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ORIGINAL ARTICLE

Rectal sparing approach after preoperative radio- and/or chemotherapy (RESARCH) in patients with rectal cancer: a multicentre observational study

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Abstract
Background Rectum-sparing approaches appear to be appropriate in rectal cancer patients with a major (mCR) or complete clinical response (cCR) after neoadjuvant therapy. The aim of the present study is to evaluate the effectiveness of rectum-sparing approaches at 2 years after the completion of neoadjuvant treatment.
Study design Patients with rectal adenocarcinoma eligible to receive neoadjuvant therapy will be prospectively enrolled. Patients will be restaged 7–8 weeks after the completion of neoadjuvant therapy and those with mCR (defined as absence of mass, small mucosal irregularity no more than 2 cm in diameter at endoscopy and no metastatic nodes at MRI) or cCR will be enrolled in the trial. Patients with mCR will undergo local excision, while patients with cCR will either undergo local excision or watch and wait policy. The main end point of the study is to determine the percentage of rectum preservation at 2 years in the enrolled patients.
Conclusion This protocol is the first prospective trial that investigates the role of both local excision and watch and wait approaches in patients treated with neoadjuvant therapy for rectal cancer. The trial is registered at clinicaltrials.gov (NCT02710812).

Keywords Rectal cancer · Local excision · Watch and wait · Neoadjuvant therapy · Rectum-preserving approach

Introduction

The goals of rectal cancer treatment are to improve both oncological and patient-reported outcomes. Neoadjuvant therapy, either preoperative chemoradiotherapy (CRT) or

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short-course radiotherapy, followed by total mesorectal excision (TME) is standard of care for mid–low locally advanced rectal cancer [1, 2]. With these approaches, a statistically significant improvement in local control has been observed when compared with TME alone [1] or with postoperative CRT [2]. Moreover, patients with pathological complete response (pCR) after preoperative CRT show statistically significant better oncological outcomes than patients with residual tumour [3]. However, the combination of neoadjuvant therapy and TME is associated with high rates of early and late surgical complications, radiation- and chemotherapy-associated toxicity, impairment of bowel, sexual and urinary functions, faecal continence and quality of life [4].

There is therefore increasing interest in rectum-preserving strategies such as transanal local excision (LE) and observation only (watch and wait), which are able to reduce the TME-associated side effects and provide acceptable oncological outcomes. Patients who show a major or complete clinical response (cCR) after neoadjuvant treatment are widely accepted as the best candidates for this strategy.

The watch and wait policy was designed and developed in Brazil for patients with a cCR after preoperative CRT [5]. The encouraging outcomes of the Brazilian experience have recently been reproduced in other institutions, stimulating increased interest for this strategy (Table 1).

An alternative rectum-preserving approach is transanal LE of the residual tumour, which is indicated in both patients with cCR and those with major clinical response (mCR). Few recent prospective studies have suggested that oncological outcomes of LE approach are comparable to conventional TME (Table 2).

Most of the studies on rectum-preserving approaches are limited because they are small in size and/or single centre. Further limitations include variability of study methodology, patient selection and definition of clinical response. Moreover, a major concern in rectum-preserving strategies is the discrepancy between assessment of clinical and pathological response.

Despite these limitations and although the international guidelines still do not consider rectum-sparing strategies as standard of care, they are increasingly used in clinical practice. Since phase 3 studies on this issue are challenging, prospective phase 2 or careful large observational studies supplying accurate oncological safety and quality-of-life (QoL) outcomes are required [17].

The principal objective of this large prospective trial was to evaluate the ability of rectum-sparing approaches to preserve the rectum at 2 years after the completion of neoadjuvant treatment followed by conservative treatment (local excision (LE) or watch and wait).

Study design

Study objectives

The study aims to assess the rate of rectum preservation at 2 years in patients with rectal cancer treated with neoadjuvant therapy followed by conservative treatment [local excision (LE) or watch and wait].

Secondary objectives are to determine the overall survival (OS), the disease-free survival (DFS), the local recurrence-free survival (LRFS), the frequency of stoma-free patients at 2 and 5 years, the clinical- and tumour-related factors associated with pCR in the primary tumour, the frequency of pCR after neoadjuvant therapy and the association between clinical and pathological response, the morbidity and mortality rates after neoadjuvant therapy followed by rectum-sparing approaches, the ratio between number of patients who undergo a rectum-sparing approach, the total number of patients who receive neoadjuvant therapy, and the impact of rectum-sparing approaches on bowel function and QoL.

Inclusion and exclusion criteria

All patients with a histologically proven adenocarcinoma of the rectum, located up to 12 cm from the anal verge at proctoscopy, aged $\geq$ 18 years, candidates to receive neoadjuvant treatment and able to undergo a TME surgery, will be registered. After registration, if these patients show a mCR or cCR at restaging after the completion of neoadjuvant therapy and sign the informed consent to undergo a rectum-preserving approach, they will be enrolled. Patients unfit for neoadjuvant treatment or TME surgery will be excluded.

Clinical evaluation and staging

Clinical staging and pathological TNM staging are reported according to the American Joint Committee on Cancer 7th Edition [18]. Clinical staging will be performed at baseline (before neoadjuvant treatment), at 7–8 weeks after the completion of neoadjuvant treatment (first restaging) and, only in patients with a mCR or cCR, at 10–12 weeks (second restaging). No-responder patients will undergo TME surgery after the first restaging, while those with mCR or with cCR after the second restaging will be enrolled in the trial.

LE is indicated in patients with mCR, while both LE or watch and wait approach, at the surgeon's discretion, are indicated in patients with cCR. LE is considered primarily as an excisional biopsy. Based on histopathology, patients

Table 1 Studies on the watch and wait approach after neoadjuvant therapy for rectal cancer

References	cCR N (%)	LR (%)	FU (months)	Salvage surgery after LR	DFS (%-years)	OS (%-years)
Habr-Gama et al. [5]	71 (27)	2	57	2/2	92–5	100–5
Smith et al. [6]	32 (12)	18	43	6/6	88–2	96–2
Li et al. [7]	122 (14)	7	58	2/2	90–5	100–5
Appelt et al. [8]	40 (78)	26	24	9/9	58–2	100–2
Martens et al. [9]	85 (85)	14	41	12/12	85–3	96–5
Renehan et al. [10]	129 (30)	34	33	37/44	88–3	96–3

cCR N number of patients with a complete clinical response, *LR* local recurrence, *FU* follow-up, *DFS* disease-free survival, *OS* overall survival

Table 2 Prospective studies on local excision approach after neoadjuvant therapy for rectal cancer

References	Number of patients	cT	ypT0–ypT1 (%)	FU (months)	LR (%)	Salvage surgery after LR	DFS (%-years)	OS (%-years)
Lezoche et al. [11]	50	2	28–24	64	9	N/A	92–5	81–5
Bujko et al. [12]	89	1–3	44–26	24	20	8/13	N/A	N/A
Pucciarelli et al. [13]	63	2–3	68–1	36	3	2/2	91–3	91–3
Rullier et al. [14]	74	2–3	40–21	36	5	26/34	78–3	91–3
Verseveld et al. [15]	47	1–3	45–19	17	9	3/4	N/A	N/A
Garcia-Aguilar et al. [16]	79	2	49–14	56	4	2/2	88–3	95–3
Martens et al. [9]	15	N/A	60–7	41	20	3/3	80–3	100–3

cT clinical tumour stage, *ypT* pathologic tumour stage after neoadjuvant therapy, *FU* follow-up, *LR* local recurrence, *DFS* disease-free survival, *OS* overall survival, *N/A* data not available

are observed if a pCR (ypT0) or a ypT1 with favourable features is found. The following are considered favourable features: well or moderately differentiated adenocarcinoma with a tumour regression grade (TRG) of 2, and free margins. Patients are recommended for subsequent TME surgery if, after LE, one of the following features is found: adenocarcinoma ypT $\geq$ 2, low degree of differentiation, positive margins, or TRG $\geq$ 3. A flow chart of the study is provided in Fig. 1.

Baseline clinical staging includes clinical history and routine laboratory tests, digital rectal examination (DRE), proctoscopy with a rigid endoscope and complete colonoscopy, carcinoembryonic (CEA) levels, chest and abdomen computed tomography (CT) scan and pelvic magnetic resonance imaging (MRI). As reported elsewhere, lymph nodes with a diameter $>$ 0.5 cm along the short axis at imaging will be considered metastatic [13].

First restaging includes clinical history, routine laboratory tests, DRE, proctoscopy, CEA, chest and abdomen CT scan and pelvic MRI. Second restaging includes DRE and proctoscopy.

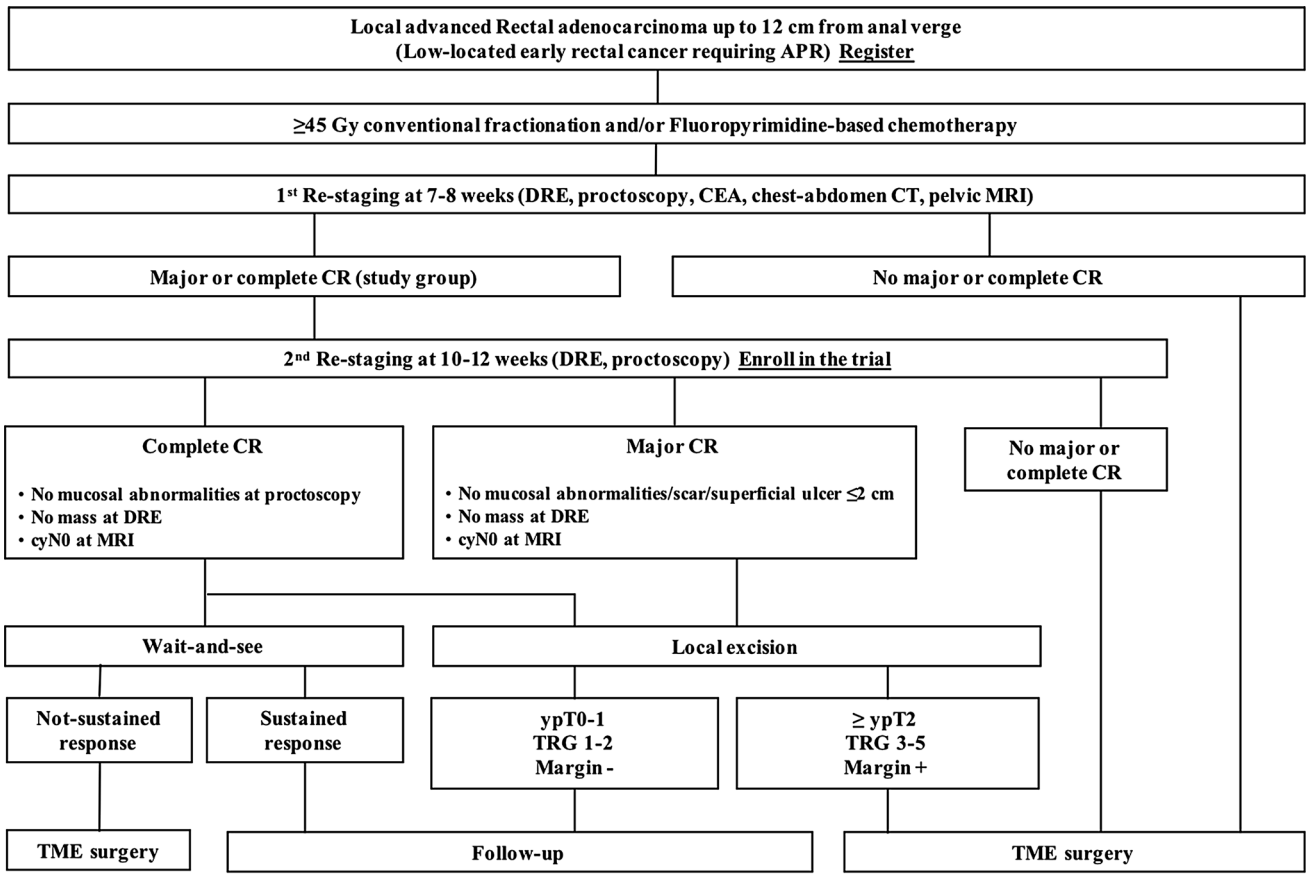
Neoadjuvant treatment

While all neoadjuvant treatments are permitted, treatments according to the National Comprehensive Cancer Network (NCCN) rectal guidelines [17] are recommended.

Surgical treatment

Conventional surgery is performed with an open or laparoscopic TME technique.

LE is performed using either the traditional transanal approach or endoscopic techniques. Regardless of the technique performed, the following principles should be respected: a gross margin of at least 0.5 cm, full-thickness excision including mucosa, submucosa, muscularis propria and perirectal fat. The surgical specimen should be placed on cardboard using pins at the edges in order to facilitate the interpretation by the pathologist. Mechanical bowel preparation, antibiotic and antithrombotic prophylaxis are performed in the same way as for TME surgery.



APR: abdominoperineal excision; DRE: digital rectal examination; CEA: carcinoembryonic antigen; CT: computed tomography; MRI: magnetic resonance imaging; CR: clinical response; TRG: tumor regression grade; TME: total mesorectal excision

Fig. 1 Flow chart of the study

Histopathology

Histopathology reports must include ypT status, TRG according to the modified Mandard classification [13], and, when residual cancer is present, the involvement of margins, degree of differentiation and presence/absence of lymphatic, perineural or vascular invasion.

Response definitions

Clinical response is defined as complete when all the following features are observed: no palpable mass at DRE, no mucosal abnormality at endoscopy (a flat scar or teleangectasia will be considered as no mucosal abnormality) and no metastatic nodes at MRI.

Clinical response is defined as major when there is absence of mass at DRE (smooth indurations of the rectal wall will be considered as absence of mass), small mucosal irregularity or superficial ulcer no more than 2 cm in diameter at endoscopy and no metastatic nodes at MRI. All other features not included in cCR or mCR will be considered as no response.

Different definitions of mCR and cCR after neoadjuvant therapy have been reported [19]. Therefore, we decided to use our own definition which was published in a previous paper [13].

Pathologic response is defined as complete when there is absence of any viable tumour cell in the specimen (ypT0NX) in patients who undergo a LE and ypT0N0 in patients who undergo TME.

Follow-up

In patients who undergo a rectum-sparing strategy, a strict follow-up is performed (Fig. 2).

Ancillary studies

To add value, bowel function, faecal continence and QoL in patients treated with rectum-sparing approaches will be

measured. The participation in this ancillary study will be voluntary and will cover only those centres that have the ability to manage distribution/collection of the questionnaires. Bowel function is evaluated using the Memorial Sloan Kettering Cancer Center bowel function instrument, faecal continence, and its impact on QoL is evaluated by the Fecal Incontinence Quality of Life scale (FIQL) and QoL by the generic European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 and specific EORTC QLQ-CR29 questionnaires. All questionnaires are translated into Italian and validated.

Sample size and statistical considerations

Sample size

The rectum-sparing approach can be considered clinically acceptable if at 2 years $\geq$50% of the rectum is conserved. A sample size of 164 patients who undergo a rectum-sparing approach will allow testing of the hypothesis that the rectum is preserved in 60% of patients with 80% power (exact binomial test for proportions, alpha = 5%, 1 tail) and the study is considered positive if the rectum is preserved in at least 87 cases.

Statistical analysis

Results will be reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [20]. All continuous variables will be described using means, standard deviation (SD) and quantiles when appropriated. Nominal and ordinal variables will be described using contingency tables.

The main analysis will be assessment of rectum preservation at 2 years in patients with rectal cancer after neoadjuvant treatment followed by a rectum-sparing approach. The percentage of rectum preservation will be estimated by the ratio between the number of patients with rectum preservation at 2 years and the total number of patients who undergo a LE or watch and wait and will be reported with the 95% confidence interval (CI).

Analysis of secondary endpoints

Secondary analyses will evaluate the OS, DFS, LRFS, the LE-associated morbidity, the frequency of patients without stoma, the association between mCR or cCR and pCR, between tumour and clinical factors and pCR, and the impact of rectum-sparing or conventional approach on bowel function and QoL. Survival will be determined as the time from the date of registration to the date of the event. Patients alive at the time of analysis will be censored at the date of last assessment. The event is defined as death for any cause, local recurrence defined as pelvic (intraluminal or extraluminal) and distant recurrence (outside the pelvis). In patients who are treated using a watch and wait policy, the regrowth of tumour is considered as local recurrence. The diagnosis of recurrence is determined by clinical examination, radiological imaging or biopsy. Survival will be estimated by the Kaplan–Meier method and the 2- and 5-year proportions of surviving patients will be reported with the 95% CI. The hazard ratio and its 95% CI of "rectum-sparing" to conventional surgery will be estimated using a Cox proportional hazards model. The frequencies of different treatments administered preoperatively, and morbidity and presence of stoma at 2 and 5 years will be described in terms of percentages and reported with 95% CI; their association with the type of surgical treatment will be tested by using the Chi-square test. The agreement between mCR or cCR and pCR will be evaluated by estimating the Kappa statistics and results will be reported with a 95% bootstrap CI. The analysis of

Follow-up month	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**30**	**36**	**42**	**48**	**54**	**60**
Physical examination, DRE	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
BT + CEA	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Proctoscopy	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Pelvic MRI		**X**		**X**		**X**		**X**		**X**		**X**		**X**
Chest-abdomen CT				**X**				**X**		**X**		**X**		**X**
Colonoscopy				**X**								**X**		

DRE: digital rectal examination; BT: blood test; CEA: carcinoembryonic antigen; MRI: magnetic resonance imaging; CT: computed tomography

Fig. 2 Follow-up timetable

factors associated with a pCR will be performed by a multivariable logistic regression model with the following as explanatory variables: patient demographics, baseline stage, type of preoperative treatment and type of surgery (TME, LE, watch and wait). The bowel function, faecal continence and QoL scales will be scored using the standard procedures given in the reference manuals. Mean scores and SD will be estimated for each scale and reported with their 95% CI. The changes during the study period will be analysed using a generalized linear mixed model with a gamma distribution.

Coordination and monitoring

The study has been designed by colorectal surgeons, oncologists and radiotherapists with the support of a statistician. The Department of Surgery, Oncology and Gastroenterology (DiSCOG), Clinica Chirurgica I of the Padova University (Italy), is the coordinating centre of the trial and is responsible for data collection and management.

The trial has been endorsed by the Italian Association of Radiotherapy and Oncology (Associazione Italiana Radioterapisti Oncologi (AIRO)), the Italian Society of Colorectal Surgery (Società Italiana di Chirurgia ColoRettale (SICCR)), the Italian Society of Surgical Oncology (Società Italiana di Chirurgia Oncologica (SICO)), and by the Venetian Cancer Institute (Istituto Oncologico Veneto (IOV)). Every 3 months, an update of the study will be distributed to the investigators of each participating centre.

Ethics, informed consent and safety

The Institutional Review Board of Padova Hospital has approved the final protocol, and appropriate approval is required to be obtained by each participating institution. The RESARCH study is registered at clinicaltrials.gov (NCT02710812).

Discussion

Historically, rectum-preserving approaches after neoadjuvant therapy have been reserved for patients unfit for or refusing conventional transabdominal surgery. Recently, an increasing number of prospective studies (Tables 1, 2) seem to support the hypothesis that, in patients with a major or complete clinical response after neoadjuvant therapy, the rectum-sparing strategy is feasibile and safe [21]. This strategy is therefore gaining worldwide acceptance and will be widely used in clinical practice. However, most of these studies have limitations because they are small, single-centre phase 2 studies. Additionally, a clear definition of clinical response is lacking and the accuracy of the imaging modalities in identifying pCR is still poor. It also seems difficult and unethical to perform prospective randomized trials aiming to compare rectum-preserving strategies and standard TME. Therefore, it has been suggested [17, 22] that prospective observational multicentre studies are performed, with large sample size and with reproducible and simple definitions of both mCR and cCR.

Basically, two rectum-sparing strategies (watch and wait and LE) have been developed. The watch and wait policy avoids surgery and has the potential to increase patient compliance. With this policy, good oncological outcomes, initially reported from a single institution only, have been replicated by others [9]. However, the watch and wait policy has been criticized because it is indicated in patients with cCR, whereas Smith et al. [23] found that only 26% of patients with pCR show cCR at endoscopy. This means that most patients with pCR will undergo conventional TME surgery, even though they are good candidates for rectum preservation.

Compared to the watch and wait approach, transanal LE has the advantage that a greater proportion of patients may have their rectum preserved because LE is indicated in both patients with cCR and those with mCR. Moreover, a histopathology report on the primary rectal cancer response makes it easier to quantify the risk of mesorectal metastases. In a previous study, we found that oncological outcomes with transanal LE are similar to that of radical surgery with a rate of rectum preservation of about 90% [13]. However, postoperative complications after LE are not uncommon and one-third of patients would require a subsequent, challenging, TME. Additionally, in this subgroup of patients, bowel dysfunction is even worse than in those who have TME as the initial procedure [24]. A further limitation of these previous studies is related to the variations in the interval between the end of neoadjuvant therapy and LE procedure. While, in these studies, it was usually 4–8 weeks, it is now widely accepted that higher rates of pCR can be achieved by increasing this interval up to 12–14 weeks [25, 26].

Compared with a previous trial, the present study includes any patient who receives neoadjuvant treatment. Usually, rectum-sparing strategies have been proposed for rectal cancer patients who, at baseline, are clinically staged as low-lying cT2 or mid–low cT3 without lymph node involvement and treated with conventional radiotherapy associated with chemotherapy. However, not infrequently, a pCR after neoadjuvant therapy has been found in patients with clinical T4 tumours or node positives. More recently, many different neoadjuvant therapy schemes have been proposed (chemotherapy only, induction and consolidation chemotherapy associated with preoperative CRT, short-course radiotherapy with long interval to surgery) and they

may result in higher rates of pCR than those observed with the conventional approach. Therefore, it seems rational to consider any patient who receives neoadjuvant therapy as a potential candidate for a rectum-sparing approach. We have chosen 50% of organ preservation as a successful cut-off of the study because, based on our previous study [13], the potential TME surgery rate after transanal LE is about 30%. Since the present study is a multicentre study, we expect that this rate will exceed 30%. Moreover, in a recent randomized prospective study [14], 74 patients randomized to receive transanal LE instead of TME surgery after neoadjuvant therapy. One underwent TME surgery instead of transanal LE and 34 had histopathological ypT2-3 potentially requiring a subsequent TME. These findings show that 52.7% of patients were potentially candidates for organ-sparing treatment. This percentage is very close to the cut-off of 50% that we planned in our study.

Consideration should also be given to the role of MRI in restaging patients after neoadjuvant therapy. Although a tumour regression grade based on MRI has been recently proposed [27], the performance of MRI in distinguishing fibrotic tissue from residual tumour after neoadjuvant therapy is still poor [28].

The negative predictive value of negative lymph node status is of key importance when planning a conservative strategy. A major concern of pursuing a conservative strategy is related to the risk of leaving metastatic lymph nodes in the mesorectum. It is therefore crucial to exclude the presence of lymph node metastases when restaging patients after neoadjuvant treatment. Since the MRI dimensional criterion in defining mesorectal lymph node infiltration (lymph nodes with a diameter > 0.5 cm along the short axis) is able to reach a negative predictive value of more than 80% [29, 30], we used this simple and reproducible criterion to define ycN0 at restaging. On the other hand, because there is an acceptable concordance between endoscopic definition of cCR and pCR [23], we used DRE and endoscopic examination to define a cCR in the rectal wall.

The definition of this study as observational may arouse criticism because the conservative approaches for rectal cancer after neoadjuvant therapy are still not considered standard of care. However, in clinical practice, an increasing number of patients are recommended or choose themselves to have conservative treatment. Therefore, we designed this study as observational following the suggestions of NCCN guidelines [17].

In conclusion, this is a observational, multicentre trial on rectum-sparing approaches after neoadjuvant therapy that incorporates both LE and watch and wait policies. Compared to older trials, the interval between the completion of neoadjuvant therapy and the decision to perform a rectum-sparing approach is at least 12 weeks; the definition of clinical response is clear and incorporates either DRE, then endoscopy and MRI, and all patients who undergo neoadjuvant therapy are registered, while only those who are treated with a rectum-preserving approach are enrolled.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from the patient included in the case report.

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