Research Square

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Efficacy and Safety Analyses of Immunotherapy versus Conventional Chemotherapy as Adjuvant Therapy for Resectable MSI-H/dMMR Colorectal Cancer

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Abstract

Objective

To evaluate the clinical efficacy and adverse events of immunotherapy in patients with resectable microsatellite instability-high/mismatch repair–deficient (MSI-H/dMMR) colorectal cancer (CRC).

Methods

A total of 106 patients with stage II–III MSI-H/dMMR CRC treated at The Affiliated Hospital of Xuzhou Medical University from May 2018 to August 2024 were enrolled and divided into a chemotherapy group (n = 52) and an immunotherapy group (n = 54). The chemotherapy group received capecitabine monotherapy, mFOLFOX, or CAPEOX according to treatment tolerance, whereas the immunotherapy group received envafolimab, serplulimab, or camrelizumab. Clinical efficacy and adverse events were compared between the two groups.

Results

MSI-H/dMMR CRC was more prevalent in the right colon, and its incidence declined with advancing tumor stage. The 3-year disease-free survival (DFS) rate in the immunotherapy group was 88.9%, which was higher than that in the chemotherapy group (71.2%, $P < 0.05$). Notably, immunotherapy conferred more pronounced benefits in right-sided colon cancer than in left-sided disease. The immunotherapy group showed improved safety relative to the chemotherapy group.

Conclusions

For patients with MSI-H/dMMR CRC after radical resection, adjuvant immunotherapy provides superior efficacy compared with conventional adjuvant chemotherapy and is associated with milder adverse events, supporting its further clinical application.

Trial Registration

MR3226035724, registered on 20260508. Retrospectively registered.

1. Introduction

Colorectal cancer (CRC) is one of the most common malignancies worldwide, with high morbidity and mortality, and the disease burden is particularly severe in China [1]. According to the latest cancer burden data released by China's National Cancer Center (NCC) in February 2024, there were 517,100 new CRC cases and 240,000 deaths in China in 2022. CRC has become the second most prevalent malignancy and the fourth leading cause of cancer-related death in China, imposing a substantial burden on both society and families [2]. A considerable proportion of patients are diagnosed at locally advanced or metastatic stages, posing significant challenges for treatment.

Approximately 5%–15% of CRC patients exhibit the microsatellite instability-high/mismatch repair–deficient (MSI-H/dMMR) molecular subtype. These tumors are characterized by a high tumor mutational burden (TMB) and strong

immunogenicity, rendering them highly sensitive to immune checkpoint inhibitors (ICIs) but poorly responsive to traditional fluoropyrimidine-based chemotherapy [3]. Early studies have shown that patients with MSI-H CRC generally have a better prognosis than those with microsatellite stable (MSS) tumors; however, their recurrence patterns differ, with higher risks of local recurrence and peritoneal metastasis and lower incidences of liver and lung metastases [4]. Current guidelines recommend a “watch-and-wait” strategy for low-risk stage II MSI-H/dMMR CRC patients, without the need for adjuvant therapy. High-risk patients may consider single-agent or dual-agent chemotherapy. For stage III MSI-H/dMMR CRC, oxaliplatin-based FOLFOX or CAPEOX regimens are the standard adjuvant treatments [5]. Notably, oxaliplatin-based adjuvant chemotherapy is associated with toxicities such as sensory neuropathy and gastrointestinal events, which severely impair patients’ quality of life [6, 7]. Many patients develop chemotherapy intolerance and fail to complete adjuvant treatment, leading to rapid disease recurrence and progression.

In recent years, ICIs have achieved revolutionary breakthroughs in the treatment of metastatic MSI-H/dMMR CRC. The KEYNOTE-177 study [8] demonstrated that pembrolizumab, as first-line therapy for metastatic MSI-H/dMMR CRC, achieved a median progression-free survival (mPFS) of 16.5 months, which was significantly superior to the 8.2 months observed in the chemotherapy group, with a 3-year overall survival (OS) rate of 61%. The CheckMate 8HW study [9] further showed that the objective response rate (ORR) of nivolumab combined with ipilimumab (dual immunotherapy) reached 71%, and the mPFS was 54.1 months compared with 5.9 months in the chemotherapy group, shwoign significantly reduced risk of disease progression (HR = 0.21). The application of immunotherapy has gradually extended to the perioperative setting, and multiple studies have confirmed the efficacy of ICIs in the neoadjuvant treatment of MSI-H/dMMR CRC [10]. For example, in the NICHE series studies: the NICHE study [11] first reported the use of nivolumab combined with low-dose ipilimumab as neoadjuvant treatment for dMMR colon cancer, achieving a pathological complete response (pCR) rate of 69%, with 97% of patients attaining a major pathological response (MPR). The subsequent NICHE-2 study [12] further expanded the sample size (n = 111); with the same regimen, the pCR rate was 68%, the MPR rate was 95%, and the 3-year DFS rate was as high as 100%, thereby further solidifying the role of immunotherapy in neoadjuvant treatment. Research on the adjuvant treatment stage has long remained limited until the publication of the ATOMIC study [13], which marked a significant milestone. This study evaluated the efficacy of mFOLFOX6 chemotherapy combined with atezolizumab versus chemotherapy alone in patients with stage III dMMR CRC. The results showed that the 3-year DFS rate in the combination group was 86.4% (76.6% in the control group), reducing the risk of disease recurrence or death by 50% (HR = 0.50). This outcome provided the first evidence confirming the survival benefit of adjuvant immunotherapy combined with chemotherapy. However, evidence regarding the efficacy and safety of immunotherapy monotherapy in the postoperative adjuvant treatment of MSI-H/dMMR CRC remains limited.

Therefore, this study aimed to evaluate the clinical efficacy and safety of adjuvant immunotherapy monotherapy in patients with stage II–III MSI-H/dMMR CRC, so as to provide a novel chemotherapy-free adjuvant treatment strategy for resectable MSI-H/dMMR CRC.

2. Methods

2.1 Patients and Study Design

A total of 106 CRC patients treated at The Affiliated Hospital of Xuzhou Medical University from May 2018 to August 2024 were enrolled. The patients were assigned to two groups based on their treatment regimens, as follows:

chemotherapy (n = 52, receiving capecitabine monotherapy, mFOLFOX, or CAPEOX) and immunotherapy (n = 54) groups.

Inclusion Criteria: (1) Age 18–80 years; (2) Pathologically confirmed CRC after radical resection, with stage II–III disease; stage II patients requiring high-risk factors (such as T4, poor histological differentiation, nerve/vascular invasion, preoperative intestinal obstruction or tumor perforation, positive or unknown surgical margins, insufficient safety margin, or < 12 lymph nodes examined); rectal cancer patients with radiotherapy indications who were allowed to receive adjuvant radiotherapy; (3) MSI-H confirmed by next-generation sequencing (NGS) or polymerase chain reaction, or dMMR confirmed by immunohistochemistry; (4) No prior immunotherapy, chemotherapy, or targeted therapy for CRC; (5) Eastern Cooperative Oncology Group (ECOG) score 0–2, with expected survival ≥ 3 months; (6) Normal bone marrow function, without any significant liver or kidney dysfunction.

The study was registered in the Medical Research Registration Information System of the National Healthcare Security Information Platform of China (identifier: MR-32-26-035724) on 2026-05-08, and was retrospectively registered.

2.2 Treatment methods

1. Chemotherapy group: Capecitabine 1000 mg/m² orally twice daily on Days 1–14, repeated every 3 weeks; or CAPEOX (oxaliplatin 130 mg/m² intravenously on Day 1 + capecitabine 1000 mg/m² orally twice daily on Days 1–14, repeated every 3 weeks); or mFOLFOX6 (oxaliplatin 85 mg/m² intravenously, leucovorin [LV] 400 mg/m² intravenously, 5-fluorouracil [5-FU] 400 mg/m² intravenous bolus, followed by 5-FU 2400 mg/m² intravenous infusion for 46 h, repeated every 2 weeks). Total adjuvant chemotherapy duration was 6 months; stage II patients could opt for a 3-month course based on personal preference. Doses were adjusted according to patient tolerance.
2. Immunotherapy group: Camrelizumab 200 mg intravenously on Day 1; or envafolimab 400 mg subcutaneously on Day 1; or serplulimab 200 mg intravenously on Day 1. Each cycle lasted 21 days, with the treatment duration of 1 year.

Rectal cancer patients with radiotherapy indications could receive local radiotherapy. Observation was terminated in cases of tumor recurrence/progression, intolerable adverse events, patient death, or voluntary withdrawal.

2.3 Outcome Assessments

The endpoints included the 3-year disease-free survival (DFS) rate and safety. DFS was defined as the time from enrollment to disease recurrence (confirmed by computed tomography [CT]/magnetic resonance imaging [MRI] or pathological biopsy) or death from any cause. Baseline assessment was performed within 28 days before enrollment and included chest, abdominal, and pelvic CT (with abdominal/pelvic MRI if necessary) to confirm the absence of tumor recurrence. Follow-up assessments were conducted every 12 weeks using the same imaging modalities for 3 years and every 6 months thereafter. Adverse events were evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE, version 5.0). The follow-up cut-off date was February 19, 2026.

2.4 Statistical analysis

Data were analyzed using Graphpad Prism 10.1.2 software. Categorical data were presented as percentages (%) and analyzed by the chi-square test or Fisher's exact test. Continuous data were expressed as the mean ± standard deviation (SD) or median (interquartile range [IQR]) and analyzed by *t*-test or Mann–Whitney U-test. Survival curves

were plotted using the Kaplan–Meier (KM) method, with the survival differences compared by log-rank test. $P < 0.05$ was considered to indicate statistical significance.

3. Results

3.1 Patients' characteristics

As shown in Table 1, no significant differences were noted in the baseline characteristics between the two groups (all $P > 0.05$), indicating a balanced comparability. In the chemotherapy group, 28 patients were administered capecitabine monotherapy, 9 received the FOLFOX regimen, and 15 received the CAPEOX regimen. Among them, 18 patients completed a 3-month chemotherapy course, and 34 patients finished a 6-month course. Of these patients, 2 with rectal cancer received radiotherapy; they were at Stage III (T3N1M0) and Stage IIB (T4aN0M0), respectively. In the immunotherapy group, 15 patients were treated with camrelizumab, 18 with serplulimab, and 21 with envolimab. No patients received radiotherapy.

Table 1
Comparison of baseline data between the two study groups

Clinical features	Chemotherapy group (n = 52)	Immunotherapy group (n = 54)	Statistic	*P*
Gender, n(%)			χ^2=0.302	0.683
male	33 (63.5%)	37 (68.5%)		
female	19 (36.5%)	17 (31.5%)		
Age (years), n(%)			χ^2=0.188	0.696
<60	32 (61.5%)	31 (57.4%)		
≥60	20 (38.5%)	23 (42.6%)		
Tumor Site, n(%)			χ^2=0.002	1.000
left hemicolon	20 (38.5%)	21 (38.9%)		
right hemicolon	32 (61.5%)	33 (61.1%)		
Pathological Stage, n(%)			χ^2=1.392	0.296
II (high-risk)	33 (63.5%)	40 (74.1%)		
III	19 (36.5%)	14 (25.9%)		
RAS/BRAF gene status, n(%)			χ^2=0.302	0.678
RAS or BRAF mutation	34 (65.4%)	38 (70.4%)		
Wild-type	18 (34.6%)	16 (29.6%)		
ECOG score, n(%)			χ^2=0.522	0.286
0–1	42 (80.8%)	48 (88.9%)		
2	10 19.2%)	6 (11.1%)		
ICIs				
Camrelizumab		15 (27.8%)		
Serplulimab		18 (33.3%)		
Envolimab		21 (38.9%)		

ECOG, Eastern Cooperative Oncology Group; RAS, Rat Sarcoma Viral Oncogene Homolog; BRAF, B-Raf Proto-Oncogene, Serine/Threonine Kinase; ICIs, Immune checkpoint inhibitors

3.2 Effects of Immunotherapy versus Chemotherapy on DFS in Patients with MSI-H/dMMR CRC

This study performed KM survival analysis on the DFS of 106 enrolled patients and presented individual-level follow-up outcomes using a swimmer plot **(**Fig. 1**).** The results analysis of KM curve showed that the 3-year DFS rate of the immunotherapy group was 88.9%, which was higher than that of the chemotherapy group (71.2%), albeit with a

statistically difference (P = 0.037, 0.493 [95% CI: 0.241–1.010]). Further analysis of individual outcomes combined with the swimmer plot revealed that recurrence or progression events in the chemotherapy group mostly occurred in the early follow-up period, with the vast majority of events developing within approximately 36 months, and the proportion of disease-free patients continued to decline in the later period. In contrast, the number of recurrence or progression events in the immunotherapy group was significantly lower, and most patients maintained a recurrence-free survival status during the 60-month long follow-up period, with a markedly higher proportion of censored events. In addition, in the immunotherapy group, different clinical subgroup analysis of DFS was conducted. The DFS of the right-sided colon cancer was found to be better than that of the left-sided colon/rectal cancer (P = 0.008, 0.241 [95% CI:0.077–0.753]); the DFS of the low ECOG score (= 0–1) group was longer than that of the high ECOG score (= 2) group (P = 0.003, 0.182 [95% CI: 0.016–2.117]). However, in clinical subgroups based on gender, age, pathological stage, and RAS/BRAF status, there was no significant difference in DFS (P all >0.05) **(**Fig. 2**).** In the immunotherapy group, we observed that 2 patients with right-sided colon cancer completed the entire course of postoperative minimal residual disease (MRD) monitoring. They were both positive for MRD before receiving immunotherapy and achieved MRD conversion to negative after the treatment **(**Fig. 3**)**.

3.3 Subgroup Analysis of DFS

By tumor location: the 3-year DFS rate of the immunotherapy group was significantly higher than that of the chemotherapy group in right-sided colon cancer (96.9% vs. 75.0%, P = 0.013), albeit no significant difference was detected in left-sided colon/rectal cancer (76.2% vs. 65.0%, P = 0.506) **(**Table 2 **and** Fig. 4**)**. By pathological stage: Among high-risk stage II patients, the 3-year DFS rate was significantly higher in the immunotherapy group (92.5%) than in the chemotherapy group (72.7%; P = 0.030). Stage III patients in the immunotherapy group had a 3-year DFS rate of 78.6%, compared with 68.4% in the chemotherapy group. No significant difference was noted in the DFS between stage III patients in the two groups (P = 0.698) **(**Table 2 **and** Fig. 4**)**.

Table 2
Subgroup analysis of 3-year DFS between the two groups according to tumor location and pathological stage

Subgroup	Chemotherapy Group(n = 52)	Immunotherapy Group (n = 54)	*P*
Overall	37/52 (71.2%)	48/54 (88.9%)	0.029
Tumor Location			
Right-sided colon	24/32 (75.0%)	32/33 (96.9%)	0.013
Left-sided colon/rectum	13/20 (65.0%)	16/21 (76.2%)	0.506
Pathological Stage			
Stage II (high-risk)	24/33 (72.7%)	37/40 (92.5%)	0.030
Stage III	13/19 (68.4%)	11/14 (78.6%)	0.698

3.4 Adverse Events

Chemotherapy group: The most common adverse events were myelosuppression (leukopenia [71.2%]/neutropenia [63.5%]/thrombocytopenia [36.5%]/anemia [32.7%], nausea [84.6%], fatigue [80.8%], anorexia [80.8%], and peripheral sensory neuropathy [34.6%]. More patients developed ≥grade 3 adverse events, which included myelosuppression, fatigue, nausea, peripheral sensory neuropathy, and anorexia. Immunotherapy group: The main adverse events were

immune-related adverse events (irAEs), including hypothyroidism (64.8%), fatigue (25.9%), adrenal insufficiency (14.8%), rash (35.2%), and reactive telangiosis (18.5%). Most adverse events were of grade I–II (97.4%), and only 1 (2.6%) patient developed grade III fatigue, which was well-controlled with levothyroxine supplementation or low-dose hormones. No treatment-related deaths occurred in either group **(**Table 3**)**.

Table 3
Adverse reactions of patients in the two study groups

Adverse reaction	**<Grade 3 adverse reactions**		***P***	**≥Grade 3 adverse reactions**		***P***
	Chemotherapy group (n = 52)	**Immunotherapy group (n = 54)**		**Chemotherapy group (n = 52)**	**Immunotherapy group (n = 54)**	
Leukopenia	37(71.2%)	4(7.4%)	< 0.001	10(19.2%)	0(0.0%)	0.001
Neutropenia	33(63.5%)	3(5.6%)	< 0.001	11(21.2%)	0((0.0%)	< 0.001
Thrombocytopenia	19(36.5%)	6((11.1%))	0.002	6(11.5%)	0(0.0%)	0.012
Anemia	17(32.7%)	4(7.4%))	0.001	3(5.8%)	0(0.0%)	0.115
Fatigue	42(80.8%))	14(25.9%)	< 0.001	4(7.7%)	1(1.9%)	0.202
Nausea	44(84.6%)	2(3.7%)	< 0.001	3(5.8%)	0(0.0%)	0.115
Peripheral sensory neuropathy	18(34.6%)	0(0.0%)	< 0.001	5(9.6%)	0((0.0%)	0.027
Anorexia	42(80.8%)	2(3.7%)	< 0.001	3(5.8%)	0(0.0%)	0.115
Adrenocortical insufficiency	0(0.0%)	8(14.8%))	0.006	0(0.0%)	0((0.0%)	1.000
Diarrhea	14(26.9%)	8(14.8%)	0.124	2(3.8%)	0(0.0%)	0.238
Hypothyroidism	0(0.0%)	35(64.8%)	< 0.001	0(0.0%)	0(0.0%)	1.000
Elevated transaminases	16(30.8%)	14(25.9%)	0.58	0(0.0%)	0(0.0%)	1.000
Reactive telangiosis	0(0.0%)	10(18.5%)	0.001	0(0.0%)	0(0.0%)	1.000
Rash	3(5.8%)	19(35.2%)	< 0.001	0(0.0%)	0(0.0%)	1.000

4. Discussion

CRC imposes a substantial global health burden, and the treatment of the MSI-H/dMMR subtype has emerged as a major focus of oncology research because of its unique molecular characteristics [14, 15]. To our knowledge, our study is the first to explore the role of immune monotherapy in the postoperative adjuvant treatment of MSI-H/dMMR CRC. This research fills a critical gap in the current literature regarding the efficacy of immune

monotherapy as adjuvant treatment for MSI-H/dMMR CRC. Previous studies have mainly focused on neoadjuvant immunotherapy [16–20] or chemoimmunotherapy combinations, such as the ATOMIC trial [13], which established chemotherapy combined with immunotherapy as the new standard for stage III MSI-H/dMMR CRC. Our study aims to address the unmet clinical need for chemotherapy-free adjuvant treatment in patients with resectable stage II–III MSI-H/dMMR CRC by comparing the efficacy and safety of immune monotherapy with conventional chemotherapy.

Our results showed that the 3-year DFS rate in the immunotherapy group reached 88.9%, which was significantly higher than the 71.2% observed in the chemotherapy group ($P < 0.05$). This finding not only extends the success of ICIs in advanced MSI-H/dMMR CRC (e.g., KEYNOTE-177 [8], CheckMate 8HW [9]) but also expands their application to the adjuvant treatment setting. Oxaliplatin-based regimens (FOLFOX/CAPEOX) have long been the standard adjuvant treatment for stage III or high-risk stage II MSI-H/dMMR CRC [5, 21], albeit their efficacy is limited by inherent drug resistance and poor tolerability. In contrast, ICIs exert antitumor effects by reversing immune checkpoint inhibition and inducing durable immune memory by leveraging the high immunogenicity of MSI-H/dMMR tumors [17, 18]. Our data demonstrate that immune monotherapy as adjuvant treatment can effectively reduce the risk of postoperative recurrence in patients with high-risk stage II and stage III MSI-H/dMMR CRC, providing a more effective alternative to chemotherapy. This approach is particularly relevant for patients who are intolerant to chemotherapy (e.g., elderly patients or those with comorbidities) or who refuse chemotherapy. Notably, this is of great significance for Chinese patients: with the continuous rise in CRC incidence in China (517,100 new cases in 2022) [22], the demand for effective and well-tolerated adjuvant treatments is becoming increasingly urgent. Our findings offer an evidence-based treatment option for the 5–15% of CRC patients with MSI-H/dMMR status.

Furthermore, this study corroborates the distinct clinical and molecular characteristics of MSI-H/dMMR CRC. Among the enrolled patients, the proportion of right-sided colon cancer was as high as 61.3%, compared with 38.7% for left-sided colon cancer. Stage II disease accounted for 68.9% of cases, while stage III disease comprised 31.1% (Table 1). These findings confirm that MSI-H/dMMR CRC is more prevalent in the right colon, with a declining frequency as tumor stage advances, which is consistent with previous epidemiological reports [23, 24]. More importantly, we found that immunotherapy resulted in a more significant improvement in DFS among patients with right-sided colon cancer than among those with left-sided colon cancer ($P = 0.008$). In addition, subgroup analysis based on tumor location showed that the 3-year DFS of immunotherapy in patients with right-sided colon cancer was significantly better than that of chemotherapy (96.9% vs 75.0%, $P = 0.013$). In contrast, there was no significant difference in 3-year DFS between the immunotherapy and chemotherapy groups among patients with left-sided colon cancer (76.2% vs 65.0%, $P = 0.506$). This phenomenon may be attributed to inherent biological differences between left- and right-sided colon tumors [9, 25, 26]. Right-sided MSI-H/dMMR tumors typically exhibit a higher TMB, more abundant tumor-infiltrating lymphocytes (TILs), and a proinflammatory tumor microenvironment, which synergistically enhance the antitumor activity of ICIs. In contrast, left-sided colon cancers are more closely associated with chromosomal instability (CIN) and lower immunogenicity, resulting in a relatively reduced response to immunotherapy. This finding highlights the importance of tumor location in enabling clinicians to develop adjuvant treatment strategies based on anatomical site, particularly for guiding treatment decisions in right-sided MSI-H/dMMR CRC, where the efficacy of chemotherapy is often limited. In addition, subgroup analysis stratified by pathological stage revealed that among high-risk stage II patients, the 3-year DFS rate was 92.5% in the immunotherapy group, significantly higher than the 72.7% observed in the chemotherapy group ($P = 0.030$). However, among stage III patients, no statistically significant difference in efficacy was observed between the immunotherapy and chemotherapy groups (78.6% vs 68.4%, $P = 0.698$). These results suggest that ICI monotherapy may provide sufficient therapeutic benefit in stage II patients, whereas chemoimmunotherapy combinations may be

more appropriate for stage III patients, particularly those with ultra-high-risk features (e.g., T4N2 disease). This interpretation aligns well with the findings of the ATOMIC study [13].

MRD monitoring has emerged as a key biomarker for the precise management of postoperative CRC [27]. Its major clinical values include accurate prognostic stratification, guidance related to adjuvant treatment decisions, early detection of recurrence, and dynamic monitoring of treatment efficacy [28]. In the present study, we observed that, in the immunotherapy group, two patients with right-sided colon cancer underwent dynamic MRD surveillance. After the surgery, the MRD of the patients turned positive. After the immunotherapy, the circulating tumor mutation levels in the blood gradually decreased, and finally, the MRD turned negative; these patients remained clinically stable, with no radiological evidence of recurrence at the data cutoff. These findings suggest that adjuvant immunotherapy may effectively eliminate minimal residual tumor cells, thereby achieving molecular complete remission and reducing the risk of postoperative recurrence.

Safety profiles further support the clinical value of adjuvant immunotherapy. The chemotherapy group mainly experienced myelosuppression (leukopenia, neutropenia, and thrombocytopenia), gastrointestinal toxicity (nausea, fatigue, and decreased appetite), and peripheral neuropathy, with a higher proportion of patients developing grade ≥ 3 adverse events. These toxicities are well-documented limitations of oxaliplatin- and fluoropyrimidine-based regimens [6], often leading to dose adjustments, treatment interruptions, or premature discontinuation, factors that substantially impair patients' quality of life and reduce treatment completion rates and long-term prognosis. In contrast, the immunotherapy group primarily exhibited irAEs, such as hypothyroidism, adrenal insufficiency, and rash, most of which were grade I–II. Mechanistically, these irAEs differ from chemotherapy-related toxicities and can generally be managed through targeted interventions: hypothyroidism can be effectively controlled with levothyroxine supplementation, whereas adrenal insufficiency and rash respond well to low-dose glucocorticoids [29]. Compared with chemotherapy, the immunotherapy group demonstrated higher treatment adherence and improved health-related quality of life.

Several limitations of this study should be acknowledged. First, this was a single-center retrospective study with a relatively small sample size, which may introduce selection bias and limit the generalizability of the findings. Large-scale, multicenter, prospective randomized controlled trials are therefore required to validate these results and confirm the role of ICI monotherapy in adjuvant treatment. Second, the maximum follow-up duration was only 3 years; longer-term data (e.g., 5-year OS) are needed to assess the durability of benefits from adjuvant immunotherapy. Third, the number of patients with dynamic MRD monitoring was extremely small (only 2 cases), lacking large-sample data to verify the correlation between MRD conversion and long-term survival. In addition, we did not analyze the influence of potential prognostic biomarkers (e.g., PD-L1 expression, TMB, and TIL density) on immunotherapy efficacy, warranting further investigation to identify optimal candidates for this treatment strategy.

5. Conclusions

This study demonstrates that for patients with resectable stage II–III MSI-H/dMMR CRC, ICI monotherapy provides superior efficacy (higher 3-year DFS rate) and improved safety (milder and manageable irAEs) compared with conventional chemotherapy. The more pronounced benefits observed in right-sided colon cancer further support an anatomical location-based personalized treatment strategy. These findings suggest that adjuvant immune monotherapy may become a promising treatment option for resectable MSI-H/dMMR CRC, particularly for patients seeking chemotherapy-free approaches. For Chinese clinical practice, this study provides evidence to optimize adjuvant treatment strategies for MSI-H/dMMR CRC, addressing the urgent need for effective and well-tolerated therapies in a rapidly growing patient population. Future studies should expand the sample size, conduct

prospective clinical trials to validate these findings, explore predictive biomarkers, and evaluate long-term OS outcomes.

Declarations

Author Contribution Statement

Juanjuan Tang, Di Pan and Jing Zhou: Conceptualization, Data curation, Formal analysis, Writing-original draft. Zhiyuan Yao, Xiaobing Qin, Kai Cao, Haonan Liu, Hongmei Wang, Wenlou Liu: Data curation, Investigation, Validation. Jiukang Sun: Formal analysis, Statistical analysis, Visualization. Zhengxiang Han and Huan Cao: Conceptualization, Funding acquisition, Supervision, Writing-review and editing, Project administration (equal contribution, co-corresponding authors). All authors read and approved the final manuscript.

Conflict of Interest Statement

After using this tool, the authors reviewed and edited the content as needed and took full responsibility for the content of the published article. 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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Ethics Approval and Consent to Participate

This retrospective clinical study was conducted in accordance with the Declaration of Helsinki (WMA), CIOMS International Ethical Guidelines for Biomedical Research Involving Human Subjects, and ICH-GCP guidelines. Ethical approval was obtained from the Medical Ethics Committee of The Affiliated Hospital of Xuzhou Medical University (approval number: XYFY2026-KL294-01). Owing to the retrospective design and anonymized analysis of medical records, the requirement for written informed consent was waived by the ethics committee. This study was registered with the Chinese Medical Research Registration Information System (registration number: MR-32-26-035724).

Data Availability Statement

The datasets generated and/or analysed during the current study are not publicly available due to patient privacy protection but are available from the corresponding author on reasonable request.

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Figures

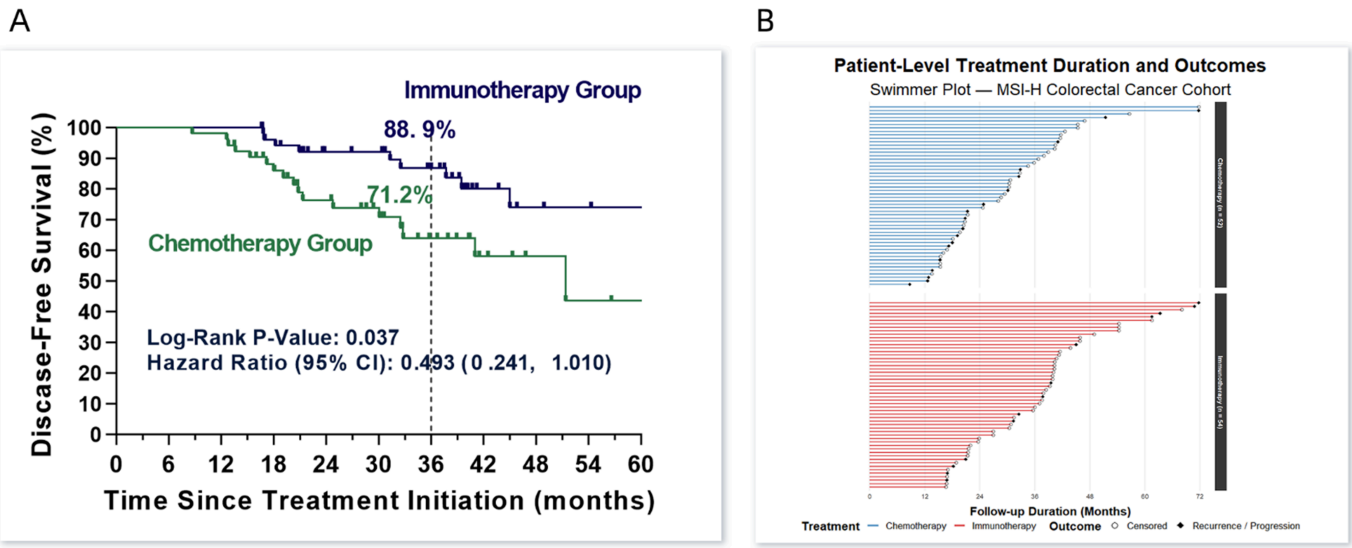


Figure 1

Overall survival curve of DFS and individual follow-up outcomes between the chemotherapy and immunotherapy groups.

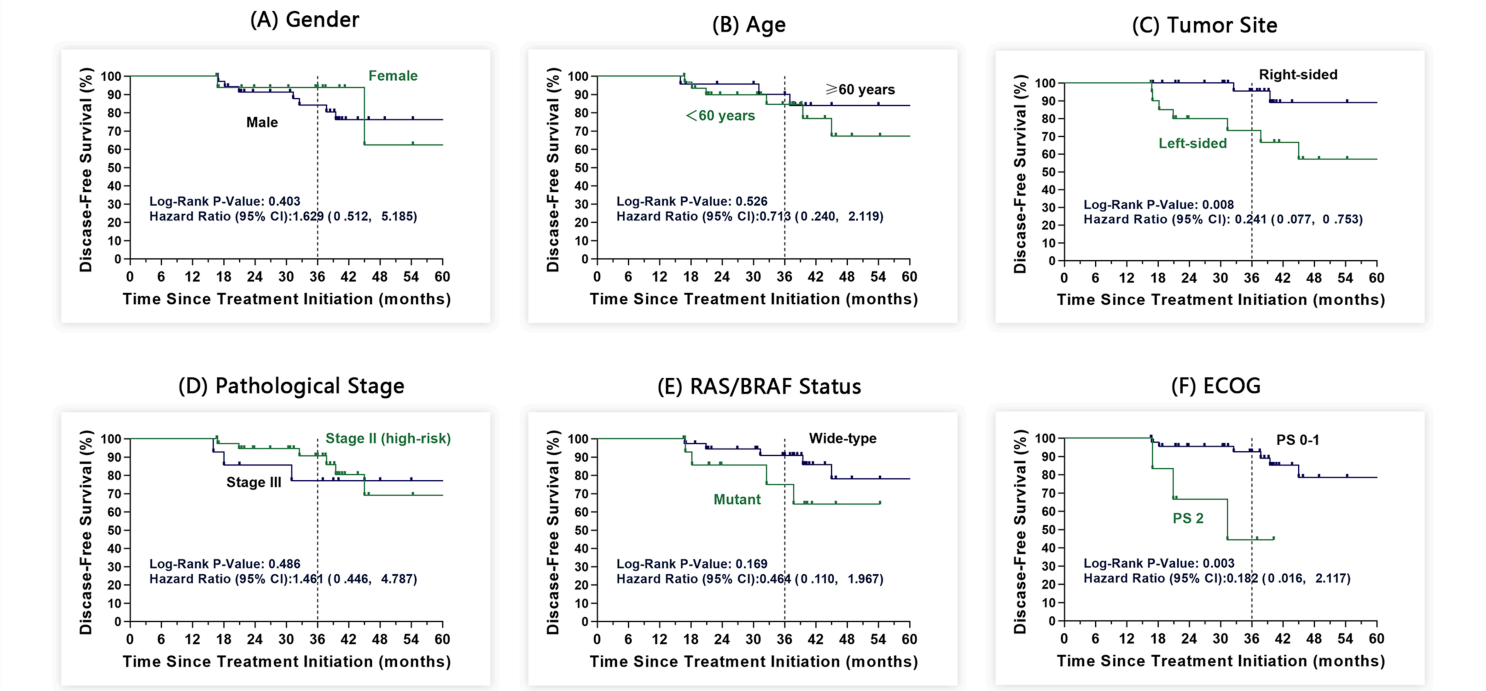


Figure 2

KM survival curves were plotted to analyze the DFS in the immunotherapy group, stratified by different clinical subgroups.

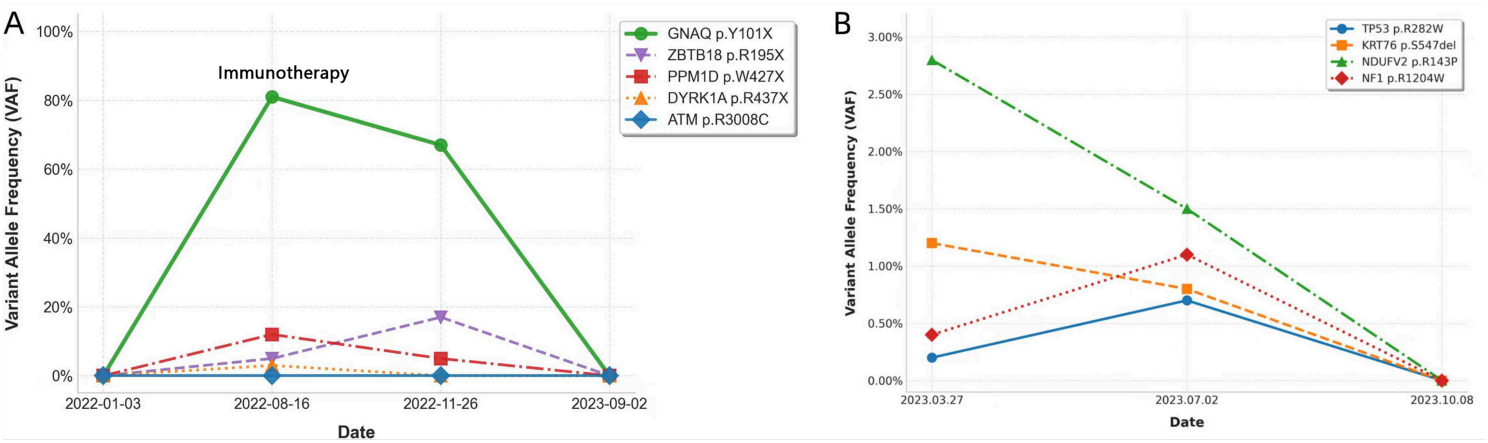


Figure 3

Assessment of minimal residual disease (MRD) status in two patients with right-sided colorectal cancer (CRC) from the immunotherapy group. A. Clinical course of a 29-year-old male patient with postoperative CRC. The first postoperative MRD test performed on January 3, 2022, was negative; therefore, no adjuvant therapy was administered. Repeat MRD testing on August 16, 2022, became positive, after which immunotherapy was initiated. MRD status converted to negative 1 year after the initiation of immunotherapy. B. Clinical course of a 65-year-old female patient with postoperative CRC. The patient showed positive MRD results after surgery, and the MRD status converted to negative after 7 cycles of immunotherapy.

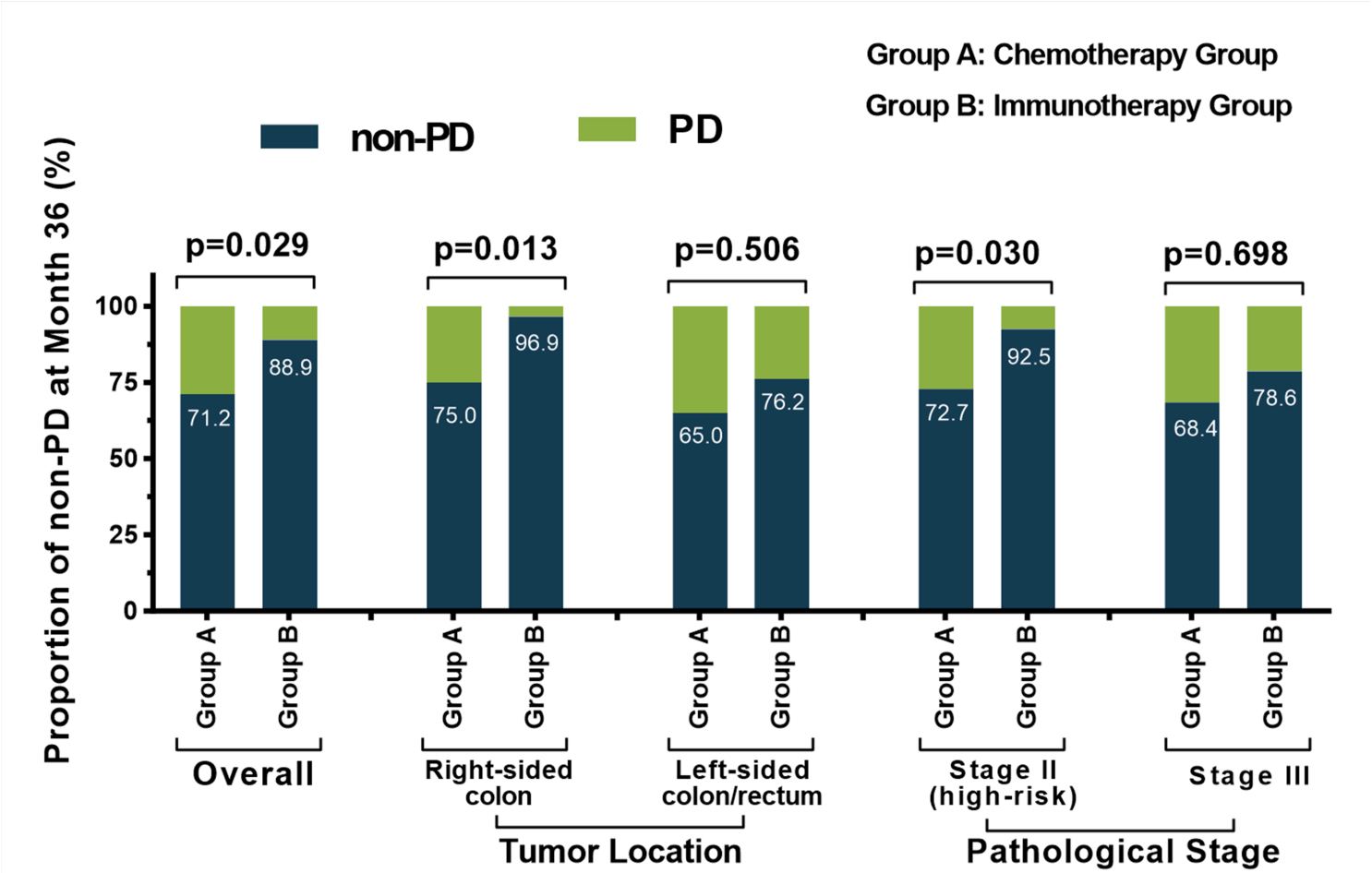


Figure 4

Subgroup analysis of 3-year DFS between the two groups according to the tumor location and pathological stage.