Prospective Cohort Study

INTERNATIONAL JOURNAL OF SURGERY

OPEN

Rectal Sparing Approach after preoperative Radio- and/or Chemo-therapy (ReSARCh): a prospective, multicenter, observational study

Gaya Spolverato, MD[a], Quoc Riccardo Bao, MD[a,*], Paolo Delrio, MD[h], Mario Guerrieri, MD[i], Monica Ortenzi, MD[i], Nicola Cillara, MD[t], Angelo Restivo, MD[u], Simona Deidda, MD[u], Antonino Spinelli, MD, PhD[v], Carmela Romano, MD[h], Francesco Bianco, MD[g], Giacomo Sarzo, MD[d], Emilio Morpurgo, MD[c], Claudio Belluco, MD, PhD[j], Elisa Palazzari, MD[k], Giuditta Chiloiro, MD, PhD[l], Elisa Meldolesi, MD, PhD[l], Claudio Coco, MD[m], Donato P. Pafundi, MD[m], Cosimo Feleppa, MD[n], Carlo Aschele, MD, PhD[o], Michele Bonomo, MD[p], Andrea Muratore, MD[q], Alfredo Mellano, MD[r], Germana Chiaulon, MD[s], Filippo Crimì, MD, PhD[b], Isacco Maretto, MD, PhD[a], Alessandro Perin, MD[a], Emanuele D.L. Urso, MD, PhD[a], Marco Scarpa, MD, PhD[a], Mariasole Bigon, BSc[a], Federico Scognamiglio, MS[a], Francesca Bergamo, MD[e], Paola Del Bianco, MS[f], Maria Antonietta Gambacorta, MD, PhD[l], Daniela Rega, MD[h], Salvatore Pucciarelli, MD[a]

Background: Rectal-sparing approaches for patients with rectal cancer who achieved a complete or major response following neoadjuvant therapy constitute a paradigm of a potential shift in the management of patients with rectal cancer; however, their role remains controversial. The aim of this study was to investigate the feasibility of rectal-sparing approaches to preserve the rectum without impairing the outcomes.

Methods: This prospective, multicenter, observational study investigated the outcomes of patients with clinical stage II–III mid-low rectal adenocarcinoma treated with any neoadjuvant therapy, and either transanal local excision or watch-and-wait approach, based on tumor response (major or complete) and patient/surgeon choice. The primary endpoint of the study was rectum preservation at a minimum follow-up of 2 years. Secondary endpoints were overall, disease-free, local and distant recurrence-free, and stoma-free survival at 3 years.

Results: Of the 178 patients enrolled in 16 centers, 112 (62.9%) were managed with local excision and 66 (37.1%) with watch-and-wait. At a median (interquartile range) follow-up of 36.1 (30.6–45.6) months, the rectum was preserved in 144 (80.9%) patients. The 3-year rectum-sparing, overall survival, disease-free survival, local recurrence-free survival, and distant recurrence-free survival was 80.6% (95% CI 73.9–85.8), 97.6% (95% CI 93.6–99.1), 90.0% (95% CI 84.3–93.7), 94.7% (95% CI 90.1–97.2), and 94.6% (95% CI 89.9–97.2), respectively. The 3-year stoma-free survival was 95.0% (95% CI 89.5–97.6). The 3-year regrowth-free survival in the watch-and-wait group was 71.8% (95% CI 59.9–81.2).

[a]General Surgery 3, Department of Surgical, Oncological and Gastroenterological Sciences (DiSCOG), University of Padova, [b]Department of Radiology, Department of Medicine (DiMED), University of Padova, [c]Department of Surgery, Hospital of Camposampiero, Camposampiero, [d]Department of Surgery, Hospital Sant' Antonio, [e]Medical Oncology Unit 1, Istituto Oncologico Veneto – IRCCS, [f]Clinical Research Unit, Istituto Oncologico Veneto IOV – IRCCS, Padova, [g]Department of Abdominal Oncology, Istituto Nazionale Tumori - IRCCS Fondazione G. Pascale, [h]Department of Colorectal Surgical Oncology, Istituto Nazionale Tumori – IRCCS Fondazione G. Pascale, Naples, [i]Surgery Clinic, Polytechnic University, Ancona, [j]Department of Surgical Oncology, CRO Aviano National Cancer Institute IRCCS, [k]Department of Radiation Oncology, CRO Aviano National Cancer Institute IRCCS, Aviano, [l]Department of Radiation Oncology, Fondazione Policlinico Universitario A. Gemelli, IRCCS, [m]Division of General Surgery 2, Fondazione Policlinico Universitario A. Gemelli, IRCCS, Roma, [n]Department of Surgery, Ospedale Sant'Andrea, [o]Medical Oncology Unit, Department of Oncology, Ospedale Sant'Andrea, La Spezia, [p]San Bortolo Hospital, Vicenza, [q]Department of General Surgery, E. Agnelli Hospital, Pinerolo, [r]Surgical Oncology Unit, Candiolo Cancer Institute-IRCCS, Turin, [s]Department of Radiation Oncology, Azienda Sanitaria Universitaria Integrata, Udine, [t]Department of Surgery, Santissima Trinità Hospital, [u]Department of Surgical Science, University of Cagliari, Cagliari and [v]Humanitas Clinical and Research Centre, Division of Colon and Rectal Surgery, Department of Biomedical Sciences, Humanitas University, Milan, Italy

Gaya Spolverato and Quoc Riccardo Bao should be considered as co-first authors.

Maria A. Gambacorta, Daniela Rega, and Salvatore Pucciarelli should be considered as co-last authors.

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

**Corresponding author. Address: General Surgery 3, Department of Surgical, Gastroenterological and Oncological Sciences, University of Padova, Via Giustiniani 2, 35128 Padova, Italy. Tel.: +39 049 821 2055. E-mail: quocriccardo.bao@unipd.it (Q.R. Bao).*

International Journal of Surgery (2024) 110:4736–4745

Received 27 December 2023; Accepted 3 March 2024

Supplemental Digital Content is available for this article. Direct URL citations are provided in the HTML and PDF versions of this article on the journal's website, www.lww.com/international-journal-of-surgery.

Published online 21 March 2024

http://dx.doi.org/10.1097/JS9.0000000000001322

Conclusions: In rectal cancer patients with major or complete clinical response after neoadjuvant therapy, the rectum can be preserved in about 80% of cases, without compromising the outcomes.

Keywords: local excision, locally advance rectal cancer, neoadjuvant chemoradiotherapy, neoadjuvant treatment, rectal-sparing approach, wait and see, watch-and-wait

Introduction

In patients with rectal cancer, the response to neoadjuvant treatment is variable, and a pathological complete response (pCR) has been found in approximately 20% of patients[1]. Two different approaches emerged with the aim of organ preservation, first the watch-and-wait (WW) strategy, which is a non-operative approach that requires only a strict follow-up, and, second, the local excision (LE) approach, which is a full-thickness excisional biopsy of the residual scar followed by observation or completion surgery. These two approaches offer advantages and disadvantages; however, they may be considered as complimentary by several[2–6]. Only few prospective trials and one randomized trial have been performed concerning the use of LE after neoadjuvant therapy[5,7–9], while a large international registry has been established on the use of WW[10]. To the best of our knowledge, there are no published prospective studies including both organ-sparing (LE and WW) strategies[11].

With the aim to investigate whether the rectal-sparing approaches are able to preserve the rectum without affecting the oncological outcomes, a prospective trial entitled '*Re*ctal *S*paring *A*pproach after preoperative *R*adio- and/or *Ch*emo-therapy' (ReSARCh) was launched in Italy in 2016, and the short-term outcomes of LE were previously published[12,13]. This manuscript reports the final results of the study, focusing on the rectal preservation and oncological outcomes of the trial.

Methods

Study design and participants

The ReSARCh study is a prospective, observational, multicenter trial, approved by the Institutional Review Board of the coordinator center, and by each participating institution thereafter, and registered to clinicaltrials.gov. The study protocol and short-term outcomes of LE were previously published[12,13]. This study has been reported in line with the STROCSS criteria[14] (Supplemental Digital Content 1, http://links.lww.com/JS9/C210).

Briefly, patients with a histologically proven adenocarcinoma of the rectum, located up to 12 cm from the anal verge at proctoscopy, and showing a major (mCR) or complete clinical response (cCR) at restaging following the completion of neoadjuvant treatment, were proposed to participate in the trial (Supplementary Figure 1). After a proper information on the study protocol, patients signed the informed consent and were enrolled in the study.

Clinical evaluation and staging

Clinical and pathological TNM staging were reported according to the American Joint Committee on Cancer 8th Edition[15]. The clinical evaluation and staging at diagnosis and at first restaging (with the exclusion of colonoscopy) was previously reported and summarized in Figure S1[12,13]. Poor responders were recommended to immediate Total Mesorectal Excision (TME) surgery, and were not included in the study group. Patients who showed a mCR or cCR at first restaging were recommended to undergo an additional proctoscopy 4–5 weeks later (second restaging). Patients with a mCR were recommended to undergo LE, while those showing a cCR were offered to undergo either WW or LE at clinicians' and patients' discretion (Supplementary Figure 1 and Supplementary Figure 2).

Neoadjuvant and surgical treatments, and histopathology

Any type of neoadjuvant treatment was considered, and classified in three groups: chemotherapy only, radiotherapy only, and chemoradiotherapy. LE technique was chosen by the surgeon's preference[12,13]. Independently from the surgical technique used, a full-thickness excision including all the rectal wall layers was recommended with a gross free margin of at least 0.5 cm. The surgical specimens were oriented on a cardboard before fixation.

A completion TME surgery was recommended in patients showing at least one of the following high-risk features: ypT $\geq$ 2, high-grade (G3) ypT1, positive margins (< 1 mm), lympho-vascular or perineural invasion, and tumor regression grade (TRG) $\geq$ 3 according to the Mandard's classification[16].

Definitions

cCR was defined as the absence of palpable mass at digital rectal examination, no mucosal abnormalities at endoscopy, and no metastatic nodes at MRI[8,17]. mCR was defined as the absence of palpable mass at digital rectal examination, the presence of small mucosal irregularity or superficial ulcer (< 2 cm in diameter) at endoscopy, and no metastatic nodes at MRI. Mesorectal nodes with a diameter less than 0.5 cm along the short axis at MRI were classified as negative[18]. pCR was defined as the absence of any viable tumor cell in the specimen following LE (ypT0NX)[12].

Local regrowth was defined as a tumor growth at the site of primary tumor after a cCR (WW only). Local recurrence was defined as a recurrence confined to the pelvis, after an adequate LE or a completion TME in the LE group, and any pelvic recurrences after the treatment of the local regrowth, or untreated local regrowth in the WW group. Any recurrences located outside the pelvis were defined as distant recurrence. The diagnosis of recurrence was based on clinical examination, suggestive radiological findings, or histopathology[1].

Follow-up and data collection

Independently from the rectal-sparing approach used, a strict follow-up was planned, which is fully reported elsewhere[12]. Data were collected by a local investigator in charge at each institution, and recorded in a REDCap database maintained by the responsible data manager. Eventual missing data were retrieved by the Principal Investigator together with the data manager and the person in charge at each institution.

Endpoints

The primary endpoint of the trial was the rate of rectal preservation at a minimum follow-up of 2 years. Secondary endpoints included the overall survival (OS), disease-free survival (DFS), local recurrence-free survival (LRFS) and distant recurrence-free (DRFS) survival, and frequency of stoma-free patients. Analysis of bowel function and quality of life were planned as ancillary study, and will be reported in a separate paper.

Sample size

The sample size of the study was calculated considering clinically acceptable rectum preservation of at least 50% at 2 years. A sample size of 164 patients was calculated in order to satisfy the hypothesis that the rectum is preserved in 60% of patients with 80% power (exact binomial test for proportions, $\alpha = 0.05$, one tail). The study was therefore considered positive if, in at least 87 patients, the rectum was preserved.

Statistical analysis

Descriptive statistics were reported as median with interquartile range (IQR) for continuous variables, and absolute numbers (percentages) for categorical variables. Rectum was considered preserved if no rectal resection or TME was performed.

Survival was considered the interval between the completion of neoadjuvant therapy and the event. OS, DFS, LRFS, DRFS, regrowth-free survival, stoma-free survival, and rectum-preservation survival were estimated using Kaplan–Meier methods. The events of DFS were the death for any cause, the local or distant recurrence, and any second primary tumor. For this calculation, local regrowth was not considered an event. The event for stoma-free survival was the construction of a definitive stoma or a temporary stoma, which was not reversed at the last follow-up. Patients without events were censored at last available follow-up in every curve.

Considering the observational design of the study, no statistical comparisons were performed between the LE and WW groups. However, an exploratory comparative analysis between

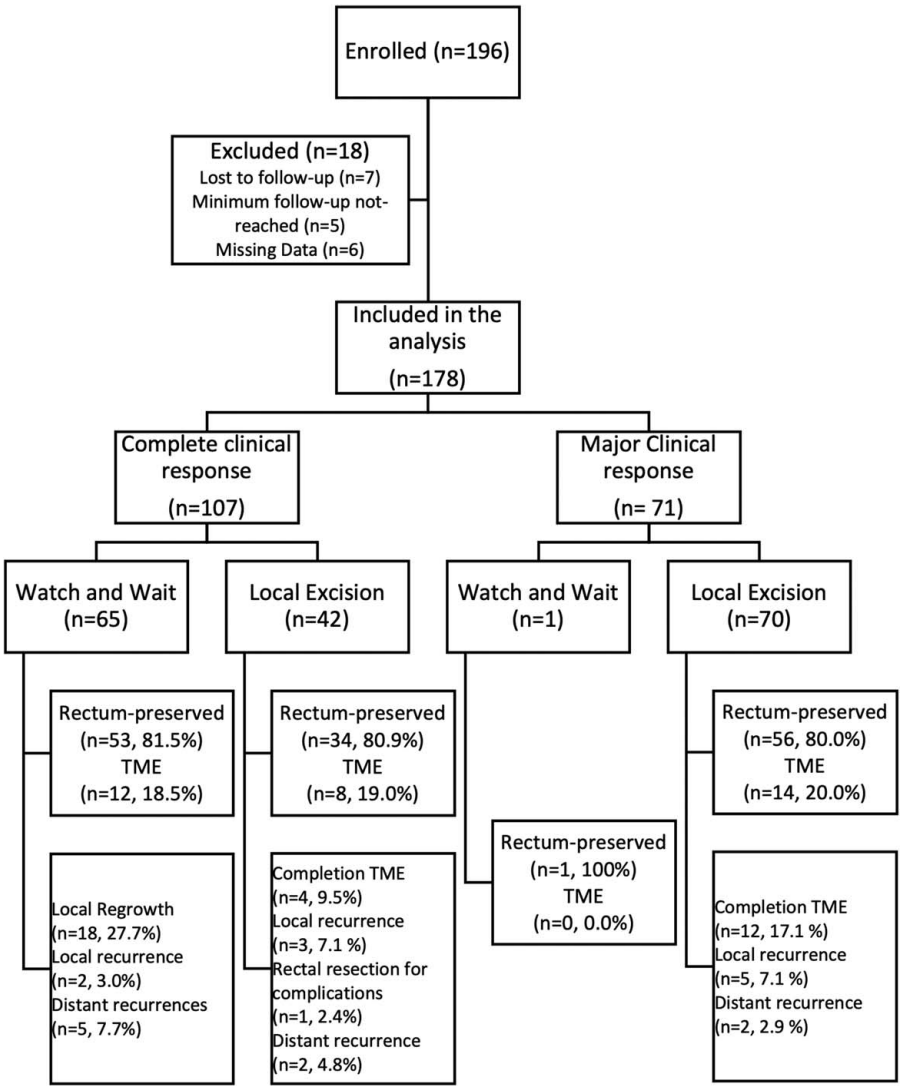

Figure 1. Flow-chart of the study.

Table 1

Characteristics, neoadjuvant therapy, and clinical and tumor response of the study group.

	Local excision (*N* = 112)	Watch-and-wait (*N* = 66)	Total (*N* = 178)
	N (%) or median (IQR)	*N* (%) or median (IQR)	*N* (%) or median (IQR)
Sex			
Female	40 (35.7)	23 (34.8)	63 (35.4)
Male	72 (64.3)	43 (65.2)	115 (64.6)
Age			
Years	65.0 (60.0–72.2)	66.0 (61.0–72.0)	65.5 (60.0–72.0)
ASA score			
1	29 (26.4)	24 (36.9)	53 (30.3)
2	63 (57.3)	30 (46.2)	93 (53.1)
3	16 (14.5)	10 (15.4)	26 (14.9)
4	2 (1.8)	1 (1.5)	3 (1.7)
NA	2	1	3
ECOG performance status			
0	72 (75.8)	57 (90.5)	129 (81.6)
1	17 (17.9)	6 (9.5)	23 (14.6)
2	4 (4.2)	0 (0.0)	4 (2.5)
4	2 (2.1)	0 (0.0)	2 (1.3)
NA	17	3	20
BMI			
kg/m^2	26.0 (24.0–29.0)	25.0 (22.0–27.0)	25.0 (23.0–28.0)
NA	1	6	7
CEA			
ng/ml	2.0 (1.1–3.4)	2.2 (1.4–3.5)	2.0 (1.2–3.5)
NA	23	11	34
Distance from anal verge			
Cm	5.0 (3.0–7.0)	5.0 (3.0–7.0)	5.0 (3.0–7.0)
NA	2	0	2
Clinical T stage			
1	2 (1.8)	2 (3.0)	4 (2.2)
2	18 (16.1)	18 (27.3)	36 (20.2)
3	82 (73.2)	42 (63.6)	124 (69.7)
4	10 (8.9)	4 (6.1)	14 (7.9)
Clinical N stage			
N0	36 (32.1)	21 (31.8)	57 (32.0)
N+	76 (67.9)	45 (68.2)	121 (68.0)
Neoadjuvant treatment			
Chemotherapy only	0 (0.0)	1 (1.5)	1 (0.6)
Long-course CRT	99 (88.4)	57 (86.4)	156 (87.6)
Short-course RT	9 (8.0)	6 (9.1)	15 (8.4)
TNT	4 (3.6)	2 (3.0)	6 (3.4)
Radiotherapy dose			
Gray	50.4 (49.0–54.2)	50.4 (50.0–55.0)	50.4 (50.0–55.0)
Neoadjuvant chemotherapy			
5-FU	2 (2.0)	2 (3.3)	4 (2.5)
5-FU-Oxaliplatin	0 (0.0)	1 (1.7)	1 (0.6)
Capecitabine	97 (94.2)	55 (91.7)	152 (93.3)
Capox	4 (3.9)	1 (1.7)	5 (3.1)
Folfox-4	0 (0.0)	1 (1.7)	1 (0.6)
ycT stage at first restaging			
0	32 (29.4)	35 (54.7)	67 (38.7)
1	49 (45.0)	23 (35.9)	72 (41.6)
2	16 (14.7)	5 (7.8)	21 (12.1)
3	10 (9.2)	1 (1.6)	11 (6.4)
X	2 (1.8)	0 (0.0)	2 (1.2)
NA	3	2	5
Tumor response at first restaging			
Complete	23 (20.5)	43 (65.2)	66 (37.1)
Major	89 (79.5)	23 (34.8)	112 (62.9)
Tumor response at second restaging			
Complete	42 (37.5)	65 (98.5)	107 (60.1)
Major	70 (62.5)	1 (1.5)	71 (39.9)

ASA, American Society of Anesthesiologists; BMI, body mass index; CEA, carcinoembryonic antigene; CRT, chemoradiotherapy; ECOG, Eastern Cooperative Oncology Group; NA, not available; TNT, total neoadjuvant therapy.

Table 2

Characteristics of local excision (*N* = 112).

	Local excision (*N* = 112)
	N (%) or median (interquartile range)
Local excision technique	
Transanal excision	43 (38.4)
Transanal minimally invasive surgery	12 (10.7)
Transanal endoscopic microsurgery	38 (33.9)
Transanal endoscopic operation	19 (17.0)
30-day complications	
No	91 (81.2)
Yes	21 (18.8)
Time from completion of neoadjuvant therapy to surgery	
Weeks	15.7 (13.3–18.3)
Length-of-stay	
Days	3 (2–4)
Clavien–Dindo classification	
1	8 (40.0)
2	9 (45.0)
3	2 (10.0)
4	1 (5.0)
Not available	1
Tumor regression grade	
1	64 (57.1)
2	25 (22.3)
3	14 (12.5)
4	9 (8.0)
ypT stage	
0	66 (58.9)
1	20 (17.9)
2	24 (21.4)
3	2 (1.8)
Completion surgery required	
No	81 (72.3)
Yes	31 (27.7)
Completion surgery performed	
No	15 (48.4)
Yes	16 (51.6)
Type of surgery	
Abdominoperineal resection	4 (25.0)
Low anterior resection	12 (75.0)
30-day complications after completion surgery	
No	11 (67.7)
Clavien–Dindo 1	2 (12.5)
Clavien–Dindo 2	3 (18.8)

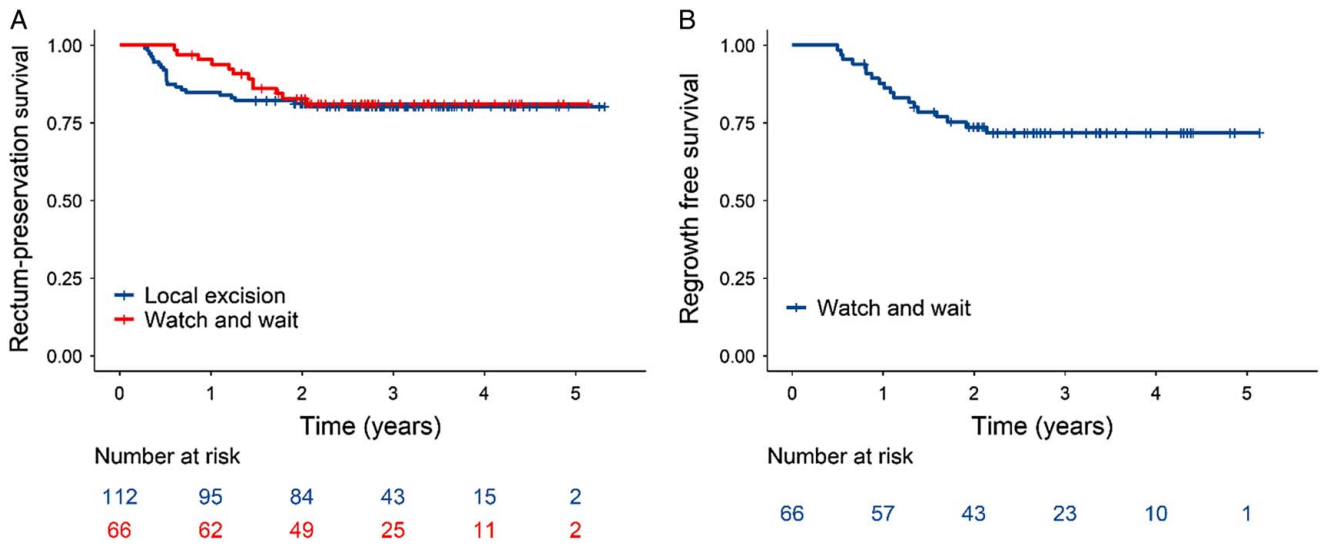

Figure 2. Kaplan–Meier estimate of rectum-preservation survival (A) and regrowth-free survival (B).

LE and WW was performed, including only patients with a cCR at the second restaging. Descriptive analysis comparison was performed by using Pearson's χ^2 test, Wilcoxon rank sum test, and Fisher's exact test. Survival analysis comparison was performed using the Kaplan–Meier method as reported above and compared with log-rank test.

Results

Clinicopathological characteristics of the study group

From April 2016 to June 2020, a total of 178 patients from 16 centers were included in the final analysis (Fig. 1) (Supplementary Table 1, Supplemental Digital Content 2, http://links.lww.com/JS9/C211). At baseline, 138 (77.6%) patients were cT ≥ 3 and 121 (68.0%) cN+ (Table 1). The majority of patients ($n = 156$, 87.6%) underwent long-course external beam radiotherapy with concurrent fluoropyridine-based chemotherapy. LE was performed in 112 (62.9%) patients, and WW in 66 (37.1%). At last restaging, a cCR was achieved in 65 of 66 (98.5%) in the WW group, and in 42 of 112 (37.5%) patients in the LE group. The overall cCR rate increased from 37.1% at first restaging to 60.1% at the second restaging.

The median (IQR) follow-up of the whole cohort was 36.1 (30.6–45.6) months, and 35.6 (30.6–44.0) and 36.9 (30.7–47.4) months in the LE and WW groups, respectively.

Local excision

LE was performed at a median (IQR) interval time of 15.7 (13.3–18.3) weeks after the completion of neoadjuvant therapy (Table 2). At the final histopathology, of 42 patients classified as cCR, 31 (73.8%) were found to have ypT0, whereas only four (9.5%) patients were found to have ypT > 1 (Supplementary Table 2, Supplemental Digital Content 2, http://links.lww.com/JS9/C211). Conversely, of 70 patients classified as mCR, 35 (50.0%) were found to have an ypT0, whereas 22 (31.4%) were found to have ypT stage > 1.

Completion TME

Unfavorable histopathologic features requiring a completion TME surgery were found in 31 (27.7%) patients after the LE, the most frequent being ypT > 1 ($n = 26$, 23.2%), and TRG > 2 ($n = 23$, 20.5%) (Supplementary Table 3, Supplemental Digital Content 2, http://links.lww.com/JS9/C211). Among these patients, 16 underwent surgery, one chemoradiotherapy only, and the remaining 14 were observed. The most frequent reason for not performing a completion TME surgery was the patient refusal ($n = 9$, 29.0%). Among 16 patients who underwent a completion TME, 13 (81.3%) showed no residual cancer on the surgical specimen.

Rectum preservation

The rectum was preserved in 144 (80.9%) patients, with a 3-year rectum-preservation survival of 80.6% (95% CI 73.9–85.8) in the entire cohort, and 80.2% (95% CI 71.5–86.5) and 81.2% (95% CI 69.2–88.8) in the LE and WW groups, respectively (Fig. 2A). Among the remaining 34 (19.1%) patients who did not have their rectum preserved, 16 had early completion TME, 11 salvage surgery for regrowth, six salvage surgery for local recurrence, and one surgery for a late pelvic abscess.

Local regrowth in the WW group

In the WW group, 18 (27.3%) patients experienced a local regrowth, with a median (IQR) time to regrowth of 12.5 (9.0–16.0) months (Supplementary Table 4, Supplemental Digital Content 2, http://links.lww.com/JS9/C211). Among them, 11 patients underwent a salvage TME, and four underwent a LE (one requiring a following salvage TME). One patient was treated with brachytherapy, and one with chemotherapy alone for concomitant disease progression to the liver. The 3-year regrowth-free survival was 71.8% (95% CI 58.9–81.2) (Fig. 2B).

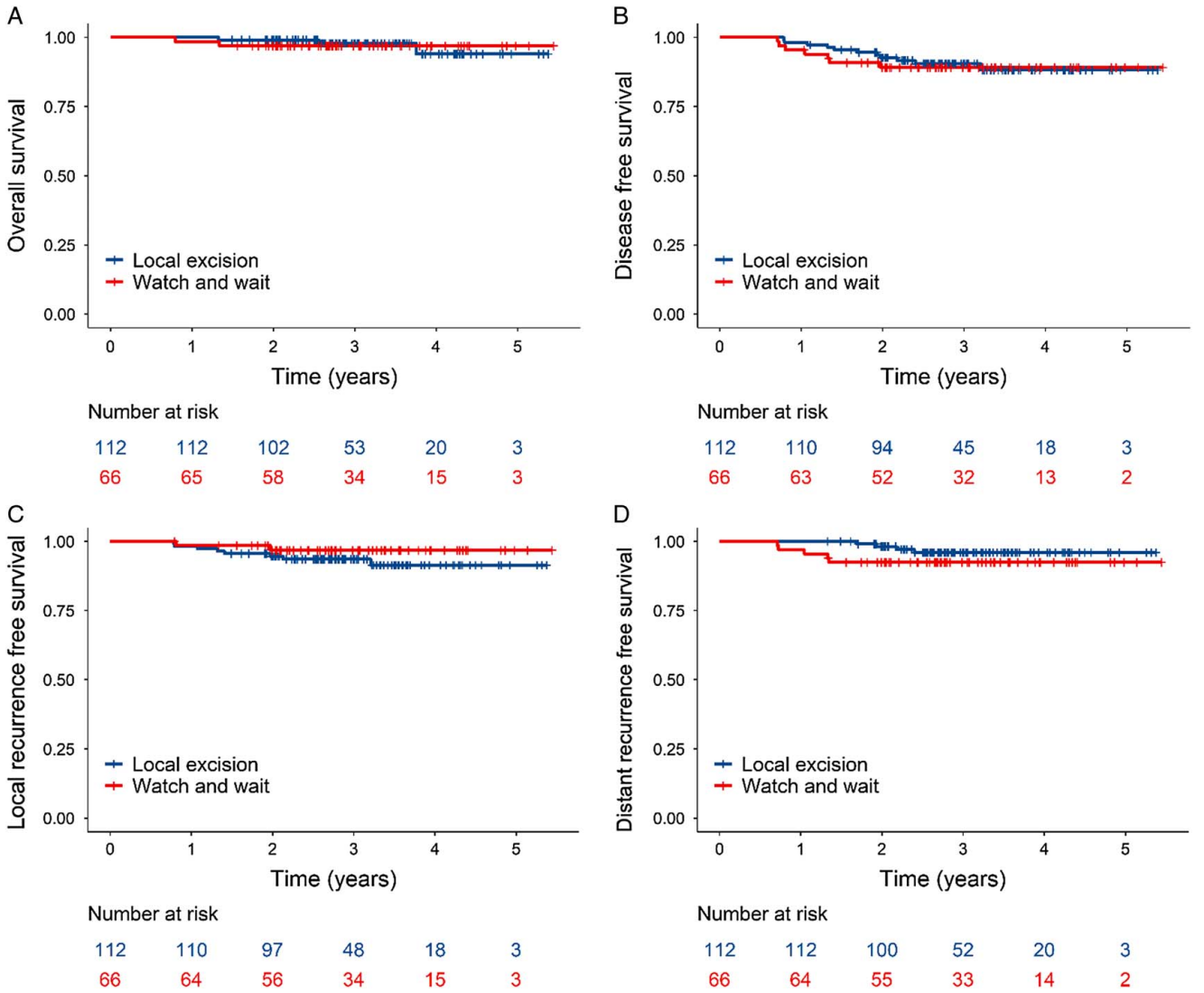

Figure 3. Kaplan–Meier estimate for overall survival (OS) (A), disease-free survival (DFS) (B), local recurrence-free survival (LRFS) (C), and distant recurrence-free survival (DRFS) (D).

Overall and disease-free survival

A total of five patients died (LE $n=3$; WW $n=2$), four for disease progression. The 3-year OS was 97.6% (95% CI 93.6–99.1) in the entire cohort, and 97.9% (95% CI 91.8–99.5) and 97.0% (95% CI 88.4–99.2) in the LE and WW groups, respectively (Fig. 3A).

Six patients (3.3%) were diagnosed with a second primary tumor (LE $n=4$; WW $n=2$) including renal cancer ($n=1$), uterine cancer ($n=1$), chondrosarcoma ($n=1$), and thyroid cancer ($n=1$), and two hematological malignancies ($n=2$). The 3-year DFS was 90.0% (95% CI 84.3–93.7) in the entire cohort, and 90.5% (95% CI 83.0–94.8) and 89.1% (95% CI 78.5–94.7) in the LE and WW groups, respectively (Fig. 3B).

Local recurrence

Local recurrence occurred in 11 patients (6.2%) (Supplementary Table 5, Supplemental Digital Content 2, http://links.lww.com/JS9/C211). In the LE group, eight (7.1%) patients experienced a local recurrence. Of them, five patients underwent TME surgery, two patients underwent local re-excision, and the last one received chemotherapy alone. None of the patients treated with completion TME had a local recurrence.

In the WW group, one patient, who underwent a salvage TME surgery for regrowth, developed a massive pelvic recurrence after 18 months, and he was still alive with the disease at the time of last follow-up. Two patients had an untreated local regrowth. The 3-year LRFS was 94.7% (95% CI 90.1–97.2) in the entire group, and 93.6% (95% CI 86.9–96.9) and 96.8% (95% CI 87.6–99.2) in the WW and LE groups, respectively (Fig. 3C).

Distant recurrence

Overall, nine patients (5.0%) developed a distant recurrence (LE = 4; WW = 5). The most common sites of distant recurrence were liver ($n=5$) and lungs ($n=4$) (Supplementary Table 5, Supplemental Digital Content 2, http://links.lww.com/JS9/C211). Among patients treated with LE, one had a synchronous

local recurrence and lung metastasis, and one had a lung metastasis 18 months after the completion surgery. In the WW group, one patient experienced synchronous distant recurrence and local regrowth, one had distant recurrence 6 months after a salvage TME.

The 3-year DRFS was 94.6% (95% CI 89.9–97.2) in the entire cohort, and 96.0% (95% CI 89.5–98.5) and 92.4% (95% CI 82.7–96.8) in the LE and WW groups, respectively (Fig. 3D).

Stoma-free survival

Overall, 31 (17.4%) patients underwent a stoma construction, of whom 13 had the stoma reversed, 18 (10.1%) are still with the stoma, and 13 (7.3%) had a definitive stoma. The 3-year stoma-free survival was 95.0% (95% CI 89.5–97.6), and 95.2% (95% CI 87.5–98.2) and 94.6% (95% CI 83.9–98.2) in the LE and WW groups, respectively.

Explorative comparative analysis in cCR patients

Overall, 107 patients who showed a cCR at the last restaging were included (LE $n=42$, WW $n=65$) (Supplementary Table 6, Supplemental Digital Content 2, http://links.lww.com/JS9/C211). In the LE group, 31 (73.8%) patients were confirmed to have a pCR (Supplementary Table 2, Supplemental Digital Content 2, http://links.lww.com/JS9/C211). Completion surgery was recommended in five patients (11.9%) and performed in four. Overall, local recurrence occurred in 3 (7.1%) patients, all of them underwent salvage TME surgery, and one died due to post-operative complications. Distant recurrence occurred in two (4.8%) patients. The rectum was preserved in 34 of 42 (80.9%) patients, and 38 (90.5%) patients were stoma-free at the time of last follow-up. In the WW group, 18 patients (27.7%) had a local regrowth, the rectum was preserved in 53 (81.5%) patients, and 57 (87.7%) were stoma-free at the last follow-up.

Altogether, in the patients with cCR, the rectum was preserved in 87 patients (81.3%), and 95 (88.7%) were stoma-free at the last follow-up (Supplementary Table 7, Supplemental Digital Content 2, http://links.lww.com/JS9/C211). The 3-year rectum-preservation survival was 79.5% vs. 82.5% ($P=0.8$) in the LE and WW patients, respectively (Supplementary Fig. 3, Supplemental Digital Content 2, http://links.lww.com/JS9/C211). The 3-year OS was 97.6% vs. 96.9% ($P=0.8$) in the LE and WW patients, respectively. The 3-year DFS was 87.8% vs. 88.7% ($P=0.8$) in the LE and WW patients, respectively. The 3-year LRFS was 92.8% vs. 95.2% ($P=0.6$) in the LE and WW patients, respectively. The 3-year DRFS was 94.8% vs. 92.3% ($P=0.5$) in the LE and WW patients, respectively (Supplementary Fig. 4, Supplemental Digital Content 2, http://links.lww.com/JS9/C211). The 3-year stoma-free survival was 90.3% vs. 86.9% ($P=0.6$) in the LE and WW patients, respectively (Supplementary Fig. 4, Supplemental Digital Content 2, http://links.lww.com/JS9/C211).

Discussion

The main finding of the trial was that 80.9% of the patients had their rectum preserved at a median follow-up of 36.1 months. When comparing our results to those of the literature[5,7–10], it should be underlined that the present is the only prospective study that included both rectal-sparing approaches.

The rate of rectal preservation found in the present trial was comparable with previous ones. Smith *et al*.[19] reported 81% of rectum preservation using a WW approach in patients experiencing cCR. In the largest cohort of WW patients retrospectively collected, out of 880 patients with a cCR, the rectum was preserved in about 87% of patients after a follow-up of over 3 years[10]. Most recently, in the randomized phase II OPRA trial, the overall organ preservation was possible in 72% of the patients with a cCR after total neoadjuvant therapy[20]. In the GRECCAR 2 trial, the rate of rectum preservation was approximately 60% after LE, likely due to the wide inclusion criteria of patients' candidate to LE[7]. Finally, the long-term analysis of our previous multicenter phase 2 trial, which had similar inclusion criteria to those of the present study, reported a rate of 78% of rectum preservation. In this trial, the rectal-sparing approach used was only the LE[17].

In the present trial, the rate of local regrowth after the WW approach was 27%. This finding is consistent with previous series, which reported rates of local regrowth ranging between 20% and 34%[10,21–23]. Our data confirm also that most of the local regrowths occur within 1 year, and that, after 2 years, local regrowth is uncommon[24]. In the OPRA trial, approximately 1/3 of the patients managed by WW experienced local regrowth. However, a similar DFS was registered among patients undergoing TME and patients undergoing delay-TME due to a local regrowth[20]. To note, in the secondary analysis, the rate of local regrowth in patients with mCR was approximately 50%[25]. In our study, most of the patients had a curative salvage surgery after regrowth. While the present study supports the use of WW approach for patients with cCR, the use of WW for patients with mCR is more controversial. Differently from the inclusion criteria of the OPRA trial, and in agreement with those adopted by the International WW database, the WW approach was reserved only to the patients with cCR. In our opinion, there is no rationale to leave untreated (only observation) patients with residual cancer (mCR) even after a total neoadjuvant therapy.

This study shows encouraging results in terms of survival in the whole cohort, with a 3-year OS and DFS of 97% and 90%, respectively. In our previous prospective study, the 5-year relapse-free survival was 89% in patients who showed cCR or mCR after LE[17]. The GRECCAR 2 trial reported a 5-year OS and DFS of 84% and 70%, respectively, in patients who underwent LE[3]. Similarly, the CARTS study reported a 5-year DFS of 82%[5]. According to the International WW database, patients with sustained cCR had a 5-year OS of 88%, that decreased to 75% in those who experienced a local regrowth[10]. To the best of our knowledge, there are no studies comparing the oncological long-term outcomes of WW and LE[11]. A strict follow-up has been advocated as the way to detect early recurrences in both groups of treatment. The rate of local recurrence after LE was approximately 7%, which is consistent with other prospective or randomized studies, where the 5-year local recurrence rate ranges between 7% and 11%[3,5,17,26]. Actually, a local recurrence rate of 7% in patients with mCR or cCR may arise some concerns because, as reported by Maas *et al*., the rate of local recurrence after TME in patients with pCR was only 2.6%[27]. Patients and physicians should be aware that the use of a rectal-sparing strategy implies a higher risk of local recurrence compared to TME.

Only 5% of the patients treated with rectal-sparing approaches experienced distant recurrence. The rate of distant metastases was 7.5% in the WW group, which is in line with the approximately 8% reported by others[10,21]. Regarding patients experiencing a local regrowth and distant recurrences, while Van der Valk *et al*.[10] suggests that distant recurrences are related to the tumor biology rather than to the omission of immediate surgery. Smith *et al*.[21] supports the hypothesis that the distant recurrence could be associated to the local regrowth. Fernandez *et al*.[24] found a five-fold higher risk of developing a distant recurrence in patients who experienced local regrowth. Since distant recurrence is a rare event, in our opinion, only larger prospective studies might properly analyze this aspect. On the other hand, in patients who underwent LE, the rate of distant recurrence was 3.6%, which is lower than the 5-year distant-recurrence rate of 13% and 18% of the previous trials, respectively[3,5]. The higher rate of distant recurrences in these two trials may depend on the longer follow-up. In fact, in our previous trial, we found that half of distant recurrences occurred after 3 years of follow-up[17].

Our study is the first prospective study, which includes both rectal-sparing approaches. No comparisons were originally planned since the indications for LE and WW were different, and the exploratory comparative analysis was made including only patients with cCR. Definition of cCR is crucial in rectal-sparing setting. However, it is to underline that the definition of cCR is not always uniform, the accuracy of clinical response is poor, and a wide interobserver agreement was reported[28–30]. Given these premises, some considerations are required when comparing two different rectal-sparing approaches. In our study, 27% of the patients after LE required a completion surgery, and most of them had no cancer on the surgical specimen (Supplementary Table 3, Supplemental Digital Content 2, http://links.lww.com/JS9/C211). On the other hand, in the study by Smith *et al*.[31,] 75% of the patients with pCR showed no cCR. One of the advantage of LE approach is that the histopathological analysis allowed is to obtain a confirmation of the response to neoadjuvant treatment. LE allowed the clinician to recognize those patients misdiagnosed as cCR, which may have a residual or high-risk tumor that may result in a local regrowth or recurrence. Moreover, LE allowed patients to also be treated with a rectal-sparing approach, not only patients with cCR but also with a mCR, which is not amenable to a WW approach. As a matter of fact, our study support findings previously reported that while the majority of cCR are pCR, and at least 50% of pCR are not cCR[31].

This study has limitations. First, patients were enrolled in the WW or LE group at the clinicians' discretion, no clear conclusion about the most appropriate rectal-sparing approach is suggested. Second, considering the multicenter design of the study, three centers enrolled more than 50% of the patients, and several centers contributed with few patients, reflecting the effects of centralization of patients affected by rectal cancer (Supplementary Table 1). Third, the endpoint of the study was defined at a mid-term outcome, with a median follow-up of 36 months reached. A longer follow-up will provide stronger evidence regarding oncological outcomes. Fourth, every type of neoadjuvant treatment was included. Most of the patients were treated with standard long-course chemoradiotherapy, less than 10% with short-course radiotherapy, and even if total neoadjuvant therapy is increasingly used nowadays and also reported to increase the rate of cCR[32,33], in the present study, it was administered to less than 4% of the patients. To note, different types of neoadjuvant approaches are emerging associated with promising results allowing also rectal preservation[34,35]. Last, the COVID pandemic may cause a little delay in management, treatment, and follow-up of patients enrolled in the study in the last few months of enrollment, even if oncological service was always guaranteed in Italy. However, the multicenter nature of the study and the inclusion of patients with locally advanced rectal cancer who received any neoadjuvant therapy and underwent any rectal-sparing approach may make the results of the present study more generalizable. Finally, this study still lacks quality of life and bowel function analysis, which were planned as ancillary study.

Conclusions

This is the first prospective study including WW and LE. More than 80% of patients with local advanced rectal cancer who showed a complete or major clinical response after neoadjuvant therapy can have their rectum preserved without compromising long-term outcomes.

Ethical approval

Approved by the Institutional Review Board of the Azienda Ospedale-Università Padova as the coordinator center (Registration number 3554/AO/15), and by each participating institution thereafter.

Consent

After a proper information on the study protocol, patients signed the informed consent and were enrolled in the study.

Sources of funding

None.

Author contribution

Conceptualization: G.Sp., A.R., C.B., C.A., I.M., E.D.L.U., M.S., P.D.B., A.G., P.D., and S.P.; data curation: Q.R.B., S.D., D.R., Gi.Ch., A.P., and M.B.; formal analysis: Q.R.B., M.S., and P.D.B.; investigation: M.G., M.O., N.C., S.D., A.S., D.R., C.R., F.B., G.Sa., E.Mo., C.B., E.P., Gi.Ch., E.Me., C.C., D.P.P., C.F., C.A., M.B., A.Mu., A.Me., Ge.Ch., F.C., I.M., A.P., E.D.L.U., M.S., and F.B.; methodology: G.Sp., Q.R.B., A.R., I.M., M.S., P.D.B., M.A.G., P.D., and S.P.; project administration: M.B., M.A.G., P.D., and S.P.; supervision: M.A.G., P.D., and S.P.; validation: G.Sp., Q.R.B., D.R., Gi.Ch., M.A.G., P.D., and S.P.; writing original draft: G.Sp., Q.R.B., A.R., F.P., I.M., A.P., and M.S.; writing – review and editing: C.A., M.A.G., P.D., and S.P. All the authors contributed to data interpretation and approved the final version of the manuscript.

Conflicts of interest disclosure

There are no conflicts of interest.

Research registration unique identifying number (UIN)

1. Name of the registry: Clinicaltrial.gov
2. Unique identifying number or registration ID: NCT02710812.
3. Hyperlink to your specific registration (must be publicly accessible and will be checked): not applicable.

Guarantor

Salvatore Pucciarelli and Quoc Riccardo Bao.

Data availability statement

The dataset used in the final analysis of the study is available on reasonable request to the corresponding author.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Presentation

The preliminary results of the study were presented at the 41st Congress of the European Society of Surgical Oncology (ESSO) 19–21 October 2022.

Acknowledgements

Assistance with the study: this work was endorsed by the Italian Society of Surgical Oncology [Società Italiana di Chirurgia Oncologica (SICO)].

References

[1] Habr-Gama A, Perez RO, Nadalin W, *et al*. Operative versus nonoperative treatment for stage 0 distal rectal cancer following chemoradiation therapy: long-term results. Ann Surg 2004;240:711–7.
[2] Teste B, Rouanet P, Tuech J-J, *et al*. Early and late morbidity of local excision after chemoradiotherapy for rectal cancer. BJS Open 2021;5: zrab043.
[3] Rullier E, Vendrely V, Asselineau J, *et al*. Organ preservation with chemoradiotherapy plus local excision for rectal cancer: 5-year results of the GRECCAR 2 randomised trial. Lancet Gastroenterol Hepatol 2020;5: 465–74.
[4] Garcia-Aguilar J, Renfro LA, Chow OS, *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;16:1537–46.
[5] Stijns RCH, de Graaf EJR, Punt CJA, *et al*. Long-term oncological and functional outcomes of chemoradiotherapy followed by organ-sparing transanal endoscopic microsurgery for distal rectal cancer: The CARTS Study. JAMA Surg 2019;154:47–54.
[6] Hallam S, Messenger DE, Thomas MG. A systematic review of local excision after neoadjuvant therapy for rectal cancer: are ypT0 tumors the limit? Dis Colon Rectum 2016;59:984–97.
[7] Rullier E, Rouanet P, Tuech JJ, *et al*. Organ preservation for rectal cancer (GRECCAR 2): a prospective, randomised, open-label, multicentre, phase 3 trial. Lancet 2017;390:469–79.
[8] Pucciarelli S, De Paoli A, Guerrieri M, *et al*. Local excision after preoperative chemoradiotherapy for rectal cancer: results of a multicenter phase II clinical trial. Dis Colon Rectum 2013;56:1349–56.
[9] Bujko K, Richter P, Smith FM, *et al*. Preoperative radiotherapy and local excision of rectal cancer with immediate radical re-operation for poor responders: a prospective multicentre study. Radiother Oncol 2013;106: 198–205.
[10] van der Valk MJM, Hilling DE, Bastiaannet E, *et al*. Long-term outcomes of clinical complete responders after neoadjuvant treatment for rectal cancer in the International Watch & Wait Database (IWWD): an international multicentre registry study. Lancet 2018;391:2537–45.
[11] Bao QR, Ferrari S, Capelli G, *et al*. Rectal sparing approaches after neoadjuvant treatment for rectal cancer: a systematic review and meta-analysis comparing local excision and watch and wait. Cancers (Basel) 2023;15:465.
[12] Barina A, De Paoli A, Delrio P, *et al*. Rectal sparing approach after preoperative radio- and/or chemotherapy (RESARCH) in patients with rectal cancer: a multicentre observational study. Tech Coloproctol 2017; 21:633–40.
[13] Marchegiani F, Palatucci V, Capelli G, *et al*. Rectal sparing approach after neoadjuvant therapy in patients with rectal cancer: the preliminary results of the ReSARCh trial. Ann Surg Oncol 2022;29:1880–9.
[14] Mathew G, Agha R, Albrecht J, *et al*. STROCSS 2021: strengthening the reporting of cohort, cross-sectional and case-control studies in surgery. Int J Surg Open 2021;37:100430.
[15] Amin MB, Edge SB, Greene FL, *et al*. AJCC Cancer Staging Manual. Springer; 2017;2017.
[16] Mandard A-M, Dalibard F, Mandard J-C, *et al*. Pathologic assessment of tumor regression after preoperative chemoradiotherapy of esophageal carcinoma. Clinicopathologic correlations. Cancer 1994;73: 2680–6.
[17] D'Alimonte L, Bao QR, Spolverato G, *et al*. Long-term outcomes of local excision following neoadjuvant chemoradiotherapy for locally advanced rectal cancer. Ann Surg Oncol 2021;28:2801–8.
[18] Beets-Tan RG, Lambregts DM, Maas M, *et al*. Magnetic resonance imaging for clinical management of rectal cancer: updated recommendations from the 2016 European Society of Gastrointestinal and Abdominal Radiology (ESGAR) consensus meeting. Eur Radiol 2018;28: 1465–75.
[19] Smith JD, Ruby JA, Goodman KA, *et al*. Nonoperative management of rectal cancer with complete clinical response after neoadjuvant therapy. Ann Surg 2012;256:965–72.
[20] Garcia-Aguilar J, Patil S, Gollub MJ, *et al*. Organ preservation in patients with rectal adenocarcinoma treated with total neoadjuvant therapy. J Clin Oncol 2022;40:2546–56.
[21] Smith JJ, Strombom P, Chow OS, *et al*. Assessment of a watch-and-wait strategy for rectal cancer in patients with a complete response after neoadjuvant therapy. JAMA Oncol 2019;5:e185896.
[22] Dattani M, Heald RJ, Goussous G, *et al*. Oncological and survival outcomes in watch and wait patients with a clinical complete response after neoadjuvant chemoradiotherapy for rectal cancer: a systematic review and pooled analysis. Ann Surg 2018;268:955–67.
[23] Renehan AG, Malcomson L, Emsley R, *et al*. Watch-and-wait approach versus surgical resection after chemoradiotherapy for patients with rectal cancer (the OnCoRe project): a propensity-score matched cohort analysis. Lancet Oncol 2016;17:174–83.
[24] Fernandez LM, São Julião GP, Figueiredo NL, *et al*. Conditional recurrence-free survival of clinical complete responders managed by watch and wait after neoadjuvant chemoradiotherapy for rectal cancer in the International Watch & Wait Database: a retrospective, international, multicentre registry study. Lancet Oncol 2021;22:43–50.
[25] Thompson HM, Omer DM, Lin S, *et al*. Organ preservation and survival by clinical response grade in patients with rectal cancer treated with total neoadjuvant therapy: a secondary analysis of the OPRA randomized clinical trial. JAMA Netw Open 2024;7:e2350903.
[26] Bach SP, Gilbert A, Brock K, *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: 92–105.
[27] Maas M, Nelemans PJ, Valentini V, *et al*. Long-term outcome in patients with a pathological complete response after chemoradiation for rectal cancer: a pooled analysis of individual patient data. Lancet Oncol 2010; 11:835–44.
[28] Felder SI, Patil S, Kennedy E, *et al*. Endoscopic feature and response reproducibility in tumor assessment after neoadjuvant therapy for rectal adenocarcinoma. Ann Surg Oncol 2021;28:5205–23.
[29] Williams H, Thompson HM, Lin ST, *et al*. Endoscopic predictors of residual tumor after total neoadjuvant therapy: a post hoc analysis from

the organ preservation in rectal adenocarcinoma trial. Dis Colon Rectum 2024;67:369–76.
[30] Deidda S, Spolverato G, Capelli G, *et al*. Limits of clinical restaging in detecting responders after neoadjuvant therapies for rectal cancer. Dis Colon Rectum 2023;66:957–64.
[31] Smith FM, Wiland H, Mace A, *et al*. Clinical criteria underestimate complete pathological response in rectal cancer treated with neoadjuvant chemoradiotherapy. Dis Colon Rectum 2014;57:311–5.
[32] O'Brien T, Hospers G, Conroy T, *et al*. The role of total neoadjuvant therapy in locally advanced rectal cancer: a survey of specialists attending the All-Ireland Colorectal Cancer Conference 2022 including lead investigators of OPRA, PRODIGE-23 and RAPIDO. Ir J Med Sci 2023; Dec 23 [Epub ahead of print]. doi:10.1007/s11845-023-03591-4
[33] Rettig RL, Beard BW, Ryoo JJ, *et al*. Total neoadjuvant therapy significantly increases complete clinical response. Dis Colon Rectum 2023; 66:374–82.
[34] Geubels BM, van Triest B, Peters FP, *et al*. Optimisation of organ preservation treatment strategies in patients with rectal cancer with a good clinical response after neoadjuvant (chemo)radiotherapy: additional contact X-ray brachytherapy versus eXtending the observation period and local excision (OPAXX) - protocol for two multicentre, parallel, single-arm, phase II studies. BMJ Open 2023;13: e076866.
[35] Cercek A, Lumish M, Sinopoli J, *et al*. PD-1 blockade in mismatch repair-deficient, locally advanced rectal cancer. N Engl J Med 2022;386: 2363–76.