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# Analysis of the Treatment for Advanced Microsatellite Stable Colorectal Cancer in Middle-Aged and Elderly People

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**Abstract:** Microsatellite stabilized (MSS) rectal cancer is a highly prevalent cancer in the middle-aged and elderly population. There exists some expertise in detecting and evaluating the chemotherapy effect in advanced colorectal cancer patients. Multiple studies have combined targeted therapy, chemotherapy, and immunotherapy as a breakthrough. Programmed cell death protein 1 (PD-1) inhibitors have certain therapeutic effects in the treatment of MSS rectal cancer patients. The combination of PD-1 inhibitors and furoquinib can improve the disease control rate (DCR) and progression-free survival (PFS) in colorectal cancer (CRC) patients with advanced MSS, and the adverse reactions are controllable. The combination of erlotinib hydrochloride and Xindilizumab was more effective in treating MSS-type colorectal cancer patients than clinical standard treatment. This study analyzes the various treatment methods for MSS-type CRC in middle-aged and elderly people to provide a reference basis in clinical practice.

**Keywords:** Microsatellite stability (MSS); Colorectal cancer; immunotherapy

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## 1. Introduction

Microsatellite stabilized (MSS) rectal cancer is a common molecular subtype of middle-aged and elderly rectal cancer and has attracted the attention of many researchers [1–3], with a moderate malignancy. MSS rectal cancer is sensitive to chemotherapy, resulting in a better overall prognosis for patients. In 2020, there were approximately 1.9 million new cases of cancer worldwide, with colorectal cancer (CRC) accounting for 10% of the total number of cancer cases, ranking third among all cancers and second in mortality rate. The clinical symptoms of colorectal cancer appear relatively late and about 85% of patients are already in the middle and late stages at the time of disease diagnosis [4,5].

## 2. Assessment and detection of microsatellite stable colorectal cancer

Hu conducted a study involving 200 patients with advanced colorectal cancer and treated them with the FOLFOX (folinic acid, fluorouracil, and oxaliplatin) chemotherapy regimen [6]. All primary tumor tissues from these patients were tested with DNA mismatch repair gene (MMR). The patients were then classified into two groups based on their microsatellite instability analysis results: the MSS group and the microsatellite instability (MSI) group. A retrospective analysis was performed to compare the clinical characteristics and chemotherapy efficacy between these two groups. In a study comparing these two groups of CRC patients, no statistically significant differences in age and gender were found. However, significant differences were observed in tumor location, pathological type, degree of differentiation, and metastasis status. The MSI group demonstrated a substantially lower disease control rate compared to the MSS group. MSI status has been identified as a crucial factor influencing chemotherapy efficacy and prognosis in late-stage CRC, making it a potential predictor for these outcomes. Wang collected primary tumor tissues from 181 patients with late-stage CRC [7]. Immunohistochemical testing was conducted to assess the expression of four proteins: MSH2, MSH6, MLH1, and PMS2 in these tissues. The patients were subsequently divided into MSI and MSS groups, and the differences in chemotherapy sensitivity and prognosis were analyzed. Although the MSI status did not correlate with overall survival time in late-stage CRC patients, it was significantly associated with the disease control rate, indicating its importance in evaluating the effectiveness of chemotherapy. In another study, Wu employed immunohistochemical methods to examine 41 CRC tumors [8]. A pathological slice scanner was utilized to count cells and measure CD68+ and CD163+ expression in atypical hyperplasia (AH) tissues located 5 cm (M5) and 10 cm (M10) adjacent to the tumor. The findings revealed a higher expression of CD68+ and CD163+ in the stromal tissues of colorectal cancer tumors as compared to adjacent non-cancerous tissues. No correlation was observed between their expression in tumors and AH tissues. Notably, CD163+ expression in tumors was associated with mutations in the Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (KRAS) gene.

Cheng performed a retrospective analysis on 154 patients undergoing palliative chemotherapy for metastatic colorectal cancer [9]. The study involved using immunohistochemistry to detect the expression of mismatch repair (MMR) genes: MSH2, MLH1, PMS2, and MSH6 proteins in tumor tissues. The analysis focused on the relationship between MSI and various factors such as clinical features, chemotherapy response, and prognosis. The findings showed that the non-progression survival rate was significantly higher in the MSI-H group (85.71%) compared to the MSS group (57.86%), suggesting a pivotal role of MSI in influencing chemotherapy efficacy and prognosis in mCRC patients. The study underscores the necessity of routine MSI-H testing in this context. Wu collected primary tumor tissues from patients with stage IV intestinal cancer who were treated with either FOLFOX or XELOX (oxaliplatin and capecitabine) as their first-line chemotherapy regimen [10]. Immunohistochemistry was used to detect the expression of MMR genes: hMSH6, hPMS2, hMLH1, and hMSH2 proteins in these tissues. The study aimed to evaluate the relationship between the microsatellite status and the patient's clinical characteristics, prognosis, and chemotherapy response. Among the 79 patients who underwent palliative resection of the primary lesion, those with MSI exhibited a significantly longer median progression-free survival (PFS) compared to those with MSS. In patients with stage IV colorectal cancer who underwent palliative resection of the primary tumor, a positive correlation was observed between MSI status and both the DCR and PFS from chemotherapy. This finding emphasizes the importance of conducting microsatellite testing in mCRC patients.

## 3. Exploring treatment approaches for MSS CRC

### 3.1. Evaluating the efficacy of PD-1 inhibitors in treating MSS CRC

Zhu reported that multiple clinical trials have shown certain effectiveness in immunotherapy combined with targeted chemotherapy for KRAS mutated microsatellite stable mCRC [11]. Zhou found that the addition of PD-1 inhibitors to the treatment process of MSS-type CRC patients improved the immune status and levels of angiogenic factors in the body, which was beneficial for improving patient efficacy [12]. The use of PD-1 inhibitors was also safe. Rosixi found that the combination of Regorafenib and PD-1 inhibitors as a third line or higher treatment for advanced MSS type CRC may be more effective in PFS [13]. Li found that the combination of PD-1 inhibitors and furoquinib can improve the DCR and PFS of CRC patients with advanced MSS, with controllable adverse reactions [14]. Jia retrospectively analyzed the clinical data of 41 patients with MSS- or pMMR-type mCRC [15]. Patients who received third-line or above treatment with fruqintinib monotherapy or a combination of fruqintinib and PD-1 inhibitors were found to exhibit better clinical effects on MSS- or pMMR-type mCRC, and the combination therapy did not significantly increase toxicity.

### 3.2. The efficacy of alternative combination therapies in treating MSS CRC

Yu conducted a retrospective analysis of clinical data from 40 patients with inoperable MSS CRC [16]. The patients were evenly split into a control group and an observation group, each comprising 20 patients, based on their respective treatment protocols. The control group received XELOX chemotherapy combined with apatinib, whereas the observation group was treated with XELOX combined with apatinib and carrelizumab over a 6-week continuous period. The study measured the disease control rate, progression-free survival, objective response rate, overall survival, and adverse events of both groups. The results demonstrated that the combination of XELOX chemotherapy with apatinib and carrelizumab in treating inoperable metastatic MSS CRC was as effective as the combination of XELOX with apatinib alone. However, it showed superior results in terms of tumor objective response rate (ORR), PFS, and overall survival (OS), while maintaining a manageable safety profile. Sun focused on hospitalized CRC patients who underwent integrated treatment combining traditional Chinese and Western medicine, particularly those who had experienced first to third-line treatments in advanced stages [17]. The study collected information including disease specifics, treatment protocols, the start and failure times of each treatment stage, and traditional Chinese medicine (TCM) diagnoses from medical records. Descriptive statistics were used for the analysis and the Kaplan-Meier analysis was used to assess the third-line PFS of patients with various disease specifics and treatment regimens. Further, multivariate Cox regression analysis was used to identify key influencing factors. The findings suggested that the integration of traditional Chinese and Western medicine in the third-line treatment of advanced CRC might enhance patient survival, with benefits linked to TCM diagnostic types and the status of genetic testing. Ma conducted a retrospective analysis of the clinical data of 36 patients with advanced CRC [18]. These patients were divided into two groups based on their microsatellite status: MSI-H and MSS. All patients underwent treatment with carrelizumab combined with apatinib. The study compared the two groups in terms of mean PFS, DCR, ORR, and adverse reactions. Results showed that the combination of carrelizumab and apatinib was effective in advanced CRC patients who had not responded to second-line or higher treatments, with MSI-H CRC patients experiencing more significant benefits than MSS patients. Gi investigated a complex case of a patient with multiple metastatic rectal cancer (MSS with NRAS gene mutation) who also suffered from acute intestinal obstruction [19]. After the failure of second-line chemotherapy, the patient was treated with Regorafenib as a targeted therapy. Despite the progression of some lesions, the disease was controlled following the introduction of combined PD-1 inhibitor treatment. Notably, from the onset of third-line treatment, the patient primarily received home-based care. This approach significantly improved the patient's treatment compliance and safety, offering valuable insights into the clinical

management of patients with similar conditions.

In Zhu's study, 76 patients with late-stage colon cancer were randomly divided into two groups of 38 each: a control group treated with fruquintinib, and an observation group receiving a combination of sintilimab and fruquintinib [20]. After 6 months of treatment, it was observed that the efficacy of fruquintinib monotherapy was less effective compared to the combined treatment with sintilimab in MSS late-stage colon cancer. The combination treatment showed a minor impact on immune function and was well-tolerated by patients, indicating its potential application value in clinical settings. Ji focused on 30 patients with MSS CRC, dividing them into a control group, which received oral anlotinib hydrochloride capsules, and an observation group, treated with intravenous sintilimab injections in addition to anlotinib [21]. After 6 months, the clinical efficacy was evaluated using parameters such as ORR, DCR, complete tumor response (CR), partial tumor response (PR), stable disease (SD), and progressive disease (PD). Adverse drug reactions were assessed using the Common Adverse Reaction Event Criteria 4.2, and the patient's quality of life was evaluated using a cancer patient-specific scoring system. The study found that the combination of anlotinib hydrochloride and sintilimab improved the clinical efficacy and quality of life in MSS CRC patients with manageable adverse reactions.

## 4. Discussion

CRC is one of the common malignant tumors in middle-aged and elderly people. Previously, only approved drugs could be considered for the third-line treatment of advanced CRC. Targeted therapy research mainly focuses on molecular targets that inhibit tumor growth and proliferation. Among them, anti-vascular endothelial growth factor receptor drugs and anti-epidermal growth factor receptor drugs were the basic choices for the third-line treatment of advanced CRC. The MSI status is closely related to the chemotherapy efficacy and prognosis of advanced CRC and can be used as an indicator for predicting chemotherapy efficacy and prognosis in advanced CRC and routine MSI-H testing is necessary. CD68+ and CD163+ are highly expressed in the stroma of colorectal cancer tumors, and the expression of CD163+ in tumors is correlated with KRAS gene mutations.

## 5. Conclusion

The addition of PD-1 inhibitors to the treatment process of MSS CRC improved the immune status and angiogenic factor levels of the body, which was beneficial for enhancing the efficacy of patient treatment. The combination of Regorafenib and PD-1 inhibitors as a third line or higher treatment for advanced MSS-type CRC may be more effective in PFS. The combination of PD-1 inhibitors and furoquinib can improve DCR and PFS in CRC patients with advanced MSS, and the adverse reactions are controllable. The combination of XELOX chemotherapy with apatinib and calerizumab had a significant effect on non-surgical metastatic MSS-type CRC patients. The combination of carolizumab and apatinib regimen has potential efficacy and controllable adverse reactions in advanced CRC patients who have failed second-line or above treatment. The combination of xindilizumab and furoquinib had a relatively small impact on the immune function of patients and has potential application value. The clinical efficacy of the combination of enrotinib hydrochloride and xindilizumab in the treatment of MSS-type CRC patients after standard treatment failure was good, and the adverse reactions were controllable.

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## References

[1] Led T, Uram JN, Wang H, et al., 2015, PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. N Engl J Med, 372(26): 2509–2520.

[2] Dudley JC, Lin MT, Le DT, et al., 2016, Microsatellite Instability as A Biomarker for PD-1 Blockade. Clin Cancer Res, 22(4): 813–820.

[3] Gou H, Fang L, Zhong X, 2023, The Relationship Between KRAS, NRAS, and BRAF Gene Mutations and Liver Metastasis in Colorectal Cancer. Journal of Kunming Medical University, 44(1): 19–24.

[4] Sung H, Ferlay J, Siegel RL, et al., 2021, Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin, 71(3): 209–249.

[5] Xia C, Dong X, Li H, et al., 2022, Cancer Statistics in China and the United States, 2022: Profiles, Trends, and Determinants. Chin Med J (Engl), 135(5): 584–590.

[6] Hu W, Ying X, Wang J, 2020, The Significance Analysis of MSI in Evaluating The Chemotherapy Efficacy of Advanced Colorectal Cancer. Jiangxi Pharmaceutical, 55(5): 539–541.

[7] Wang L, Mao H, Tong J, et al., 2019, The Impact of Mismatch Repair/Microsatellite Instability on Chemotherapy Sensitivity and Prognosis of Advanced Colorectal Cancer. Chinese Medical Journal, 16(8): 108–111.

[8] Wu Y, Bai X, Wang Z, 2019, Analysis and Study of Tumor-Associated Macrophages and Gene Phenotypes in Colorectal Cancer. Modern Chinese Medicine, 57(17): 36–40.

[9] Cheng C, Jie Z, Wang J, et al., 2021, The Correlation Between Microsatellite Instability and The Efficacy and Prognosis of Palliative Chemotherapy in Patients with Advanced Colorectal Cancer. Journal of Henan University (Medical Edition), 40(4): 269–272.

[10] Wu Y, Zhang C, Liang F, et al., 2015, The Impact of Microsatellite Instability on Chemotherapy Response and Prognosis in Patients with Stage IV Colorectal Cancer. Chinese Journal of Cancer, 25(7): 522–527.

[11] Zhu Z, Ji F, 2023, Treatment of Late-Stage Colorectal Cancer with KRAS Mutant Microsatellite Stable Type. Clinical Medical Progress, 13(5): 8128–8134.

[12] Zhou L, Ge X, Xu R, et al., 2022, Analysis of Therapeutic Effects of PD-1 Inhibitors on Microsatellite Stable Colorectal Cancer Patients. Journal of Digestive Oncology (Electronic Edition), 14(2): 153–157.

[13] Luo X, Chen J, Shi W, et al., 2022, The Efficacy and Safety of Regorafenib Combined With PD-1 Inhibitors in Advanced Microsatellite Stable Colorectal Cancer. Chinese Journal of Cancer Prevention and Treatment, 14(5): 521–527.

[14] Li R, Xing X, Liu Y, et al., 2023, Clinical Efficacy Observation of Programmed Cell Death Protein-1 Inhibitor Combined with Furquinib in The Treatment of Advanced Colorectal Cancer. Journal of Digestive Oncology (Electronic Edition), 15(2): 126–131.

[15] Jia Z, Xu J, Da J, et al., 2023, Clinical Efficacy and Safety Observation of The Combination of Furoquinib and Programmed Death Receptor-1 Inhibitors in The Treatment of Microsatellite Stable or Mismatched Repair Normal Metastatic Colorectal Cancer. Journal of Clinical Military Medicine, 51(9): 945–948.

[16] Yu W, Wang X, Zhao L, et al., 2023, Clinical Observation of Chemotherapy Combined with Karelizumab for Unsurgical Microsatellite Stable Colorectal Cancer. China Pharmacy, 34(10): 1242–1246.

[17] Sun L, Yan Y, Xu Y, et al., 2022, Current Status and Efficacy Analysis of Combined Traditional Chinese and Western Medicine Treatment for Advanced Colorectal Cancer Based on A Single Center Retrospective Real-World Study. Journal of Traditional Chinese Oncology, 4(1): 1–23.

[18] Ma Q, Yang Y, Li X, et al., 2022, The Therapeutic Effect of Combination Therapy with Carolizumab and Apatinib on Advanced Colorectal Cancer with Different Microsatellite Status. Henan Medical Research, 31(7): 1194–1198.

[19] Gi L, Yang W, 2022, One Case of Advanced Rectal Cancer Treated with Regorafenib. Electronic Journal of Liver Cancer, 9(2): 49–52.

[20] Zhu L, Liu Q, Xiao M, et al., 2023, Clinical Efficacy and Impact on Immune Function of Patients with Microsatellite Stable Advanced Colon Cancer Treated with Xindilimab Combined with Furoquantinib. Chinese Journal of Immunology, 39(9): 1922–1927.

[21] Ji Y, Yang X, Meng X, et al., 2021, Observation of The Therapeutic Effect of Combination Therapy of Amlotinib Hydrochloride and Xindilimab on Microsatellite Stable Colorectal Cancer after Standard Treatment Failure. Journal of Xinxiang Medical College, 38(8): 719–724.