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Original Research

Anti-PD-1-based immunotherapy as curative-intent treatment in dMMR/MSI-H rectal cancer: A multicentre cohort study

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Abbreviations: TME, total mesorectal excision; dMMR/MSI-H, DNA mismatch repair-deficient/microsatellite instability-high; MMR, mismatch repair; ICI, immune checkpoint inhibitor; PD-1, programmed cell death−1; CTLA-4, cytotoxic T lymphocyte antigen-4; pCR, pathological complete response; cCR, clinical complete response; MRI, magnetic resonance imaging; CT, computer tomography; CEA, carcinoembryonic antigen; DFS, disease-free survival; ORR, overall response rate; pMMR/MSS, proficient DNA mismatch repair/microsatellite stable.

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KEYWORDS
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Rectal cancer;
Organ preservation

Abstract ***Background:*** In a portion of patients with DNA mismatch repair-deficient (dMMR)/microsatellite instability-high (MSI-H) rectal cancer, clinical complete response (cCR) could be achieved after anti-programmed cell death protein 1 (anti-PD-1) immunotherapy. However, no data are available concerning the safety of omitting surgery and adopting immunotherapy as a curative-intent treatment for these patients.
Methods: We retrospectively collected a series of patients with dMMR/MSI-H rectal adenocarcinoma who had cCR after receiving anti-PD-1 immunotherapy and adopted immunotherapy as curative-intent treatment from six institutions. Survival outcomes were analysed using the Kaplan–Meier method.
Results: Nineteen patients were included with a median age of 48 (range 19–63). One patient was diagnosed with stage I disease, four with stage II disease and fourteen with stage III disease. Sixteen patients received anti-PD-1 immunotherapy as the first line of therapy, and eleven patients were treated with single-agent anti-PD-1 antibodies. The median time from the start of treatment to cCR was 3.8 (range 0.7–6.5) months. During a median follow-up of 17.1 (range 3.1–33.5) months since achieving cCR, no local or distant relapse was observed. Two-year local recurrence-free survival, distant metastasis-free survival, disease free-survival and overall survival for the whole cohort were 100%, 100%, 100% and 100%, respectively.
Conclusions: For patients with dMMR/MSI-H locally advanced rectal cancer who achieved cCR during anti-PD-1 immunotherapy, adopting immunotherapy as curative-intent treatment might be an alternative option. Longer follow-up and larger cohorts are warranted to verify this innovative treatment approach.

1. Introduction

The standard therapy for locally advanced rectal cancer includes neoadjuvant chemoradiotherapy followed by surgical resection [1]. Although surgical resection based on the principle of total mesorectal excision (TME) is still the mainstay of treatment for resectable rectal cancer, neoadjuvant chemoradiotherapy is added for locally advanced cases to reduce the risk of local recurrence [2,3]. However, this multidisciplinary treatment strategy may, at times, lead to life-threatening perioperative complications such as anastomotic leak [4] and long-term urinary, anal, fertility and sexual functional impairment [5,6]. Also, for patients with a tumour located in the distal part of the rectum, a permanent colostomy might be necessitated [7]. All these complications are associated with impaired quality of life.

Deficient DNA mismatch repair (dMMR)/microsatellite instability-high (MSI-H) colorectal cancer is a unique subtype, accounting for 10%–20% of all colorectal cancers [8]. Some of these patients carry germline mutations in DNA mismatch repair (MMR) genes resulting in Lynch syndrome and have tumours diagnosed at a young age [9]. It has been reported that dMMR/MSI-H colorectal cancers are less responsive to traditional cytotoxic agents [8]. As demonstrated in the FOxTROT trial, over 60% of stage II/III dMMR colon cancers had no regression after neoadjuvant therapy [10]. The development of immune checkpoint inhibitor (ICI) directed against programmed cell death–1 (PD-1) protein and cytotoxic T lymphocyte antigen-4 (CTLA-4) has shed light on the treatment of dMMR/MSI-H metastatic colorectal cancer with impressive clinical efficacy and durable response [11–14]. Recent studies in the front-line use of ICI in colorectal cancer have shown an even higher response rate compared with late line use. In the NICHE study [15], a major pathological response rate of 100% and an impressive pathological complete response (pCR) rate of 60% were reported. And in a study in patients with MSI-H rectal cancer, preoperative chemoradiotherapy plus nivolumab resulted in a pCR rate of 60% [16]. These indicate that anti-PD-1 immunotherapy may have the potential to become the curative treatment for dMMR/MSI-H rectal cancer.

It has been demonstrated that patients with rectal cancer who achieved clinical complete response (cCR) after neoadjuvant chemoradiotherapy would be offered intensive surveillance instead of radical resection as an organ preservation treatment strategy [17–22]. For patients with dMMR/MSI-H rectal cancer who achieve cCR after anti-PD-1 immunotherapy, omitting surgery and adopting immunotherapy as curative-intent treatment appears to be an attractive option, which might provide the chance of cure without functional impairment. However, the oncological safety of this treatment strategy has not been explored.

In the present study, we reported the preliminary results of a cohort of patients with dMMR/MSI-H rectal cancer who had cCR after anti-PD-1-based immunotherapy and adopted immunotherapy as a curative-intent treatment to explore the possibility of further application of this treatment strategy.

2. Materials and methods

2.1. Patients

This was a retrospective cohort study. In this study, patients who were diagnosed with dMMR/MSI-H rectal cancer and treated with anti-PD-1 immunotherapy from 1 October 2017 to 31 November 2021 from six centres were screened, and eligible patients were identified for this study. The inclusion criteria were as follows: (1) pathologically confirmed rectal adenocarcinoma; (2) dMMR and/or MSI-H status; (3) stage II/III or stage I with tumour located in distal rectum; (4) received anti-PD-1 immunotherapy; (5) reached cCR status during immunotherapy and decided to omit surgery. No restrictions were applied to the use of combined treatment. Written informed consent was obtained from each patient for the collection of data, and the study protocol was approved by the ethics committee of each study centre.

2.2. Study procedures

Standardised electronic forms were sent to physicians in each centre. Data were collected from clinical chart reviews and medical records, mainly including patients' baseline characteristics, tumour stages, treatment-related parameters, and follow-ups. Pretreatment evaluation included digital rectum examination, pelvic magnetic resonance imaging (MRI) to determine the T and N stage, chest and abdominal computer tomography (CT) scan to rule out distant metastasis, the level of serum carcinoembryonic antigen (CEA), and colonoscopy with pathological examination. Patients were staged according to the 8th edition of the American Joint Committee/International Union against Cancer staging system. Lynch syndrome was diagnosed according to the Chinese expert consensus on clinical diagnosis, treatment, and pedigree management of hereditary colorectal cancer [23]. MMR status was determined using immunohistochemistry staining for MLH1, PMS2, MSH2, and MSH6 on pretreatment tumour specimens. MSI status was determined using the American National Cancer Institute-recommended Polymerase Chain Reaction for MSI with the panel that included five loci: two mononucleotides (BAT25 and BAT26) and three dinucleotides (D5S346, D2S123 and D17S250).

Tumour response was evaluated according to the RECIST criteria v1.1 after every two to three cycles of anti-PD-1 immunotherapy. Clinical complete response was defined as the absence of residual tumour on digital rectal examination, colonoscopy [24] and pelvic MRI (Fig. 1), accompanied by a normal CEA level and negative findings in the chest and abdominal CT scan. Treatment-related adverse events were assessed continuously during treatment and for 90 days after the last dose of anti-PD-1 antibody by the treating physicians and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03. Patients were followed up every 3 months after the last dose of anti-PD-1 antibody. Digital rectum examination, CEA, colonoscopy and pelvic MRI were carried out every 3 months, while chest and abdominal CT scans were performed every 6 months. The last day of follow-up was 4 April 2021.

2.3. Statistical analysis

Non-normally distributed data were described as medians with range, and categorical variables were shown as frequency. Survival was calculated using the Kaplan–Meier method.

The primary endpoint was disease-free survival (DFS). Local recurrence-free survival was defined as the absence of recurrence within the pelvis, while distant metastasis-free survival was defined as the absence of recurrence outside the pelvis. DFS was defined as the absence of local and distant recurrence and death from any cause, and overall survival as absence of death from any cause. The date that the patient visited the physician after achieving cCR and decided to omit surgery, which was documented in the medical record, was defined as the starting time point. Duration of follow-up was calculated as the time from the starting point to the event of interest or to the last follow-up that was used as a date of censoring.

All statistical analyses were done using the Statistical Package for the Social Sciences Program (SPSS Inc., Chicago, IL, version 19.0 for Windows).

3. Results

3.1. Baseline characteristics

During the period 1 October 2017 to 31 November 2021, 29 patients were diagnosed with non-metastatic dMMR/MSI-H rectal cancer and were treated with anti-PD-1 immunotherapy from six centres in China. Among them, 20 (69.0%) patients achieved complete response, eight (27.6%) patients achieved partial response, and one (3.4%) patient remained stable; the objective response rate was 96.6%. Of the 20 patients who had complete response, 19 decided to omit surgery and were included in this analysis. The remaining 10 patients were operated on, of whom five demonstrated pathological complete response. In total, the complete response rate, including both cCR and pCR, was 82.8%.

Baseline characteristics of the 19 patients who omitted surgery were provided in Table 1, and details of individual patients were provided in Table 2. Among these 19 patients, 18 (94.7%) were diagnosed with locally advanced (T3-4/N1-2) rectal cancer. Three (15.7%) patients had a previous history of colon cancer, and two (10.5%) patients presented with colon cancer synchronously. Fourteen (73.7%) patients had their tumours located in the distal rectum.

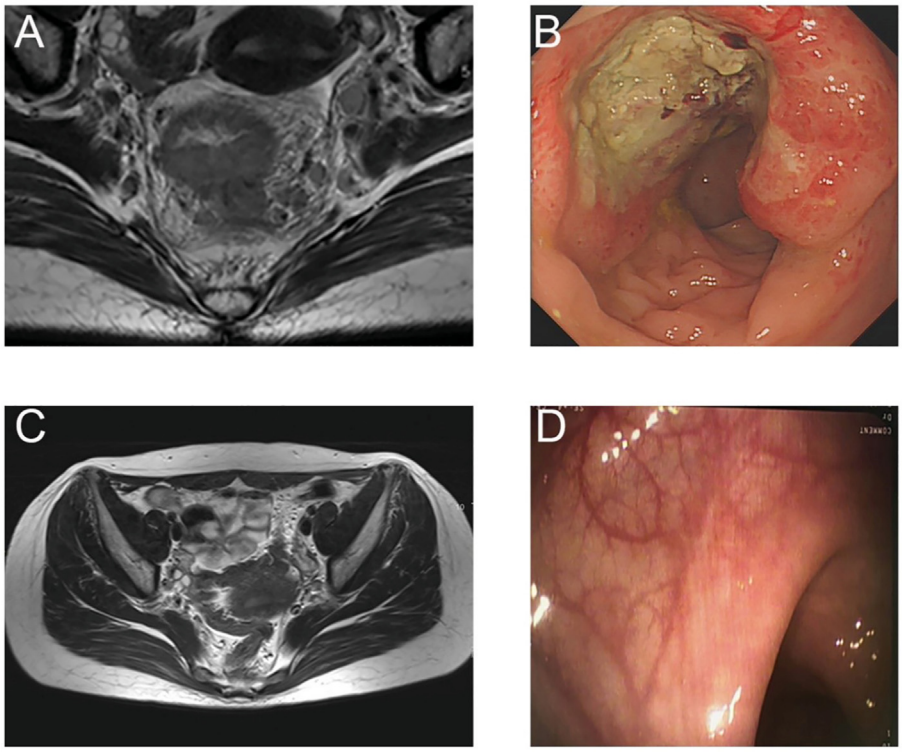

Fig. 1. Representative MRI and colonoscope images of Case 2. The representative MRI and colonoscope images of the patient showing a mass in the rectum (A and B) at diagnosis and cCR (C and D) after anti-PD-1 immunotherapy.

Table 1
Baseline characteristics of the cohort ($N = 19$).

Characteristic	
Age, years	
Median (range)	48 (19–63)
Sex-no. (%)	
Male	10 (52.6)
Female	9 (47.4)
ECOG performance status score-no. (%)	
0	10 (52.6)
1	9 (47.4)
Clinical stage-no. (%)	
I	1 (5.3)
II	4 (21.1)
III	14 (73.7)
Histological Grade-no. (%)	
Well differentiated	1 (5.3)
Moderate differentiated	11 (57.9)
Poor differentiated	4 (21.1)
Undefined	3 (15.8)
CEA-mg/mL, no. (%)	
<5.00	12 (63.2)
≥5.00	5 (26.3)
Unknown	2 (10.0)
Location from the anal verge, cm-no. (%)	
0–5	14 (73.7)
6–10	5 (26.3)
Multiple primary colorectal carcinoma-no. (%)	
Synchronous	2 (10.5)
Metachronous (previous)	3 (15.8)
No	14 (73.7)
Lynch syndrome-no. (%)	
Diagnosed	12 (63.2)
Undiagnosed	7 (36.8)

Polymerase chain reaction was performed in 18 patients demonstrating MSI-H status. Immunohistochemistry was performed on pretreatment tumour specimens on 14 patients confirming dMMR status. Of these 14 patients, one had a loss of MSH2/MSH6/PMS2 expression, five had a loss of MLH1/PMS2 expression, three had a loss of MSH2/MSH6 expression, two had single PMS2 loss, two had single MSH6 loss and one had single MSH2 loss. A family history of Lynch syndrome-related cancers was recorded in 12 (63.2%) patients, and 9 of the 12 patients were diagnosed with Lynch syndrome.

3.2. Treatment

The reasons why patients received anti-PD-1 immunotherapy were as follows: (1) dMMR/MSI-H locally advanced rectal cancer that did not respond to neoadjuvant chemoradiotherapy (three cases); (2) dMMR/MSI-H locally advanced and/or low rectal cancer who refused neoadjuvant chemoradiotherapy for fear of a permanent colostomy, reproductive toxicity and other long-term toxicity (16 cases). Sixteen patients received anti-PD-1 immunotherapy as the first line of treatment, while three patients received anti-PD-1 immunotherapy following the failure of neoadjuvant chemotherapy or chemoradiotherapy. In brief, Case 1 received four cycles of chemotherapy with the regimen of FOLFOXIRI, and Case 4 received five cycles of chemotherapy with the regimen of CapeOx, but all were evaluated as stable diseases before the

Table 2
Details of the nineteen patients who adopted anti-PD-1 immunotherapy as curative-intent treatment.

No	Age	Gender	Clinical TNM	Distance from the anal verge	Lynch syndrome	Loss of MMR protein expression	Combined treatment	Course of ICI before starting watch-and-wait	Discontinue ICI since starting watch-and-wait	Disease status at latest follow-up
1	61	Female	cT4N0M0	3.5	Undiagnosed	MSH2, MSH6	None	7	No	Died of myocardial infarction
2	19	Female	cT3N2M0	4	Yes	MSH2, MSH6	Ipilimumab	3	No	Sustained cCR
3	61	Male	cT2N1M0	4	Yes	Unknown	None	7	No	Sustained cCR
4	44	Female	cT3N0M0	4	Yes	PMS2	CapeOx	5	Yes	Sustained cCR
5	27	Male	cT4N0M0	4	Yes	Unknown	Ipilimumab	6	No	Sustained cCR
6	53	Female	cT3N1M0	8	Undiagnosed	MSH6	None	5	No	Sustained cCR
7	34	Male	cT2N1M0	1	Yes	MLH1, PMS2	Ipilimumab	6	No	Sustained cCR
8	53	Female	cT4N2M0	6	Yes	MSH2, MSH6	None	5	No	Sustained cCR
9	57	Female	cT2N0M0	5	Yes	MLH1, PMS2	None	4	No	Sustained cCR
10	36	Male	cT3N1M0	5	No	PMS2	None	4	No	Sustained cCR
11	47	Male	cT3N2M0	6	Yes	Unknown	None	12	No	Sustained cCR
12	60	Male	cT4N2M0	1.5	Yes	MSH6	None	9	No	Sustained cCR
13	26	Female	cT3N1M0	4	Undiagnosed	MLH1, PMS2	None	6	No	Sustained cCR
14	52	Male	cT3N1M0	4	Yes	MLH1, PMS2	CapeOx	1	No	Sustained cCR
15	63	Male	cT3N1M0	2	Undiagnosed	Unknown	None	4	No	Sustained cCR
16	58	Female	cT4N2M0	2	Undiagnosed	MSH2, MSH6	None	6	Yes	Sustained cCR
17	41	Male	cT3N0M0	12	Yes	Unknown	Apatinib	4	No	Sustained cCR
18	48	Male	cT3N1M0	5	No	MLH1, PMS2	CapeOx	2	Yes	Sustained cCR
19	41	Female	cT4N2M0	10	Yes	MSH2	FOLFOXIRI	2	No	Sustained cCR

change to immunotherapy. Case 5 received chemoradiotherapy plus four cycles of chemotherapy but experienced local tumour progression before switching to immunotherapy. The anti-PD-1 agents used included pembrolizumab (7/19), sintilimab (7/19), toripalimab (2/19), camrelizumab (2/19) and nivolumab (1/19).

Among all these patients, 11 were treated with single-agent anti-PD-1 antibody, while three were given ipilimumab in combination, four received chemotherapies with the regimen of CapeOx(3/4) and FOLFOXIRI(1/4) in combination and one had apatinib in combination. A median of five (range 1–9) cycles of anti-PD-1 antibody were given to patients before achieving cCR. The median time from the start of treatment to cCR was 3.8 (range 0.7–6.5) months (Fig. 2). After being assessed as cCR, three patients refused to continue immunotherapy due to financial difficulties, and the other patients continued to receive anti-PD-1 immunotherapy. The total duration of anti-PD-1 treatment was 6.4 (range 1.2–26.6) months, and all patients had discontinued immunotherapy at the time of writing this article.

Toxicity was acceptable, with 10 (52.6%) patients having any-grade treatment-related adverse events (Table 3). No patient had adverse events leading to discontinuation of treatment.

3.3. Follow-up

The median follow-up since the start of immunotherapy was 20.9 (range 4.8–36.4) months. After achieving cCR and deciding to omit surgery, patients were followed for a median of 17.1 (range 3.1–33.5) months. During the follow-up time, no local recurrence or distant metastasis was observed. Case 1 patient died of myocardial infarction 25 months after the cessation of anti-PD-1 antibody. Two-year local recurrence-free survival, distant metastasis-free survival, DFS (Fig. 3) and overall survival for the whole cohort were 100%, 100%, 100% and 100%, respectively.

4. Discussion

In this study, we presented a cohort of patients with dMMR/MSI-H rectal cancer who achieved cCR after anti-PD-1-based immunotherapy and omitted the surgical resection. Our study indicated that anti-PD-1-based immunotherapy could be curative-intent treatment in a subset of dMMR/MSI-H rectal cancer and could be offered as a new treatment option after more extensive verification.

It has been reported that the concordance of pCR and cCR was insufficient (~38.7%) in patients with rectal cancer who received neoadjuvant chemoradiotherapy [25]. Currently, the criteria we used to assess cCR after immunotherapy were still based on

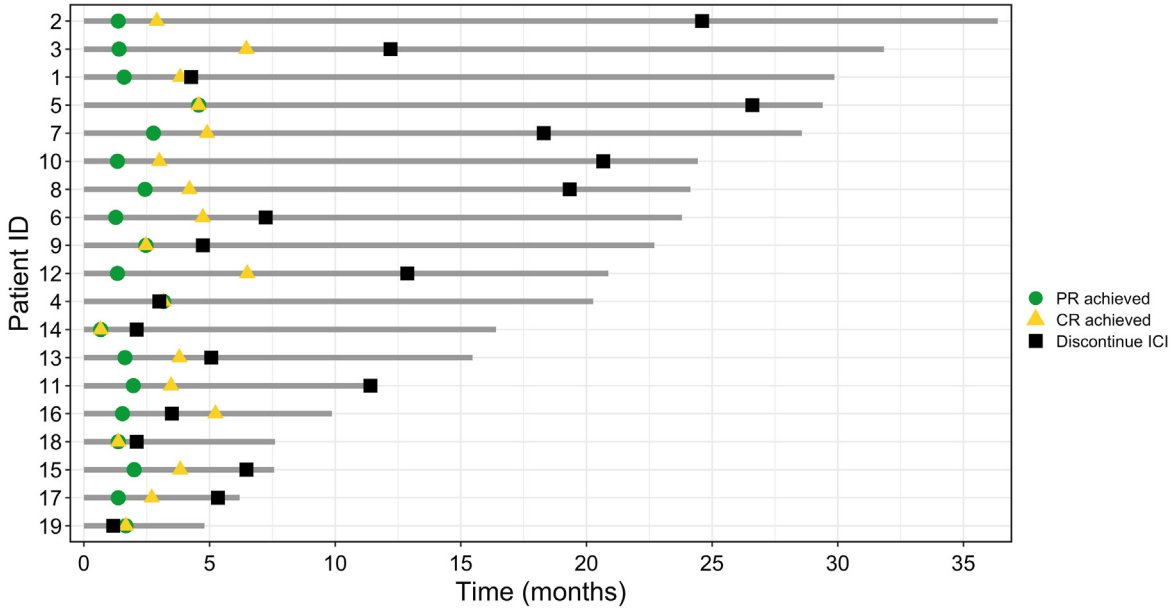

Fig. 2. Swimmer's plot of patients adopting anti-PD-1 immunotherapy as curative-intent treatment (N = 19). Each bar represents one subject in this study.

Table 3
Treatment-related adverse events of the cohort (N = 19).

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Hypothyroidism	0	2	0	0	0
Rash	3	1	1	0	0
Pruritus	2	0	0	0	0
Aminotransferase increased	0	1	0	0	0
Hypoadrenalism	0	0	1	0	0
Nervous system injury	0	0	1	0	0

digital rectum examination, CEA level test, colonoscopy and pelvic MRI, just as we performed on patients after chemoradiotherapy. Meanwhile, the accuracy of MRI in predicting cCR after immunotherapy remains unknown. Due to the lack of more discerning tools, similar

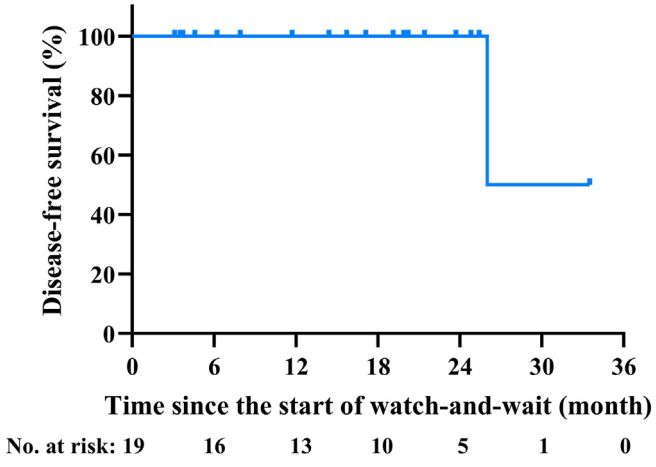

Fig. 3. Disease-free survival in the whole cohort (N = 19).

dilemmas exist in the assessment of cCR in immunotherapy. In the NICHE study [15], the correlation between radiological assessment of response and histopathological findings was poor, and patients who had ≤10% residual viable tumour on histopathological findings were often presenting as having a gross residual tumour on CT imaging. This might be due to a mixed inflammatory infiltration in these tumours that presented as a mass on CT imaging and is hard to distinguish from cancer. Therefore, patients may have reached pCR earlier than when they were actually assessed as having cCR. In the current study, the median time from the start of treatment to cCR was 3.8 months, which is much longer than the interval of radiological assessment in the NICHE study. Thus, for those patients who intend to omit surgery after immunotherapy, early surgical resection should be avoided although cCR has not been reached. More cycles of immunotherapy and longer time of observation could be provided for responders, waiting for additional possibilities of cCR.

It was notable that the cycles of anti-PD-1 antibody needed for each patient to reach cCR varied in this study. Similar situations have been reported in the literature discussing the neoadjuvant use of an anti-PD-1 antibody in the treatment of rectal cancer. In a previous study, L. Mans [26] reported a case of rectal cancer considered to be a complete endoscopic response after only one course of ipilimumab (1 mg/kg) and nivolumab (3 mg/kg). In contrast, in Zhang's report [27], one patient reached CR after six cycles of anti-PD-1 antibody. This discrepancy might partly be explained by the combined treatment. Previous studies in lung cancer [28] and melanoma [29] have suggested that combined nivolumab and ipilimumab

have provided enhanced activity over nivolumab monotherapy. In a direct comparison of overall response rate (ORR) in metastatic colorectal cancers, ORR with nivolumab plus ipilimumab (69%) [30] was numerically higher compared to nivolumab monotherapy in checkmate 142(34%) [31]. In the NICHE study [32], patients received only one dose of ipilimumab and two doses of nivolumab, and this combination treatment led to an impressive high pCR rate of 60% in dMMR early stage colon cancers. All of these indicated that the addition of CTLA-4 antibody might have the potential to accelerate the regression of the tumour. In addition, there might be inconsistencies in the timing and frequency of assessment of cCR between different physicians, and this may also contribute to the different time intervals from the first dose of anti-PD-1 antibody to cCR between patients.

Although the time for a response seems to be shorter in patients receiving dual CTLA-4 and PD-1 immunotherapy, PD-1 monotherapy demonstrates a potentially curative effect in 11 of the patients in our cohort. Meanwhile, the combination of anti-PD-1 immunotherapy with chemotherapy or radiotherapy in dMMR/MSI-H tumours has not been well studied. In our study and one case in a previous study [33], the addition of chemotherapy did not seem to shorten the courses of anti-PD-1 antibody, and no cohort studies addressing the additive effect of chemotherapy or radiotherapy in dMMR/MSI-H tumours have been reported. Considering the increased risk of side effects brought by dual immunotherapy or chemotherapy, for patients with early-stage disease, anti-PD-1 monotherapy might be sufficient.

Currently, there is no standard proposal on the courses of immunotherapy after cCR. In KEYNOTE 164 [14] and KEYNOTE 177 [34] studies, all enrolled patients with metastatic MSI-H/dMMR colorectal cancers were recommended to receive pembrolizumab for up to 2 years unless the disease progressed or were censored for other reasons [14]. In contrast, in the NICHE study, for patients with dMMR tumours who had a pathological response, only two doses of nivolumab plus one dose of ipilimumab were given, and no adjuvant immunotherapy was provided. In previous reports [27,33] of three patients with rectal cancer who adopted the watch-and-wait strategy, a total of 6–11 doses of immunotherapy were given, and no relapse was observed. For patients with dMMR/MSI-H locally advanced rectal cancer who have a cCR after immunotherapy, treatment for 1 year or less might be sufficient. The value of adjuvant immunotherapy remains unknown. More prospective data will be needed to provide an answer.

In a recent study from Memorial Sloan Kettering Cancer Center [35], over one-fourth of the patients with dMMR rectal cancer experienced disease progression after neoadjuvant chemotherapy. And in a National Cancer Database analysis [36], MSI positive was demonstrated to be an independent predictor for reduced pCR rate in locally advanced rectal cancer treated with chemoradiation followed by surgery. All these studies indicated that dMMR/MSI-H rectal cancer might be more resistant to chemotherapy or chemoradiotherapy in comparison to proficient DNA mismatch repair/microsatellite stable (pMMR/MSS) rectal cancer, and neoadjuvant immunotherapy could be a better choice for dMMR/MSI-H rectal cancer. Thus, we suggest that MMR status, MSI status, or even somatic mutation analyses should be performed upfront in all locally advanced rectal patients for more precise treatment decisions, especially for young patients or patients with a family history of Lynch syndrome-associated tumours. Ideally, patients with dMMR/MSI-H rectal cancer would be referred to clinical trials of neoadjuvant immunotherapy.

The limitations of this study were the small sample size and a short follow-up time period. However, to the best of our knowledge, this study still comprised the largest cohort of patients with locally advanced rectal cancer who have adopted immunotherapy as curative-intent treatment so far and could provide useful indications for future prospective trials. As an innovative approach with the possibility to preserve fertility and sexual and anal function, anti-PD-1-based immunotherapy is a promising treatment option for dMMR/MSI-H locally advanced rectal cancers, which is worthy of further investigation.

In conclusion, our study shows that for patients with dMMR/MSI-H locally advanced rectal cancer who achieved cCR during anti-PD-1 immunotherapy, adopting anti-PD-1 immunotherapy as curative-intent treatment and omitting surgical resection might be an alternative option. Longer follow-up and larger cohorts are warranted to verify this innovative treatment approach.

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Author contributions

Qiao-Xuan Wang: Data curation; Formal analysis; Project administration; Writing – original draft. Bin-Yi Xiao: Data curation; Formal analysis; Project administration; Writing – original draft. Yong Cheng: Data curation; Project administration. Ai-Wen Wu: Data

curation; Project administration. Tao Zhang: Data curation; Project administration. Hui Wang: Data curation; Project administration. Xuan Zhang: Data curation; Project administration. Wei-Xin Huang: Data curation; Project administration. Jing-Hua Tang: Project administration. Wu Jiang: Project administration. Scott R. Steele: Supervision; Writing – review and editing. Smitha Krishnamurthi: Supervision; Writing – review and editing. Yuan Li: Project administration. Jian Cai: Project administration. Ling-Heng Kong: Project administration. Dan-Dan Li: Project administration.Zhi-Zhong Pan: Conceptualisation; Supervision; Writing – review and editing. Xiao-Shi Zhang: Conceptualisation; Supervision; Writing – review and editing. Pei-Rong Ding: Conceptualisation; Funding acquisition; Supervision; Writing – review and editing.

Conflict of interest statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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