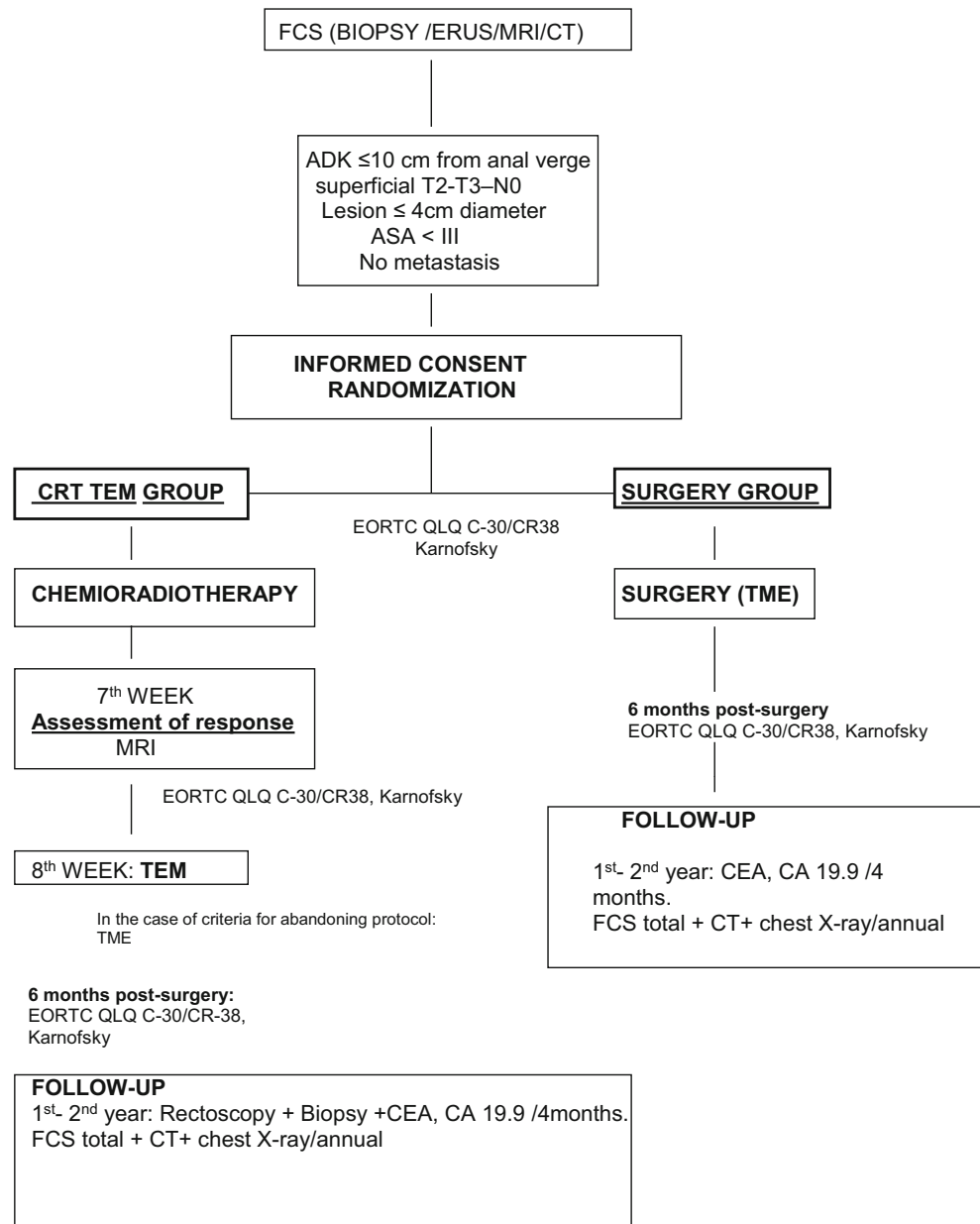
All patients will undergo mechanical preparation of the colon prior to surgery. The standard antibiotic and thromboembolic prophylaxis protocol will be applied. Patients will complete the EORTC QLQ-C30, EORTC QLQ-CR38, and Karnofsky quality of life questionnaires either at the time of admission or previously at the outpatient clinic.

CRT/TEM group

Neoadjuvant treatment: preoperative CRT

Neoadjuvant treatment with chemotherapy will be performed concomitantly with radiotherapy and will consist of the administration of capecitabine 825 mg/m² every 12 h orally on radiotherapy days. Radiotherapy is given in daily fractions of 1.8 Gy 5 days a week according to the standard regimen [27, 28]. The total dose will be 45 Gy plus a boost of 5.4 Gy in the tumor area.

Fig. 1 Trial flow chart. FCS fibrocolonoscopy, ERUS endorectal ultrasound, MRI magnetic resonance, CT CT scan, ADK adenocarcinoma, ASA American Society of Anesthesiologists, CRT chemoradiation, TEM transanal endoscopic microsurgery, TME total mesorectal excision. EORTC QLQ C-30/CR38, Karnofsky: quality of life questionnaires



Seven weeks after the end of the CRT, the clinical response will be evaluated by means of a new MRI. Standard protocols for monitoring morbidity and mortality secondary to CRT will be followed.

Surgical technique: 8th week after neoadjuvant treatment

Local surgery applying transanal endoscopic surgery includes transanal endoscopic microsurgery (TEM) [6], transanal endoscopic operation (TEO) [29], or transanal minimally invasive surgery (TAMIS) [30].

The patient will be operated under general or spinal anesthesia. Surgery will comprise excision with lesion margins superior to 15–20 mm. Full thickness resection will be

followed by washing with physiological saline plus povidone iodine 1%. Suturing of the wall defect will also be followed by washing with saline plus povidone iodine 1%.

Radical surgery group (TME)

Surgical technique: Surgery will be carried out within 1 month of the first outpatient visit. The classical TME procedure described by Heald [31] will be performed, with the choice of one of the following techniques depending on the tumor location and on the criteria applied at the particular service: TME-abdomino-perineal resection (APR), TME-lower anterior resection (LAR), TME-LAR and TME-APR laparoscopy,

TME-LAR laparoscopy, TME-LAR and loop ileostomy-laparoscopy, transanal TME and loop ileostomy.

Pathology study

Two classifications are used to study the degree of histological regression in rectal tumors treated with chemoradiotherapy: the Bouzourene [32] and the Dworak classifications [33].

The presence of a correct histological response after chemoradiotherapy is determined by the pathology study of the tumor excised after TEM, in order to establish TRG1, TRG 2, or TRG 3 in Bouzourene's classification, or TRG 4, TRG 3, or TRG 2 in Dworak's classification.

The pathology study of the local surgery specimen will determine the size of the lesion (maximum and minimum diameter in mm), the degree of ADK differentiation, the degree of response to CRT, according to Bouzourene's or Dworak's tumor regression grade, T stage, presence of venous, lymphatic, or perineural infiltration, and margins of the TEM specimen (mm).

The pathology study of the TME specimen will determine the size of the lesion (maximum and minimum diameter in mm); the degree of ADK differentiation; the presence of venous, lymphatic, or perineural infiltration; and margins of the TME specimen, distal, and circumferential in millimeters. N stage (nodes found, nodes affected).

Definition of clinical and pathological responses to preoperative chemoradiotherapy

Definition of the possible clinical responses of the tumor 7 weeks after preoperative CRT, prior to local surgery (TEM). According to the RECIST [20] criteria by MRI: Complete response: Complete disappearance of tumor. Partial response: Reduction of maximum diameter of the lesion by more 30%. Disease stabilization: Reduction of diameter by less than 30% or increase in size of less than 20%. Disease progression: increase in maximum lesion diameter above 20%.

By MRI: Onset or growth of non-target lesions (lymphadenopathies), Reduction in T stage.

Histological response to CRT according to the degree of regression: TRG1, TRG 2, or TRG 3 in Bouzourene's classification. TRG4, TRG3, or TRG2 in Dworak's classification.

Patients in the CRT-TEM group with complete or partial clinical response or pathological response will enter the comparative per protocol analysis with conventional surgery (TME).

Criteria for abandoning protocol

Patients who after neoadjuvant treatment present the following: absence of clinical response: disease stabilization, disease

progression, and absence of histological response. Degree of response to CRT of TRG 4 or TRG 5 in Bouzourene's classification or TRG 1 or TRG 2 in Dworak's classification.

Patients who present the following features in the pathology study of the tumor after TEM: characteristics of poor prognosis (lack of differentiation, venous, lymphatic, or perineural infiltration), a stage superior to superficial T3, N0 (ypT3), surgical margin affected.

Patients with criteria for abandoning the study will be rescued with conventional radical surgery within 4–6 weeks. These patients will be analyzed independently on an intention-to-treat basis.

Follow-up (Fig. 1)

EORTC QLQ-C30, EORTC QLQ-CR38, and Karnofsky quality of life questionnaires will be administered to all patients in both groups 6 months after surgery.

CRT/TEM group

During the first 2 years, rectosigmoidoscopy will be performed every 4 months along with a multifocal scar biopsy (if the biopsy is positive for adenocarcinoma, ERUS, MRI, and measurements of tumor markers CEA and CA 19.9 will be performed every 4 months. Abdominal-pelvic CT and chest X-ray every 6 months). Full colonoscopy annually: if normal, the follow-up protocol in place at each center will be applied.

TME group

During the 2-year follow-up: measurement of tumor markers (CEA and CA 19.9) every 4 months. Abdominal-pelvic CT and chest X-ray every 6 months. Full colonoscopy annually: if normal, the follow-up protocol in place at each center will be applied.

Subsequently, the two groups will follow the protocolized follow-up at each center.

Study variables

Primary outcome

Local recurrence defined as the presence of ADK in the biopsy on the residual scar, anastomosis, or the defect area of the excised tumor.

Secondary outcomes

Survival, disease-related mortality, and quality of life were determined using the questionnaires described.

Other variables to be recorded

Demographic: age, sex, hospital of origin.

Preoperative: prior to neoadjuvant treatment: lesion size (colonoscopy, ERUS, and MRI), lesion height, tumor location (anterior, posterior, right or left lateral), degrees of the circumference occupying the rectum, ERUS staging, MRI staging (tumor size in mm), the presence of distant metastases by abdominal CT, preoperative CEA, and CA 19.9, pathology biopsy.

After preoperative neoadjuvant treatment: acute and chronic adverse effects of radiotherapy, acute, and chronic adverse effects of chemotherapy. Assessment of the clinical response of chemoradiotherapy by MRI: tumor size (mm). Measurement of the maximum diameter of the tumor.

Surgical: surgical technique, surgical time, estimated blood loss, perioperative complications, conversion after TEM, single TEM specimen, and defect suture.

Pathology: lesion size, degree of differentiation, degree of response to CRT, T stage, N stage (in TME), the presence of venous, lymphatic, or perineural infiltration. Margins in TEM specimen, margins in TME specimen.

Postoperative (30 days post-surgery): nosocomial, surgical, and non-surgical postoperative complications; complications according to the Dindo-Clavien classification and the CCI (Comprehensive Complication Index); hospital stay.

Follow-up: date of local recurrence, date of distant recurrence, mortality due to rectal cancer, date of death, and mortality due to other pathologies.

Statistical analysis

Predetermination of sample size

Assuming a one-sided 5% significance level, a power of 80%, and non-recurrence rate of 95% in the control group (TME) and a non-inferiority limit of 10% for the experimental group (TEM), 78 patients will be needed for each group. Bearing in mind the estimated losses during follow-up, the total of 173 patients will be recruited.

Analysis of patients by intention to treat, per protocol, and patients lost

Intention-to-treat analyses (ITT) of all randomized patients will be performed.

Per protocol analyses will be performed of all patients in the TME group and of all patients undergoing surgery, and in the CRT-TEM group, all those receiving at least one dose of chemotherapy.

Statistical analysis of the lost patients will be performed.

Monitoring

Monitoring will be carried out by CRO Effice Servicios para la Investigación S.L. and a data manager. The variables will be recorded on an Access database which the data manager will manage via the various hospitals.

Statistical analysis

To evaluate the main objective of the study, i.e., the non-inferiority (10%) of the TEM experimental treatment in terms of non-relapse, a one-sided 95% confidence interval of the difference in the percentage of non-relapse between the two groups [34, 35] will be used in both the intention-to-treat and the per protocol samples.

The quantitative variables will be described as means and standard deviations or as medians, interquartile range and range, as appropriate. Categorical variables will be described in absolute numbers and percentages.

The statistical analysis of the quantitative variables, with independent groups, will be performed with the parametric Student's *t* test, provided that its conditions for application are met. Otherwise, the non-parametric Mann-Whitney *U* test will be used.

Statistical analysis for categorical variables will use the Pearson χ^2 test or the Fisher exact test.

Specifically, the above methods will be used to compare the two groups in terms of baseline characteristics in order to assess whether the randomization has been effective.

Statistical analysis of the survival analysis of relapse and mortality will be performed using the Kaplan-Meier estimation method and the log-rank test.

A *p* value below 0.05 will be considered statistically significant.

Discussion

TME is the standard treatment for rectal ADK staged T2, N0, M0, or above. However, it is associated with high morbidity and a reduced quality of life due to the resection of the rectum and the need for an ostomy. This situation has prompted the search for other less aggressive therapeutic strategies, such as a neoadjuvant approach in combination with local surgery.

Several methods are used for the local excision of rectal tumors. With the classic endoanal surgery, it is difficult to ensure full thickness excision and free margins, and this approach is limited by the height of the lesion with respect to the anal verge. Transanal endoscopic microsurgery (TEM) overcomes these limitations [6, 8]. Since the introduction of TEM, other forms of transanal endoscopic surgery have been described such as TEO (transanal endoscopic operations) [29] and TAMIS [30] (transanal minimally invasive surgery), with

the intention of simplifying the technique and the equipment required.

The controversial study published by Habr-Gama [10] assessed the effect of CRT in advanced stage distal rectal cancer, reporting complete clinical or pathological response in up to 30% of patients. Neoadjuvant CRT has reduced local recurrence rates and has increased survival in patients with stage pT3–4 pN0 or any pT pN1–2 rectal cancer [36, 37].

In our study, we include superficial T3 N0, M0 ADKs. Merkel et al. reported 5-year survival rates of 54% in patients with deep T3 tumors and 85% in those with superficial T3 tumors, regardless of lymph node involvement [38]. The results are thus similar to those obtained for T2, N0, M0 cancers.

The vast majority of pCRs published in the literature have been achieved with long cycles of CRT, similar to the one described in our study. Short CRT cycles do not obtain the same results, and postoperative morbidity rates are higher [39]. In an attempt to improve the results for pCR, some authors have changed the CRT regimens. Combining capecitabine in standard doses and oxaliplatin with RT, García Aguilar et al. achieved a pCR rate of 48% [40]; however, 44% of patients had adverse effects of grade ≥ 3 , which required a reduction in the capecitabine dose. At the reduced dose, a pCR rate of 36% was obtained and the incidence of adverse events grade ≥ 3 fell to 30%. In a recent publication reviewing the results of that study, with a mean follow-up of 56 months, 6% of the 79 patients had distant metastases and 4% local recurrence [41].

Complete clinical response (cCR) does not always coincide with pCR. In a previous study by our group, 12 out of 24 patients (50%) presented cCR, while nine (37.5%) presented pCR. Therefore, three out of 24 patients considered to have cCR would have relapsed if we had applied the “wait and see” policy. For this reason, we consider this strategy to be dangerous and advocate excision of the lesion in order to confirm cPR [13].

No previous studies have assessed the impact of complications measured by the Clavien-Dindo classification and the Comprehensive Complication Index. The studies performed to date have considered that the morbidity associated with TEM in combination with neoadjuvancy is unacceptable [42].

Another important strength of the present study is the measurement of quality of life in the two groups of patients. As noted above, radical abdominal surgery controls the disease but at the price of sexual alterations, urinary dysfunctions, and the need for a temporary or definitive ostomy [43]. To date, quality of life in these two groups of patients has not been compared.

Similar studies which have been published or are in the final stages include “Organ Preservation in Rectal Adenocarcinoma: a phase II randomized controlled trial” [44], by the Memorial Sloan Kettering Cancer Center, but the main objective of that study was to assess consolidation

and induction chemotherapy in an evaluation protocol that allows non-surgical observational treatment. In Europe, the UK-TREK study at the University of Birmingham and the already finalized GRECCAR 2 in France [45] used different designs but had the same objective with regard to neoadjuvant treatment and local surgery, from the point of view of control of local and systemic disease. But none of these studies have compared the quality of life in patients with superficial T2–3, N0, M0 rectal cancer treated with neoadjuvant CRT plus local excision or with radical surgery.

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TAU-TEM study group Hospital Parc Taulí: Xavier Serra-Aracil, Carles Pericay, Laura Mora, Sheila Serra, Eugeni Saigi, Emma Dotor, Aleidis Pisa, Ismael Macias, Anna Palliser, Salvador Navarro. Hospital Clinic I Provincial: Antonio Lacy, Anna Otero. Hospital de Bellvitge: Sebastiano Biondo, Thomas Golda. Hospital de la Santa Creu i Sant Pau: Eduardo Tarragona, Pilar Hernández; M^a Carmen Martínez, Juan Carlos Pernas, Marta Martín, Dolores González, David Paez, Xavier Cussó, C. Balagué. Hospital General Universitari de València: M^a José García Coret, Francisco Villalba Ferrer. Hospital Universitario La Paz: Beatriz Díaz San Andrés, Álvarez Gallego, Higuera, Prieto. Hospital Universitario de Getafe: Jose Luis Ramos, Javier Jiménez Miramó, Javier García Septiem, Francisco Angulo. Hospital Marqués de Valdecilla: Julio Castillo, Joaquín Alonso Martín, Isabel Seco, Carlos Manuel Palazuelo. Hospital Torrecárdenas de Almería: Ángel Reina, Francisco A. Rubio Gil, Carmen Caro, Rubén Varela, Fco. Manuel Ramos, Ana Fernández, Ricardo Belda, Ramon Solbes, Begoña Medina, Piedad Reche. Hospital Universitari Vall d’Hebrón: Eloy Espín, Francesc Vallribera, Stefania Landolfini, Jaume Capdevila. Hospital del Mar: Marta Pascual, Silvia Salvans, Miguel Pera. Hospital Reina Sofía. Córdoba: César Díaz, Jose Gomez Barbadillo, Amalia Palacios, Carlos Villar Pastor, María Pleguezuelo, Francisco Triviño, José L. Martínez de Dueñas, Auxiliadora Gómez España y Elena Navarro Rodríguez. Hospital de Sagunto: Roberto Lozoya Trujillo, Andrés Frangi, M^a Dolores Ruiz Carmona, Rodolfo Rodríguez Carrillo, Mireia Gil, Vicente Miranda. Hospital de Cabueñes. Gijón: Carlos Álvarez Laso, Paola Lora. Hospital de Donosti: José M^a Enriquez Navascues, Carlos Placer, Dra. Nerea Borda, Adelaida La Casta, JL Elosegui, Yolanda Saralegui, Elena Guimón, JA Múgica. Hospital General Universitario de Elche: Javier Gallego Plazas, Antonio Arroyo. Hospital Universitari Juan XXIII: Aleidis Caro, Monica Millan.

Authors’ contributions XSA, CP, and LM wrote and edited the paper. TG, AR, SD, and ET will contribute patients to the study and are active in the management of the protocol. All authors have reviewed the research protocol, revising it critically for intellectual content. Each author has participated sufficiently in the work of reviewing and approving the protocol as written. In addition, FV, JMEN, AA, MP, JC, CD, AC, and RL will contribute patients and have reviewed and approved the protocol. JCGP and SS are the clinical research managers of the trial.

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Compliance with ethical standards

Competing interests The authors have no competing interests to declare.

Consent for publication Not applicable.

Ethics approval and consent to participate The study has been approved by the local ethics committees of the participating centers.

Availability of data and materials Not applicable.

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