CIRUGÍA ESPAÑOLA

www.elsevier.es/cirugia

Study protocol

Local Excision for organ preservation in early REctal cancer with No Adjuvant treatment (LORENA Trial): prospective observational study protocol☆

Rodrigo Tovar Pérez,[a] *Carlos Cerdán Santacruz,*[b,c,*] *Óscar Cano-Valderrama,*[d] *Fernando Jiménez Escovar,*[e] *Blas Flor Lorente,*[f] *Rodrigo O. Perez,*[g,h,i,1] *Javier García Septiem*[b,1]

[a] *General and Digestive Surgery Department, Hospital Universitario de la Princesa, Instituto de Investigación Sanitaria Princesa (IIS-IP), Universidad Autónoma de Madrid (UAM), Madrid, Spain*

[b] *Colorectal Surgery Department, Hospital Universitario de la Princesa, Instituto de Investigación Sanitaria Princesa (IIS-IP), Universidad Autónoma de Madrid (UAM), Madrid, Spain*

[c] *Colorectal Surgery Department, Clínica Santa Elena, Madrid, Spain*

[d] *Colorectal Surgery Department, Complejo Hospitalario Universitario de Vigo, Vigo, Spain*

[e] *Colorectal Surgery Department, Hospital de Galdakao Usansolo, Bilbao, Spain*

[f] *Colorectal Surgery Department, Hospital Politécnico Universitario la Fe, Valencia, Spain*

[g] *Department of Surgical Oncology, Hospital Beneficencia Portuguesa, São Paulo, Brasil*

[h] *Division of Colorectal Surgery, Hospital Alemão Oswaldo Cruz, São Paulo, Brasil*

[i] *Angelita and Joaquim Gama Institute, São Paulo, Brasil*

ARTICLE INFO

Article history:
Received 19 February 2024
Accepted 12 April 2024
Available online 18 May 2024

Keywords:
Early rectal cancer
Organ preservation
Total mesorrectal excision
Rectal cancer local excision

ABSTRACT

Introduction: Local resection (LR) is an alternative to total mesorectal excision (TME) that avoids its associated morbidity to the detriment of oncological radicality in early stages of rectal cancer. There are several conditioning factors for the success of this strategy, such as poor prognosis histological factors (PPHF), involvement of resection margins, clinical under staging, or complications that may lead to the indication for radical surgery with TME.
Patients and method: An international multicenter prospective observational open-label study has been designed. Consecutive patients diagnosed with early rectal cancer (cT1N0 on MRI +/− endorectal ultrasound) whose lower limit is a maximum of 2 cm proximal to the ano-rectal junction will be included. The primary objective of the study is to determine the overall prevalence of PPHF after LR and requiring TME or postoperative radio-chemotherapy.
Discussion: The prevalence of PPHF conditioning the success of LR in early distal rectal cancer has been scarcely studied in the literature, and there are very few prospective data.

☆ Please cite this article as: Tovar Pérez R, Cerdán Santacruz C, Cano-Valderrama Ó, Jiménez Escovar F, Flor Lorente B, Perez RO, et al. Resección local exclusiva sin tratamiento adyuvante como estrategia de preservación de órgano en cáncer de recto precoz: protocolo de estudio observacional prospectivo. Cir Esp. 2024. https://doi.org/10.1016/j.ciresp.2024.04.009

* *Corresponding author.*
E-mail address: carloscerdansantacruz@hotmail.com (C. Cerdán Santacruz).

[1] Shared senior author position.

http://dx.doi.org/10.1016/j.cireng.2024.04.013

Considering the increasing interest in the watch and wait strategy in rectal cancer and its possible application in early-stage tumors, it seems necessary to know this information.

The results of this study will help guide clinical practice in patients with early distal rectal cancer. It will also provide quality information for the design of future comparative studies to improve organ preservation success in these patients.

Trial registration number: NCT05927584.

Resección local exclusiva sin tratamiento adyuvante como estrategia de preservación de órgano en cáncer de recto precoz: protocolo de estudio observacional prospectivo

Palabras clave:
Cáncer de recto precoz
Preservación de órgano
Escisión total del mesorrecto,
escisión local de cáncer de recto

RESUMEN

Introducción: La resección local (RL) es una alternativa a la exéresis mesorrectal total (EMT) que permite evitar su morbilidad asociada en detrimento de la radicalidad oncológica en estadios precoces de cáncer de recto. Existen diversos condicionantes para el éxito de esta estrategia, como factores histológicos de mal pronóstico (FHMP), afección de márgenes de resección, infra-estadificación clínica, o complicaciones que pueden conllevar la indicación de cirugía radical con EMT.

Pacientes y método: Se ha diseñado un estudio multicéntrico internacional observacional prospectivo en régimen abierto. Se incluirán pacientes consecutivos diagnosticados de cáncer de recto precoz (cT1N0 en RMN +/− ecografía endorrectal) cuyo límite inferior esté a un máximo de 2 cm proximal a la unión ano-rectal. El objetivo primario del estudio es determinar la prevalencia global de FHMP tras RL y que obligan a EMT o realización de radio-quimioterapia postoperatoria.

Discusión: La prevalencia de FHMP como factor limitante de éxito de una RL en cáncer de recto distal precoz, apenas ha sido objeto de estudio en la literatura, existiendo muy poca información con carácter prospectivo. Considerando el progresivo interés de la estrategia *watch and wait* en cáncer de recto y su posible aplicación en tumores con estadificación precoz, parece necesario conocer esta información.

Los resultados del estudio ayudarán a guiar la práctica clínica en pacientes con cáncer de recto distal precoz. También se conseguirá información de calidad para el diseño de estudios comparativos futuros que permitan mejorar el éxito en preservación de órgano en estos pacientes.

Número de registro: NCT05927584.

Introduction

Local resection (LR) was proposed as an alternative to total mesorectal excision (TME) in cases of early rectal cancer to achieve organ preservation (OP) and thus avoid the sequelae of radical surgery.[1] However, it is known that this treatment is oncologically comparable in very specific cases in which a series of poor prognosis histological factors (PPHFs) are not detected.[2] Although some of these PPHFs have been questioned in recent years, most notably deep submucosal infiltration[3]; on the other hand, the chances of mesorectal lymph node involvement or the risk of local recurrence are unacceptable,[4,5] and LR is insufficient. In these cases, it is recommended to undertake or complete the oncological treatment through radical surgery with TME or adjuvant radio-chemotherapy (CRT), which means immediate failure as regards expecting OP in some of these cases.[6] Unfortunately, many of these PPHFs can only be known after complete histological evaluation of the specimen.[4] In addition, preoperative staging errors or postoperative complications may occur that require radical resection. With all this information, in a context in which OP is a desirable objective for patients and clinicians,[7,8] and in

which the indications for radio-chemotherapy treatment have been progressively extended towards increasingly superficial tumours in the rectum, not because of the patient's oncological compromise, but with the sole objective of achieving a complete clinical response and joining a watch and wait strategy,[9] it seems very pertinent and at the same time relevant to offer updated information on the success of LR as the only treatment strategy for early rectal cancer.[6] Paradoxically, the quality of the evidence available so far is poor, based mostly on retrospective studies, observations made in studies with a different primary objective and with sparse samples - or where cases of cancer of both colon and rectum are mixed.[3,10]

For all these reasons, we propose to carry out an international multicentre study of a prospective observational nature, which would enable us to establish the proportion of patients with distal rectal cancer staged preoperatively as cT1N0M0 who, after undergoing local resection, will present PPHF, or errors in local staging, and who would require completing their treatment in order to be considered as curative treatment options. A second objective of the study is to determine the overall success rate in OP at 3 years in patients who begin by undergoing LR for rectal cancer.

Patients and methods

Study design, variables and methods

An observational, multicentre, prospective, single-cohort study is proposed, at international level, and open to recruitment of new centres.

The aim is to include demographic and clinical variables, as regards both the patient and the characteristics of the tumour; operating details; anatomo-pathological and follow-up variables to record possible clinical complications 60 days after the intervention, and those of an oncological nature, extending this follow-up to 3 years after surgical resection of the primary tumour by LR. Oncological outcomes will be measured on a half-yearly basis.

Specifically, PPHFs in lymphadenopathy will be recorded and will define the need for additional treatment in these cases, either radical surgery or adjuvant treatment with CRT.

The study is defined as an observational study on routine clinical practice, so the researchers in charge do not issue any recommendations in this regard, especially at a time when some of the criteria considered classic are under discussion based on recent evidence.[3] The variability between centres, provided that it is done in compliance with quality standards and in the setting of multidisciplinary committees for the assessment of these cases, is part of the results that are intended to be measured, as well as the evolution in clinical and oncological terms derived from this variability that may arise.

Postoperative outcome variables or oncological follow-up will be recorded at the time of diagnosis: need for additional treatment after LR (TME vs. adjuvant CRT), local recurrence, distant recurrence, or mortality, regardless of the cause.

The date from the last follow-up should correspond to the control in the patients' third year, regardless of whether or not their evolution has been event-free and there have been no entries in their records. The only exception to this is cases where mortality occurs, in which obviously, the date of the last check-up will coincide with the date of the patient's death.

A prospective register will be compiled, including patients through the Research Electronic Data Capture (REDCap) online platform. No information that would enable the patient to be identified will be uploaded or stored in the REDCap database. In addition, the information uploaded to this platform is protected by encryption.

Study population and eligibility

Patients with early stage distal rectal cancer (cT1N0M0) will be included after clinical, radiological and endoscopic examination who meet the inclusion criteria and none of the exclusion criteria.

Patients will be informed of the objective of the study and will be offered participation in the study prior to the intervention. In all cases, the informed consent document must be duly submitted and completed.

Inclusion criteria

- Patients over 18 years of age.
- Biopsy of infiltrating rectal adenocarcinoma.
- Preoperative biopsy of adenoma or intramucosal adenocarcinoma with endoscopic or radiological criteria of lesion suspected of adenocarcinoma, with a histological diagnosis of infiltrating adenocarcinoma after local resection.

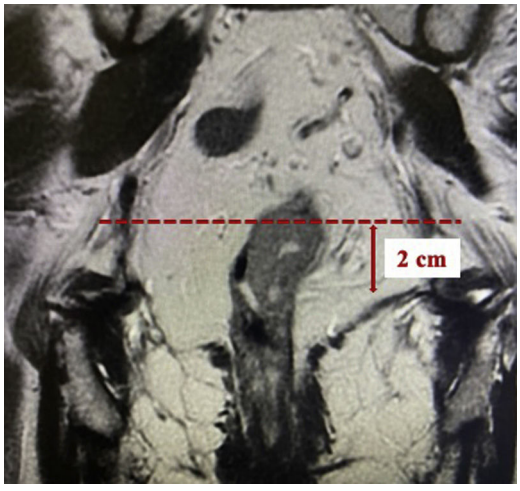

Fig. 1 – Coronal T2-weighted view of magnetic resonance imaging (MRI) showing a rectal tumour and its relationship with the sphincters and puborectalis muscle (red dotted line). Tumours to be included in the study should have an extension of no more than 3 cm and their lower limit should not exceed the dashed line shown in the figure.

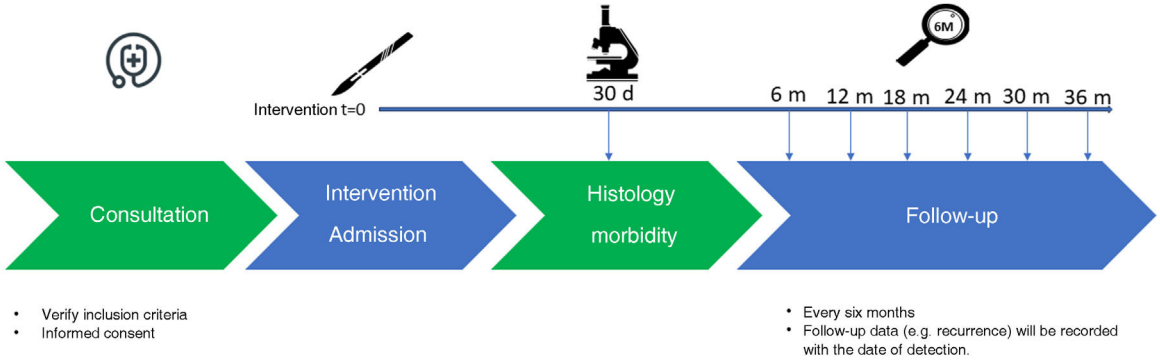

Fig. 2 – Timeline of the LORENA study with the different moments of data entry in the REDCap database. These data entries are those established in the study protocol, regardless of the usual clinical practice of each participating institution.

- Rectal tumour whose lower margin is a maximum of 2 cm proximal to the anorectal junction both on digital rectal examination and radiological tests, ideally on MRI (Fig. 1).
- Tumours less than or equal to 3 cm in size.
- Preoperative clinical staging of cT1N0M0, based on endoscopy, magnetic resonance imaging +/- endorectal ultrasound.

a Endoscopic criteria: crypt pattern V or higher depending on the Kudo classification, which defines infiltrating lesions, despite the fact that the Preoperative histology is not confirmatory.[11]

b Ultrasonographic criteria: the tumour, which has a hypoechoic appearance, invades the intermediate hyperechoic layer (submucosa), but does not invade the outermost hypoechoic layer (muscularis propria).

c Radiological criteria in MRI: the tumour invades the submucosa without extending to the muscular layer of the rectum. An anomalous signal substitution of the characteristic image is observed, with a low signal at the level of the submucosa. In other words, this would involve the loss of the zebra sign in a rectum with a wall with normal structure.[12]

- Cases in which, after discussion in a multidisciplinary committee, LR with curative intent is decided on as the only treatment, regardless of the approach, whether endoscopic or surgical trans-anally.
- Tumours with histological criteria for good prognosis or low risk that can be identified preoperatively, or where there is a lack of information in this regard:

o Submucosal infiltration less than 1000 microns (classification sm1 by Kikuchi).[13]
o Absence of tumour budding.
o One-piece resection if they have undergone previous endoscopic resection.
o Absence of lymphatic, vascular and perineural invasion.
o Low histological grade.

Exclusion criteria

- Underage patients.
- Definitive histology other than infiltrating adenocarcinoma.
- Tumours whose lower limit is above 2 cm proximal to the anorectal ring according to preoperative magnetic resonance imaging.
- Patients with rectal cancer with local staging other than cT1N0M0 (any T > 1 or any N + or M+).
- Tumours larger than 3 cm.
- Presence of histological poor prognostic factors detected in the preoperative phase:

o Submucosal infiltration greater than 1000 microns (sm2 and sm3 in the Kikuchi classification).
o Presence of tumour budding.
o Fragmented resection if they have undergone previous endoscopic resection.
o Presence of lymphatic, vascular and perineural invasion.
o High histological grade.

- Patients in whom the need for systemic treatment by radiochemotherapy combined with local resection, either neoadjuvant or adjuvant, has been planned during their discussion at a multidisciplinary tumour committee, regardless of their preoperative clinical staging or postoperative pathology staging.

Endpoints

Primary endpoint

1 To determine the overall prevalence of PPHF after LR and that require additional treatments after initial LR.
2 To determine the rate of patients with superficial distal rectum who maintain the rectum in situ at three years of follow-up, after LR as initial treatment.

Secondary endpoints

1 To record the current trend in selecting salvage treatment after LR in patients with superficial distal rectal cancer cT1N0M0 with PPHF on the part.
2 To determine the prevalence of other causes, mainly the presence of serious complications after LR or understaging, which require proctectomy and represents a failure of the LR -based strategy initially as a strategy for medium/long-term organ preservation.

3 To describe the type of salvage surgery used in cases where: TMS vs. abdomino-perineal amputation is required, as well as the quality of the surgical tissue, especially the rate of affected margins, the quality of the mesorectum and perforations at the level of the rectum.
4 To define 3-year oncological outcomes (overall survival and disease-free survival) depending on the strategies adopted and inferring whether LR is intended in cases with factors of poor prognosis a priori unknown, constitutes a risk for patients.
5 To establish the current postoperative morbidity and produce a classification according to Clavien-Dindo after surgery by LR in distal superficial rectal cancer.

An interim analysis will be run at the end of recruitment in order to describe the immediate failure rate of LR.

Time schedule

- Inclusion of participating centres: until the end of recruitment.
- Recruitment begins: January 1, 2024.
- Estimated annual volume of patients per centre: 1–5.
- Number of participating centres: a minimum of 30.
- Expected deadline for completion of patient inclusion for study: 31st December, 2024.
- Interim analysis of the incidence of PPHF and early indication for radical surgery: February 2025.
- Expected deadline for completion of follow-up of patients included: 31st December, 2027 (Fig. 2).

Sample size calculation

The success rate of LR in rectal cancer as the exclusive treatment for early rectal cancer is unknown due to the absence of prospective data in which the presence of histological risk factors in the specimen has been precisely controlled.

Extrapolating from data from the STAR-TREC study, more specifically from the sub-analysis of the TREC trial data, we establish that these criteria may appear in up to 70% of patients, although this is not part of the objectives of the study and this data cannot be considered as accurate.[14]

Accepting this figure of 70% as a reference, an α risk of 0.05 and a β risk of 0.2, in a two-tailed test a total of 181 patients would be needed to identify a difference of 0.1 units, estimating a loss ratio of 5%.

Statistical method

A descriptive analysis of demographic and clinical variables will be run. Categorical variables will be presented as percentages and frequencies. Qualitative variables will be presented as percentages and frequencies. Quantitative variables will be described as mean and standard deviation (SD) if they follow a normal distribution or as median and interquartile range (IQR) in the case of asymmetry.

The association between the collected variables and the target variables in the study will be made using Pearson's Chi-square test or Fisher's exact test, as appropriate, in the case of categorical variables and, for continuous variables, using Student's t-test for independent samples or Mann–Whitney's U test, respectively, depending on whether or not their distribution conforms to normal.

The parameters of overall survival, disease-free survival, local recurrence-free survival, and total mesorectal excision-free survival will be estimated using the Kaplan-Meier method and the Cox proportional hazards model. Patients lost to follow-up will be censored.

The data obtained on each patient will be entered into a database and analysed using a Stata 13.1 statistical programme (StataCorp, Texas, USA).

Discussion

In recent years, organ preservation has become a transcendental issue in locally advanced rectal cancer, even being a primary target in some recently published clinical trials, which is new and a clear paradigm shift in this field. In addition, several studies have already been run and others are underway, some of these with a randomised design. These have explored the oncological results of different strategies that include the administration of CRT in patients with more superficial tumours,[9,14,15] not because of their oncological risk but with the sole intention of achieving organ preservation, avoiding the postoperative and functional sequelae of radical surgery using TMS.

Progress in neoadjuvant treatment strategies for locally advanced rectal cancer following W&W has led to organ preservation rates of up to 50% at 3-year follow-up,[16] and initial experiences with this type of strategy in cases of earlier tumours, cT2N0M0, suggest that these figures could reach close to 80% survival with rectum in situ.[9]

In cases of cT1N0M0 rectal tumours, the probability of undertreatment with LR can be estimated from histological factors that we can only know after performing the procedure. Surveillance after LR and detection and treatment of local recurrence can be challenging, with a significant increase in morbidity.

LR in rectal cancer is a form of organ preservation that, when it is intended to apply in isolation, is indicated exclusively for selected cases of early rectal cancer, in the initial stages of the disease, where histological data with a good prognosis is also presented and there is no associated risk of the existence of affected mesorectal lymphadenopathies.[2,4] Several of these conditions can only be known after the intervention, thus determining the need to complete the treatment, either with radical surgery or by

postoperative radiochemotherapy. The first option is considered to be conventional,[6] and the only one accepted in most published clinical guidelines on rectal cancer.[17,18]

In addition, there are currently groups who, on the basis of recent publications, question the absolute need for supplementary treatments in the presence of certain classic risk factors, such as deep infiltration of the submucosa.[3] There is a significant limitation to be taken into account in these studies, and that is the mix of patients with colon and rectal tumours, as well as the observational and retrospective nature of both.

On the other hand, as an additional latent danger, in the event of having to complete the treatment with radical surgery, some authors warn of worsening results after LR, in relation to greater technical difficulty or due to the risk of cell dissemination during the previous intervention.[19] This situation should be controlled and measured accurately and gradually, given the high impact it may have on our patients.

The LORENA Trial is the first international prospective register of the results of LR as an exclusive treatment for early rectal cancer that focusses on PO, and which aims to establish the exact frequency with which histological criteria with a poor prognosis appear in a context of routine clinical practice, and therefore, also the potential risk of the impossibility of implementing an OP strategy in this context, depending on the various salvage options that exist.

Considering that cT1N0M0 tumours are the most privileged in oncological terms and those that, a priori, should be considered more favourable for adoption of a OP strategy, in the event that the figures achieved with LR in isolation in cases of cT1N0M0 tumours of the rectum were far from those previously mentioned in the context of locally advanced tumours (50%)[16] or not so superficial, cT2N0M0 (80%),[9] it would then be justified to design studies that investigate new therapeutic options, or some strategies already described, but this time through the design of controlled studies.

Funding

This study is a beneficiary of one of the research grants awarded by the Spanish Association of Surgeons.

Conflict of interest

None of the authors declare any potential conflicts of interest in relation to the present article.

Ethical issues

This study protocol has been approved by the local ethics committee at the Hospital de La Princesa in Madrid. Registration number 08/23-5216.

REFERENCES

1. Paty PB, Nash GM, Baron P, Zakowski M, Minsky BD, Blumberg D, et al. Long-term results of local excision for rectal cancer. Ann Surg. 2002;236(4):522–9. discussion 9-30.
2. Saraste D, Gunnarsson U, Janson M. Predicting lymph node metastases in early rectal cancer. Eur J Cancer. 2013;49(5):1104–8.
3. Zwager LW, Bastiaansen BAJ, Montazeri NSM, Hompes R, Barresi V, Ichimasa K, et al. Deep submucosal invasion is not an independent risk factor for lymph node metastasis in T1 colorectal cancer: a meta-analysis. Gastroenterology. 2022;163(1):174–89.
4. Beaton C, Twine CP, Williams GL, Radcliffe AG. Systematic review and meta-analysis of histopathological factors influencing the risk of lymph node metastasis in early colorectal cancer. Colorectal Dis. 2013;15(7):788–97.
5. Leijtens JWA, Smits LJH, Koedam TWA, Orsini RG, van Aalten SM, Verseveld M, et al. Long-term oncological outcomes after local excision of T1 rectal cancer. Tech Coloproctol. 2023;27(1):23–33.
6. Aguirre-Allende I, Enriquez-Navascues JM, Elorza-Echaniz G, Etxart-Lopetegui A, Borda-Arrizabalaga N, Saralegui Ansorena Y, et al. Early-rectal cancer treatment: a decision-tree making based on systematic review and meta-analysis. Cir Esp (Engl Ed). 2021;99(2):89–107.
7. Gunjur A, Chazan G, Newnham G, McLachlan SA. Pilot study of patients' preferences for immediate resection versus a watch and wait approach after neoadjuvant chemoradiation for locally advanced rectal cancer. JCO Oncol Pract. 2021;17(2):e149–57.
8. Cerdan Santacruz C, Vailati BB, Sao Juliao GP, Habr-Gama A, Perez RO. Watch and wait: why, to whom and how. Surg Oncol. 2022;43101774.
9. Habr-Gama A, Sao Juliao GP, Vailati BB, Sabbaga J, Aguilar PB, Fernandez LM, et al. Organ preservation in cT2N0 rectal cancer after neoadjuvant chemoradiation therapy: the impact of radiation therapy dose-escalation and consolidation chemotherapy. Ann Surg. 2019;269(1):102–7.
10. Johnstone MS, McSorley ST, McMahon AJ. Management of malignant T1 colorectal cancer polyps: results from a 10-year prospective observational study. Colorectal Dis. 2023;25(10):1960–72.
11. Kudo S, Hirota S, Nakajima T, Hosobe S, Kusaka H, Kobayashi T, et al. Colorectal tumours and pit pattern. J Clin Pathol. 1994;47(10):880–5.
12. Fernandes MC, Gollub MJ, Brown G. The importance of MRI for rectal cancer evaluation. Surg Oncol. 2022;43101739.
13. Kikuchi R, Takano M, Takagi K, Fujimoto N, Nozaki R, Fujiyoshi T, et al. Management of early invasive colorectal cancer. Risk of recurrence and clinical guidelines. Dis Colon Rectum. 1995;38(12):1286–95.
14. Bach SP, Gilbert A, Brock K, Korsgen S, Geh I, Hill J, et al. Radical surgery versus organ preservation via short-course radiotherapy followed by transanal endoscopic microsurgery for early-stage rectal cancer (TREC): a randomised, open-label feasibility study. Lancet Gastroenterol Hepatol. 2021;6(2):92–105.
15. Garcia-Aguilar J, Renfro LA, Chow OS, Shi Q, Carrero XW, Lynn PB, et al. Organ preservation for clinical T2N0 distal rectal cancer using neoadjuvant chemoradiotherapy and local excision (ACOSOG Z6041): results of an open-label, single-arm, multi-institutional, phase 2 trial. Lancet Oncol. 2015;16(15):1537–46.

16. Garcia-Aguilar J, Patil S, Gollub MJ, Kim JK, Yuval JB, Thompson HM, et al. Organ preservation in patients with rectal adenocarcinoma treated with total neoadjuvant therapy. J Clin Oncol. 2022;40(23):2546–56.
17. Glynne-Jones R, Wyrwicz L, Tiret E, Brown G, Rodel C, Cervantes A, et al. Rectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2017;28 suppl_4:iv22–40.
18. NCCN. Clinical Practice Guidelines in Oncology. Rectal Cancer, Version 2; 2021.
19. Morino M, Allaix ME, Arolfo S, Arezzo A. Previous transanal endoscopic microsurgery for rectal cancer represents a risk factor for an increased abdominoperineal resection rate. Surg Endosc. 2013;27(9):3315–21.