



Safety and clinical efficacy of neoadjuvant chemoradiation therapy with immunotherapy for organ preservation in ultra-low rectal cancer: preliminary results of the CHOICE-I trial: a prospective cohort study

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Objective: To explore the safety and efficacy of neoadjuvant chemoradiotherapy (nCRT) combined with a PD-1 antibody in improving complete clinical response (cCR) and organ preservation in patients with ultra-low rectal cancer.

Methods: This was a prospective phase II, single-arm, open-label trial. Patients with confirmed pMMR status T_{1-3a}N₀₋₁M₀ rectal adenocarcinoma were included. Long-course chemoradiotherapy was delivered to a dose of 50 Gy. A PD-1 antibody was added 2 weeks after the first radiotherapy session, and two courses were administered. After chemoradiotherapy, CapeOX plus PD-1 antibody was administered to patients for two cycles. After evaluation, patients with cCR were managed with a watch-and-wait (W&W) approach. Local excision or a W&W approach was performed for patients with near complete clinical response (ncCR) as per multidisciplinary team decision. Radical surgery was recommended for poorly regressed or progressed tumors.

Results: Twenty-five patients were enrolled, but two patients withdrew from the study. A total of 23 patients completed the entire neoadjuvant therapy. Ten and five patients achieved cCR and ncCR, respectively, and the rest had a partial clinical response. Patients with cCR were managed with W&W. Four patients with ncCR underwent local excision and were managed using W&W. Eight patients with partial clinical response underwent anus-preserving surgery. At the last follow-up, the rectum and anus preservation rates were 63.4% (14/22) and 95.5% (21/22), respectively.

Conclusion: nCRT combined with immunotherapy tended to achieve better cCR and rectum preservation rates with good tolerance in patients.

Keywords: immunotherapy, neoadjuvant chemoradiotherapy, organ preservation, ultra-low rectal cancer, watch and wait

Introduction

Neoadjuvant chemoradiotherapy (nCRT) followed by total mesorectal excision (TME) has been proposed as the standard treatment

for locally advanced rectal cancer^[1,2]. Approximately 15%–20% of patients will achieve pathologic complete response (pCR) after nCRT, which is defined as the absence of tumor cells in surgical specimens. Patients who achieved pCR have been shown to have better disease-free survival (DFS) compared with those who did not^[3]. In such cases, the benefits of radical surgery in patients with pCR are doubtful. A phenomenon of complete clinical response (cCR) also exists. cCR is defined as the absence of clinical, endoscopic, or radiographic evidence of a tumor. In 2004, Habr-Game initially reported that patients with cCR could be managed using the watch-and-wait (W&W) approach following nCRT, and the oncological outcomes were identical to those of patients who achieved pCR^[4]. Subsequent reports have supported the finding that W&W is a safe approach for organ preservation and quality of life^[5,6]. However, the rate of cCR after nCRT remains unsatisfactory, ranging from 5% to 30%^[7], and the cCR rate of rectal cancer patients receiving nCRT in our center was 17.6%. Improving the cCR rate in patients with rectal cancer after nCRT is of great importance to patients' quality of life.

Current clinical guidelines have recommended nCRT in patients with cT₃₋₄ and/or N⁺ rectal cancer. Radical surgery is recommended for patients with early-stage cancer^[1,2]; however, it can cause disability and reduce quality of life, particularly in patients with ultra-low rectal cancer who would receive intersphincteric resection (ISR) or abdominoperineal resection

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(APR)^[8]. Therefore, improving the quality of life of patients with early-stage low rectal cancer is the focus of colorectal cancer (CRC) surgeons. Previous studies have focused on organ preservation in patients with low rectal cancer after nCRT. The ACOSOG Z6041 study included patients with cT₂N₀ rectal cancer with tumors ≤8 cm away from the anal verge^[9]. The GRECCAR 2 study included patients with cT₂₋₃N₀ rectal cancer with tumors ≤8 cm away from the anal verge^[10]. To date, no prospective clinical studies have focused on organ preservation strategies in patients with early-stage ultra-low rectal cancer who would receive ISR or APR under the current clinical guidelines.

Immunotherapy has been shown to have significant survival benefits in deficient mismatch repair (dMMR)/microsatellite instability-high (MSI-H) metastatic CRC but has poor response in proficient mismatch repair (pMMR)/microsatellite stable (MSS) CRC^[11]. However, pMMR/MSS CRC accounts for >90% of all CRC cases, which indicates that most patients with CRC cannot benefit from immunotherapy^[12]. Studies have demonstrated that radiotherapy and immunotherapy have synergistic effects in cancer treatment^[13-15]. The expression levels of programmed death ligand-1 (PD-L1) and density of CD8⁺ tumor-infiltrated lymphocytes were reported to increase after radiation^[16], suggesting the potential benefit of combining radiotherapy and immunotherapy. In the VOLTAGE trial, researchers reported the clinical efficacy and safety of nCRT and subsequent immunotherapies. pCR was confirmed in 30% of the patients with MSS. Also, there were no effective biomarkers to predict the response of immunotherapy, and there were few studies reporting about the correlation of gene status and immunotherapy. Given these findings, we hypothesized that nCRT combined with immunotherapy could improve the cCR rate in patients with MSS and thus benefit organ preservation as well as improve quality of life in patients with ultra-low rectal cancer, and we also intended to explore the potential biomarkers that could predict the treatment response.

In this study, we aimed to perform a prospective single-arm, single-center, phase II trial to evaluate the safety and clinical efficacy of combining nCRT and immunotherapy in patients with MSS ultra-low rectal cancer who would initially receive ISR or APR.

Materials and methods

Study design and patients

This was a prospective, single-arm, single-center, phase II trial.

Eligible patients were aged 18 to 75 years, with a desire for anus preservation, confirmed cT_{1-3a}N₀₋₁M₀ rectal adenocarcinoma, confirmed MSS type, inferior margin of ≤2 cm from the dentate line, an Eastern Cooperative Oncology Group performance status of 0–1, and normal laboratory tests (including normal liver and kidney function, coagulation examinations, and blood routine tests).

Exclusion criteria included a history of CRC; intestinal obstruction, intestinal perforation, and intestinal bleeding that required emergency surgery; allergy to capecitabine, oxaliplatin, and programmed death-1 (PD-1) monoclonal antibody; a history of pelvic radiation and treatment with corticosteroids or other immunosuppressive agents within 14 days before the study; and the presence of autoimmune disease or any other unstable systemic diseases.

Given the paucity of data regarding the novel regimen, the sample size estimation for this phase II trial was based on preliminary pilot study results from our center. We hypothesized that the complete clinical response (cCR) rate following the new treatment regimen would be 45%, compared to the 17.6% cCR rate observed with conventional nCRT at our institution. To account for potential dropout or loss to follow-up, which is estimated to be around 10% of the total enrolled participants, we adjusted our calculations accordingly. Using these assumptions and aiming for a one-sided significance level (α) of 0.05 and a power (1- β) of 80% to detect a clinically meaningful difference between the two cCR rates, we performed sample size calculation. Based on these parameters, the initial required sample size was determined to be 21 patients. However, to accommodate the anticipated 10% dropout rate, we inflated the sample size to 23 patients.

This work has been reported in line with the STROCSS criteria^[17].

Procedures

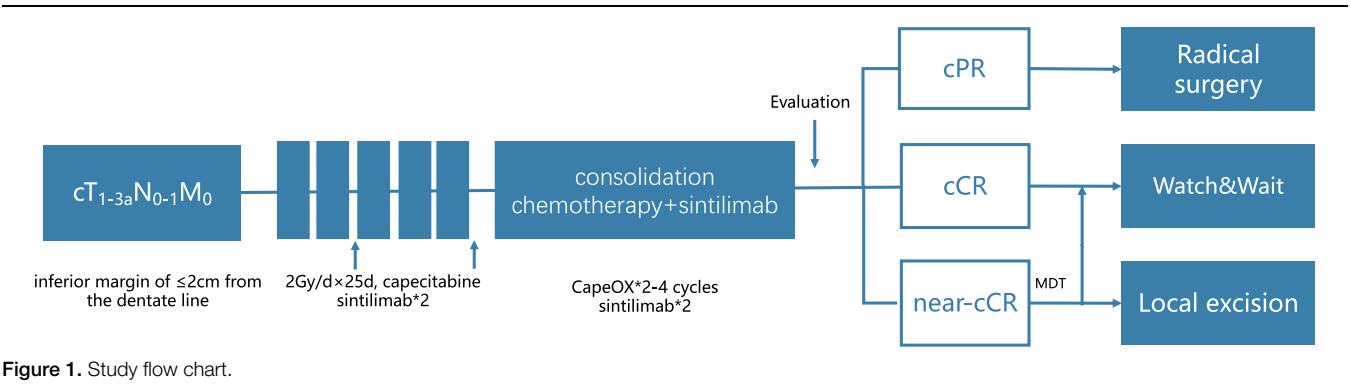
All eligible patients first received a baseline assessment, including information on demographics, medical history, disease characteristics before enrollment, systematic physical examination, and relevant laboratory and imaging tests (chest computed tomography [CT], liver magnetic resonance imaging [MRI], and abdominal and pelvic CT or MRI).

After completion of the baseline assessment, the patients received 50 Gy (2 Gy/d*25d) radiotherapy with concurrent capecitabine twice daily. Patients were administered sintilimab (200 mg intravenously) after receiving ten days of radiotherapy, which was administered every 3 weeks for two cycles. Then, the patients were administered two cycles of sintilimab with CAPOX.

After completion of all the therapies, the patients were reassessed to determine the clinical efficacy of neoadjuvant therapy. The assessment included imaging tests (chest CT, liver MRI, and abdominal and pelvic CT or MRI) and colonoscopy. Figure 1 demonstrates the flow chart of this trial.

cCR was determined by a multidisciplinary team based on digital rectal examination (DRE) and endoscopy. Endoscopic findings consistent with cCR included a flat white scar with or without telangiectasias and a lack of ulceration or nodularity^[18]. MRI of the pelvis could be used as a supplement for the judgment of cCR but is not the main standard of cCR. An intermediate status of near cCR (ncCR) was found between cCR and residual tumors. Endoscopic findings of ncCR included mucosal blanching and/or telangiectasia, but with mild mucosal unevenness, and DRE showed normal or palpable irregularities or nodules ≤2 cm in diameter.

If the patients achieved cCR, the W&W approach was performed. If ncCR is achieved, the patients were re-evaluated by the multidisciplinary team to determine whether W&W, local excision, or TME should be performed. The rest of the patients received TME. Local excision would be applied to patients with good response but yet not achieving cCR. The characteristics eligible for local excision include the following^[1]: locally normal in digital rectal examination, or only touch less than 2 cm of uneven or nodules^[2]; mucosa whitening and/or telangiectasia were observed by endoscopy, but mild mucosal unevenness was observed^[3]; high-resolution magnetic resonance imaging



showed mrT1N0, and a low signal in the original tumor site on T2-weighted and mrTRG was 1-2. pCR was defined as the absence of any remaining viable cancer cells in specimens, and all sampled regional lymph nodes (ypT0N0) and tumor regression grade (TRG) were assessed according to previously reported criteria^[19].

The primary endpoints of the study were safety and the cCR rate, and the secondary endpoints included the organ preservation (W&W and local excision) rate, anus preservation rate, pCR rate, DFS, and overall survival.

Adverse events

An adverse event (or adverse experience, AE) was defined by any adverse medical event that occurs to a subject or clinical subject and is not necessarily causally related to the treatment. An AE can therefore be any bad or unintended sign (e.g. including abnormal laboratory results), symptom, or transient drug-related illness that should be considered to be related to drug use. Version 5.0 of CTCAE5.0 is used for evaluation. AEs occurring before and after treatment are considered adverse events as required by management. Therefore, safety monitoring (reporting of adverse events or serious adverse events) should be performed from the time subjects were enrolled to the end of the study. For this reason, adverse events that occur between the signing of the informed consent and the beginning of the study treatment are also considered AEs.

Follow-up

Once cCR was confirmed, the patient was managed using the W&W approach. Endoscopy and a series of examinations, including DRE, pelvic MRI, and carcinoembryonic antigen, were performed every 3 months for the first 2 years and then every 6 months. Chest CT and abdominal CT or MRI were performed every 6 months. Local regrowth was defined as any sign of tumor recurrence, such as new rectal wall thickening and an enlarged mesorectal mass, in the rectal wall on DRE, endoscopy, or imaging findings. Local regrowth was an indication for salvage surgery via TME. Patients were examined using chest CT, liver MRI, and abdominal and pelvic CT or MRI to fully detect metastases.

Whole-exome sequencing

The biopsy specimens were obtained before treatment. DNA was extracted from formalin fixed and paraffin-embedded (FFPE) tissues. Library construction and whole-exome capture

of genomic DNA were performed, and the captured DNA was sequenced on an Illumina HiSeq 2500 sequencing platform, with 125-bp paired-end sequencing.

Statistical analysis

Clinical data were analyzed using SPSS software (version 26.0; IBM SPSS, Armonk, NY, USA). Continuous variables are summarized using medians and ranges, and categorical variables are described using frequencies and percentages. Comparisons between groups were performed using Fisher’s exact test or the χ^2 test. Statistical significance was set at $P < 0.05$.

Results

Patient characteristics

Twenty-five patients were enrolled between November 2020 and October 2021 (Fig. 2). One patient had thyroid dysfunction after sintilimab administration and withdrew informed consent. One patient had substantial leukopenia after receiving radiotherapy and was therefore excluded from the study. Twenty-three patients completed the entire neoadjuvant therapy, and Table 1 shows the baseline features of the patients. The median age of the patients was 55 (range, 39–73) years, and the median distance from the inferior margin to the dentate line was 1 cm (range, 0–2) cm. There were 14 men and 9 women. Thirteen patients had cT2 disease, and 16 patients had cN0.

Clinical efficacy

One patient received two cycles of sintilimab and was committed to thyroid dysfunction. After completion of neoadjuvant therapy, assessments of clinical efficacy were performed in all 23 patients. Ten patients achieved a cCR, five patients were evaluated as ncCR, and the rest of the patients were evaluated as having a partial clinical response. Patients with a cCR were managed using the W&W strategy. Four patients with an ncCR underwent local excision and were managed with the W&W strategy. One patient with an ncCR had cerebral infarction after the assessment and was unable to complete the subsequent therapy (Table 2). Of the four patients who received local excision, one achieved a pCR; one, TRG1; and two, TRG2. Eight patients had a partial clinical response and underwent anus-preserving surgery. Among them, one achieved a pCR; three, TRG1; and four, TRG2.(Table 3)

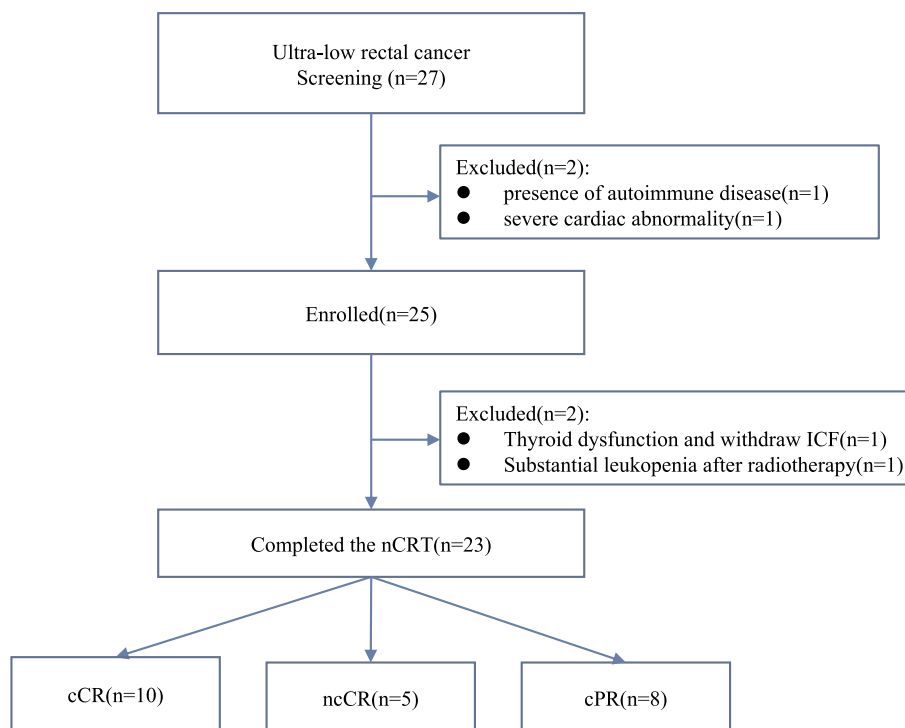


Figure 2. CONSORT flow information.

Safety and follow-up

The treatment-related adverse events are summarized in Table 4. The most frequent AE was hand-foot syndrome (21.7%, 5/23). Four patients developed severe adverse events, and two of them were hospitalized for treatment. Immune-related AEs have their unique symptoms such as immune-related myocarditis, pneumonia, hepatitis, and thyroid dysfunction, which are quite different from those of chemoradiotherapy-related AEs^[20]. But immunotherapy could also cause fatigue, nausea, vomiting, and diarrhea that are similar to symptoms after receiving chemoradiotherapy^[21]. However, as a combination therapy, overall safety was tolerable.

Table 1
Patient characteristics

Baseline features	
Age (median, range)	55 (39–73)
Sex (n)	
Male	14 (60.9%)
Female	9 (39.1%)
Distance from the dentate line (median, cm)	1 (0–2)
ECOG performance status	
0	21 (91.3%)
1	2 (8.7%)
cT stage	
cT2	13 (56.5%)
cT3a	10 (43.5%)
cN stage	
N0	16 (69.6%)
N1	7 (30.4%)

The median follow-up time was 23 months. During the last follow-up, one patient with cCR experienced local regrowth after 1 year of the completion of the treatment and underwent abdominoperineal resection. Moreover, another patient with cCR was diagnosed with polyps around the original tumor area and underwent local excision. Pathological examination confirmed no existence of tumor cells. The rest of the patients achieved a substantial cCR. The organ and anus preservation rates were 63.4% (14/22) and 95.5% (21/22), respectively.

Biomarker analysis

Whole-exosome sequencing of biopsy specimens was carried out in eight patients in this study, and the remaining were excluded due to quality control. As shown in Figure 3, 15 genes were mutated in all the patients, including APC and TP53. Owing to the limited sample size, no significant results were drawn, but KRAS wild-type patients tended to achieve cCR (3/4 vs 1/4).

Table 2
Efficacy assessment and initial treatment decisions

Efficacy assessment	N	Decisions		
		WW	Local excision	Radical surgery
cCR	10	7	0	0
ncCR	5	0	4 ^a	0
cPR	8	0	0	8

^aOne patient with ncCR had cerebral infarction after the assessment and was unable to complete the following therapy.

Table 3
Surgery and pathology

Efficacy assessment	Clinical stage	Surgery type	Pathological stage	TRG
ncCR	T3N1M0	Local excision	ypT0	0
ncCR	T2N0M0	Local excision	ypT1	1
ncCR	T0N1M0	Local excision	ypT2	2
ncCR	T2N1M0	Local excision	ypT2	2
cPR	T3N1M0	Radical surgery	ypT2N1aM0	1
cPR	T2N1M0	Radical surgery	ypT2N1M0	2
cPR	T2N0M0	Radical surgery	ypT2N0M0	2
cPR	T3N1M0	Radical surgery	ypT3N2aM0	1
cPR	T3N1M0	Radical surgery	ypT3N0M0	1
cPR	T2N0M0	Radical surgery	ypT0N0M0	0
cPR	T3N0M0	Radical surgery	ypT2N0M0	2
cPR	T3N1M0	Radical surgery	ypT3N1M0	2

Discussion

In this study, we conducted a prospective phase II, single-arm, open-label clinical trial to evaluate the safety and clinical efficacy of combining nCRT and immunotherapy in patients with early-stage MSS ultra-low rectal cancer who would initially receive ISR or APR. 23 patients were enrolled and completed the whole therapy. Ten patients achieved cCR and were managed with W&W. This preliminary results showed that nCRT plus immunotherapy would be beneficial for ultra-low rectal cancer to preserve the anus and improving the quality of life, especially for early-stage patients.

Immunotherapies that target the interaction of PD-1 with its ligand, PD-L1, have ushered in the modern oncology era. Anti-PD-(L)1 rejuvenates tumor-specific cytotoxic T cells that already reside in the tumor microenvironment (TME), causing their activation, proliferation, and trafficking to micrometastatic deposits^[22]. Immunotherapy has shown promising results in patients with deficient mismatch repair/microsatellite instability-high metastatic CRC. However, little is known regarding

Table 4
Treatment-related adverse events

Adverse events	Patients (n = 23)	
	Grades 1–2	Grade 3
ALL, n (%)	12 (52.2)	4 (17.4)
Radiation proctitis	3 (13.0)	0
Fatigue	1 (4.3)	0
Abdominal pain	1 (4.3)	0
Cerebral infarction	0	1 (4.3)
Nausea	1 (4.3)	0
Hand-foot syndrome	5 (21.7)	2 (4.3)
Abnormal liver function	1 (4.3)	0
Thyroid dysfunction	2 (8.7)	0
Fever	4 (17.4)	0
Urinary tract infection	1 (4.5)	0
Leukopenia	3 (13.6)	0
Diarrhea	1 (4.3)	0
Oral mucositis	1 (4.3)	0
Hematochezia	1 (4.3)	0
Vomiting	1 (4.3)	0
Renal insufficiency	0	1 (4.3)

neoadjuvant immunotherapy in patients with pMMR/MSS. Although neoadjuvant chemotherapy can downstage tumors pre-operatively, neoadjuvant immunotherapy aims to enhance systemic immunity against tumor antigens, eliminating micrometastatic tumor deposits that would otherwise be the source of postsurgical relapse. Moreover, neoadjuvant immunotherapy, while the primary tumor is in place, as opposed to adjuvant therapy directed only against micrometastatic disease after resection, leverages higher levels of endogenous tumor antigens present in the primary tumor to enhance T cell cytotoxicity^[22]. Recent studies have shown that radiotherapy and immunotherapy have synergistic effects in cancer treatment^[13–15]. The expression levels of PD-L1 and density of CD8⁺ tumor-infiltrated lymphocytes were reported to increase after radiation^[16], suggesting the potential benefit of combining radiotherapy and immunotherapy. The Japanese VOLTAGE trial initially reported the results of nCRT followed by nivolumab and surgery in patients with locally advanced rectal cancer, and a 30% pCR rate was observed in patients with MSS^[23]. In contrast to the VOLTAGE trial, we aimed to evaluate the rate of cCR and the concurrent application of immunotherapy during radiotherapy and consolidation chemotherapy and found a 43.5% cCR rate and two additional pCR patients. Our results were primarily better than those of the VOLTAGE trial; however, the proportion of cT₂ N₀M₀ was higher, and no control group was included. Therefore, further randomized controlled trials are required.

In 2004, Habr-Gama *et al* first reported the implementation of W&W in patients who achieved a cCR after nCRT. This specific strategy has been shown to significantly improve the quality of life of patients without affecting long-term survival^[4]. However, the current cCR rate following nCRT remains low. Martens *et al* reported that of 141 patients with rectal cancer who underwent nCRT, only 24 (17%) achieved a cCR^[24]. Perez *et al* showed that for patients with cT_{2–4}N_{0/1}, only 16 (16.2%) achieved a cCR following nCRT^[25]. In a meta-analysis by Dattani *et al*, 692 patients were included in 17 studies, of which the proportion of patients with cCR was 22.4%^[7]. In this study, the proportion of cCR after neoadjuvant therapy was 43.5%, and two patients showed pCR after radical surgery. The overall CR rate (cCR + pCR) was 52.3% (12/23), which is a great improvement compared with the results of the existing literature; this may be due to the synergistic effect of immunotherapy and radiotherapy. However, the proportion of patients with cT₂N₀M₀ in this study was rather high (10, 43.5%). A study by Habr-Gama in 2019 showed that patients with cT2N0M0 had an initial cCR rate of 56.6% after nCRT^[26]. Among the ten patients with cT₂N₀M₀ in this study, six (60%) achieved a cCR; one (10%), ncCR; one (10%), pCR; and two (20%), partial response. These findings are similar to those by Habr-Gama. Moreover, current clinical guidelines have recommended nCRT in patients with cT3–4 and/or N + rectal cancer. Radical surgery is recommended for patients with early-stage cancer^[1,2]; however, it can cause disability and reduce quality of life, particularly in patients with ultra-low rectal cancer who are unable to preserve the anus^[8]. Our results indicated that early-stage tended to show better response to nCRT with immunotherapy. But whether the addition of immunotherapy to nCRT can actually improve the cCR rate of rectal cancer patients needs to be verified in further randomized controlled studies.

The optimal organ preservation strategy for local resection after neoadjuvant therapy for rectal cancer remains controversial. Hupkens *et al* reported that patients who initially achieved

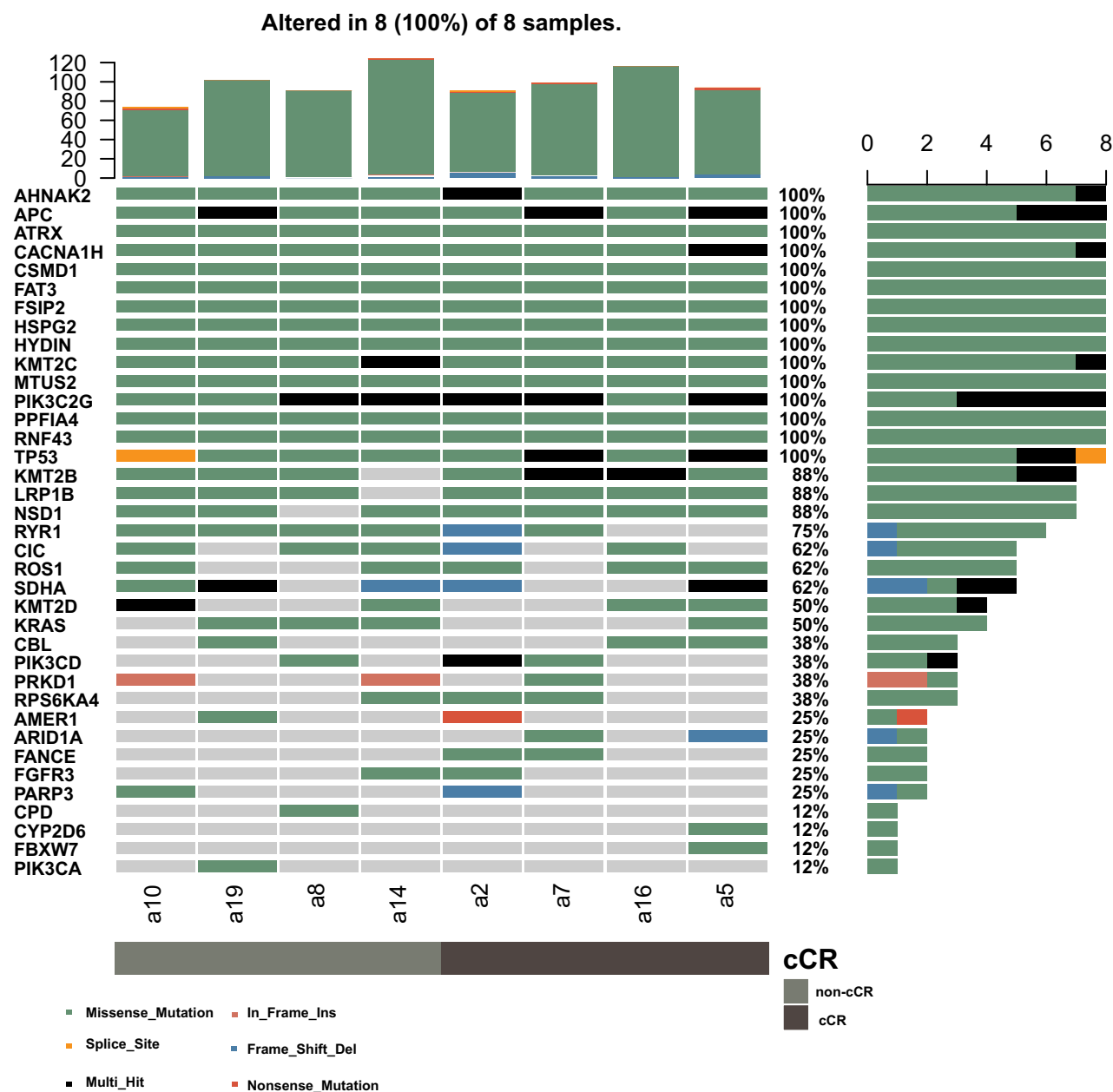


Figure 3. Biomarker analysis. Frequency of gene mutations between the cCR and non-cCR patients.

an ncCR could attain a cCR at a 12 weeks interval^[27]; therefore, appropriately extending the evaluation interval may increase the cCR rate. However, if any superficial ulcers, irregularities, or nodules are observed during prolonged intervals, local excision or radical surgery should be considered. W&W is considered for patients with pCR after local excision. W&W is also cautiously considered for patients with ypT1 without negative margins and vascular carcinoma suppositories, with early initial stage and low tumor location, and who underwent radical surgery requiring abdominoperineal resection. For patients with ypT2 or above with positive margins and vascular carcinoma suppositories, radical surgery is recommended^[9,26,28,29]. In this study, W&W was also used in patients with ypT2N0 with negative margins after local resection, mainly for the following reasons:

(1) the patient was strongly willing to preserve the anus; (2) the TRG score was 1 or 2, indicating a good response to neoadjuvant therapy; (3) no local lymph node metastasis was observed; and (4) the incision margin was negative, and no adverse pathological manifestations, such as nerve and vascular invasion, were observed. Local resection after neoadjuvant therapy significantly increases the incidence of postoperative complications, particularly incision dehiscence, especially if the tumor is located around the anus. Due to distal fixation tension, serious wound dehiscence easily occurs, and the symptoms of patients with anterior tumor resection are more severe than those with posterior tumor resection but can be managed with conservative treatments.

The present study had several limitations. First of all, this was a single-armed and single-centered trial with a small sample size

of patients. There was no control group to verify the results drawn in this study. The effect of neoadjuvant immunotherapy on the long-term prognosis of patients requires a longer time follow-up.

In conclusion, nCRT combined with immunotherapy showed good response in ultra-low rectal cancer and would be beneficial to improve organ and sphincter preservation and the quality of life of patients. To further validate this finding, our center initiated a multicenter prospective randomized controlled study of nCRT plus immunotherapy to provide more solid clinical evidence for W&W and organ preservation treatment options for ultra-low rectal cancer (Supplementary Digital Content, File 1: <http://links.lww.com/JS9/D707>).

Ethical approval

The study was approved by Shanghai Changhai Hospital Ethics Committee (CHEC2021-006).

Consent

The study protocol was approved by the ethic committee of Changhai Hospital(CHEC2021-06). And the study was registered in Chinese Clinical Trial Registry(ChiCTR2100042785). All patients were fully informed with written consent.

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Author's contribution

W.Z., L.H. and C.B. designed the study and drafted the manuscript. L.Z., G.Y., Y.S., and R.W. analysed the data, prepared the figure and tables, and drafted the manuscript; H.D. and J. Z. contributed to clinical data collection. X.Z., Y. H., H.G., L. L., H.W., and H.Z. contributed to the clinical patient recruitment and data processing. All authors participated in revising the manuscript. All authors have contributed to the manuscript and approved the submitted version.

Conflict of interest disclosure

All the authors declare to have no conflicts of interest relevant to this study.

Research registration unique identifying number (UIN)

The study was registered in Chinese Clinical Trial Registry (ChiCTR2100042785).

Guarantor

Wei Zhang, Liqiang Hao, and Chenguang Bai.

Provenance and peer review

This paper was not invited and published.

Data availability statement

Data are available on reasonable request.

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