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Original Paper

Discussion on the Benefits of Postoperative Adjuvant Therapy for Stage II MSI-H Colorectal Cancer

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Abstract

Background: *There is no consensus among mainstream guidelines worldwide regarding adjuvant therapy for colorectal cancer patients with stage II microsatellite instability (MSI-H)/mismatch repair deficiency (dMMR) after surgery. This study aims to further explore the benefits of postoperative adjuvant chemotherapy for this group of patients through a retrospective study and assist in guiding clinical decision-making for this group of patients.*

Methods: *Finally a total of 140 patients with colorectal cancer who underwent radical surgery at the First Affiliated Hospital of Chongqing Medical University from January 2018 to December 2022, with postoperative pathological stage II (T3-T4N0M0) and molecular test results of MSI-H were retrospectively collected. Disease-free survival (DFS) and overall survival (OS) were recorded through outpatient and telephone follow-ups. The Kaplan-Meier method was used to calculate DFS and OS, and the logrank method was used for significance testing; Univariate and the multivariate Cox proportional hazards model were used to analyze prognostic factors.*

Results: *There were differences in age groups between the chemotherapy group and the non-chemotherapy group (adjuvant therapy acceptance rate in patients under 65 years old: 68.2% vs 25.0%, P< 0.01), but no significant differences in the remaining clinical data and pathological features (P > 0.05). Median survival was 49.2 months (3.3-89.1 months), and 3-year DFS and OS were 90.0% and 93.6%, respectively; The DFS (p=0.011) and OS (p=0.022) in the postoperative chemotherapy group were significantly prolonged. Univariate Cox regression analysis showed that the high-risk features including age > 65 years, no adjuvant chemotherapy, lymph node dissection < 12 were associated with poorer prognostic.*

Conclusion: *Postoperative adjuvant chemotherapy based on oxaliplatin in patients with stage II MSI-H*

colorectal cancer prolongs DFS and OS.

Keywords

colorectal cancer, microsatellite instability, stage II, adjuvant therapy

1. Introduction

Colorectal cancer (CRC) represents one of the most significant global health challenges. It ranks as the third most commonly diagnosed cancer and the second leading cause of cancer-related mortality (Bray, Laversanne, Sung, et al., 2024). In China, the total incidence of colorectal cancer has risen to the second highest among all malignant tumors, surpassed only by lung cancer, while its mortality rate ranks fourth nationwide (Li Lin, Li Xu, Tan Kun, et al., 2025). There were 517,100 new cases of colorectal cancer and 240,000 associated deaths in China in 2022, corresponding to an incidence-to-mortality ratio of 2.35:1 (Xu Ruifeng, Wang Hongrui, Che Yun, et al., 2025). Among the newly diagnosed colorectal cancer patients, according to the China Colorectal Cancer Surgical Case Registry Database, the proportions of patients with stage I, II, III, and IV colorectal cancer after surgery were 17.5%, 40.6%, 34.8%, and 7.1% respectively (Yao Hongwei, Li Xinxiang, Cui Long, et al., 2023). According to the Chinese Society of Clinical Oncology (CSCO), stage II colorectal cancer is defined as T3–T4N0M0. This classification indicates a tumor at stage T3, where the tumor penetrates the muscularis propria into the pericolorectal tissues, or stage T4, where the tumor penetrates the visceral peritoneum (including cases with macroscopic perforation, continuous tumor growth through an inflammatory region to the visceral peritoneal surface, or direct invasion and adherence to adjacent organs or structures). Additionally, there must be no regional lymph node metastasis, no tumor deposits, and no distant metastasis. Regarding the indication for adjuvant therapy following stage II colorectal cancer surgery, current international guidelines highlight the critical role of microsatellite status and mismatch repair protein deficiency in prognostic stratification for this patient population (Wang, Chen, Zhang, et al., 2025; Hofheinz, Fokas, Benhaim, et al., 2025; Vogel, Felder, Bhama, et al., 2022).

Microsatellites (Microsatellites) are short tandem repeats that are widely present in the human genome. Its stability depends on a fully functional Mismatch Repair (MMR) system (key proteins include MLH1, MSH2, MSH6, and PMS2). When deficient Mismatch Repair (dMMR) is impaired, it results in the accumulation of DNA replication errors, which manifest as alterations in microsatellite length, known as Microsatellite Instability (MSI). MSI serves as a key molecular marker for colorectal cancer and is particularly indicative of Hereditary Nonpolyposis Colorectal Cancer (HNPCC), playing a significant diagnostic role in the identification of Lynch Syndrome (Boland, & Goel, 2010; Mei, Mi, Qian, et al., 2022). MSI-H/dMMR occurs in approximately 15–20% of colorectal cancer patients. Relevant studies indicate that a higher proportion of patients with right-sided colon cancer at TNM stage I–II exhibit MSI-H/dMMR, while dMMR is also frequently observed in patients with locally advanced (T4b) tumors without distant metastasis (Miyaki, Konishi, Tanaka, et al., 1997; Zheng, Huang, Nie, et al., 2018). This indicates that the T stage of this tumor type tends to be closer to T3 or

even T4, and the proportion of patients with lymph node metastasis or distant metastasis is relatively low, suggesting that dMMR/MSI-H status is associated with a favorable prognosis for this tumor category. According to the CSCO guidelines, patients with stage T3N0M0 with dMMR should be classified into the low-risk group, irrespective of the presence of high-risk factors, and only postoperative observation and follow-up are recommended. For T4N0M0 cases, the indication for adjuvant combination chemotherapy is not differentiated based on microsatellite status (Wang, Chen, Zhang, et al., 2025). According to the 2024 National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines, for patients with T4b MSI-H/dMMR tumors, postoperative adjuvant therapy options include a 3-month course of CAPEOX, 3 to 6 months of FOLFOX, or 6 months of 5-FU or capecitabine. Conversely, patients with stage II dMMR non-MSI-H tumors do not require adjuvant therapy post-surgery (Chen Zhiliang, Li Tianhao, Tian Hongkun, et al., 2025); The 2020 ESMO guidelines clearly state that for tumor patients with pT4, oxaliplatin-based adjuvant therapy should be considered regardless of MSI status (Hofheinz, Fokas, Benhaim, et al., 2025). In view of the slight contradictions among the guidelines, this study aims to further explore whether postoperative adjuvant therapy can benefit patients with stage II MSI-H colorectal cancer and assist in guiding clinical decisions for such patients.

2. Patients Selection

Clinical data of 202 patients who underwent radical colorectal cancer surgery at the First Affiliated Hospital of Chongqing Medical University between January 2018 and December 2022 and whose postoperative DNA sequencing results indicated microsatellite instability-high (MSI-H) from the hospital's Molecular Testing Center were retrospectively collected. Among these, the medical records of 140 patients with pathological stage II disease after surgery were included in this study.

2.1 Eligibility Criteria

2.2.1 Inclusion criteria: Patients who have (1)undergone radical resection of colorectal cancer at the First Affiliated Hospital of Chongqing Medical University;(2) Postoperative TNM was stage II (T3-T4N0M0); (3) Patients with MSI-H as the result of first-generation or second-generation sequencing of colorectal cancer after surgery; (4) Hospitalization information and clinical data are relatively complete were chosen.

2.2.2 Exclusion criteria: (1) Patients for whom accurate histopathological reports cannot be obtained; (2) Absence of important clinical data such as surgical records, basic information, etc. (3) Patients who received immunotherapy directly without adjuvant chemotherapy before or after surgery;

2.2 Collection and Follow-up of Clinical Data

All eligible patient data were collected based on the predefined inclusion and exclusion criteria. A clinical database was established, and all case information was compiled using an Excel spreadsheet. The following variables were extracted: general information such as gender and age; TNM staging determined from preoperative CT/MRI in combination with postoperative pathological findings;

preoperative CEA levels; and postoperative pathological details including the number of dissected lymph nodes, lymphovascular invasion (LVI), perineural invasion (PNI), pathological type, tumor size, and tumor location. Additionally, molecular testing results for colorectal cancer, including microsatellite instability (MSI) status and BRAF mutation status, were incorporated. The primary endpoints were disease-free survival (DFS) and overall survival (OS) in patients who experienced disease progression events such as recurrence, metastasis, or death. These survival outcomes were calculated on a monthly basis. Follow-up was performed via outpatient reviews and telephone interviews.

2.3 Data Analysis Methods

All data were recorded in Excel and statistically analyzed using SPSS 27.0 and GraphPad Prism 10. Continuous variables following a normal distribution were presented as means and compared using the t-test. Categorical data were compared between the two groups with the Pearson chi-square test. The Kaplan–Meier method was employed to assess the impact of postoperative adjuvant chemotherapy on disease-free survival (DFS) and overall survival (OS) in stage II MSI-H patients, with the log-rank test used to evaluate significance. The Cox proportional hazards model was applied to estimate hazard ratios (HRs) and their corresponding 95% confidence intervals (CIs) for relevant factors. Multivariate analysis was further performed on factors influencing prognosis, with a statistical significance threshold set at $P < 0.05$.

2.4 Results

Our hospital's HIS system identified a total of 202 colorectal cancer patients with complete DNA sequencing results. Among them, 140 patients successfully underwent radical resection for colorectal cancer and were pathologically confirmed as stage II according to the TNM staging system. A total of 140 patients with complete clinical records and follow-up data were included in the analysis. The mean age of the patients was 60 years (range 22 to 90). The study population consisted of 83 males (59.3%) and 57 females (40.7%). Based on postoperative pathological staging, the majority of the cases (92 patients, 65.7%) were classified as T4.; The cohort exhibited the following features: only 8.14% of cases had fewer than 12 lymph nodes dissected. Poorly differentiated pathological types, such as signet ring cell carcinoma and mucinous carcinoma, were predominant (64.29%). Most tumors were located in the right colon (59.2%) and were notably large; 58.87% of the resected specimens had a diameter of ≥5 cm. Conversely, the percentage of patients with a preoperative CEA level ≥5 ng/mL was relatively low (33.57%). More than half of the patients received postoperative adjuvant therapy, accounting for 56.43% (Table 1).

Table 1. Overall Characteristics

Basic Information	Number of cases (percentage)
Gender	
female	57 (40.7)
male	83 (59.3)
Age	60.4 (22-90)
≥65	52 (37.1)
< 65	88 (62.9)
T staging	
3	48 (34.3)
4	92 (65.7)
Lymph nodes	
< 12	10 (8.1)
≥12	130 (92.3)
Nerve invasion (PNI)	
Yes	28 (20.0)
No	112 (80.0)
Vascular invasion (VNI)	
Yes	17 (12.1)
No	123 (87.9)
Tumor location	
Right colon	83 (59.3)
Left colon	57 (40.7)
Pathological types	
Well-differentiated adenocarcinoma	50 (35.7)
Poorly differentiated adenocarcinoma	90 (64.3)
Tumor size	
≥5cm	82 (58.6)
< 5cm	58 (41.4)
Adjuvant chemotherapy	
Yes	73 (52.1)
No	67 (47.9)
CEA	
≥5ng/ml	47 (33.6)
< 5ng/ml	93 (66.4）
BRAF positive	

Yes	20 (14.3)
No	120 (85.7)

Analysis of baseline characteristics indicated that the patients in the chemotherapy and non-chemotherapy groups were poorly matched in terms of age, with a statistically significant difference between the two cohorts. Patients under 65 years of age were significantly more likely to receive adjuvant therapy postoperatively than older patients (68.2% vs. 25.0%, $P < 0.01$). No significant differences were observed between the two groups in terms of gender, T stage, number of lymph nodes examined, perineural invasion, tumor size, preoperative CEA level, or BRAF mutation status ($P > 0.05$) (Table 2). The median survival time was 49.2 months (range, 3.3–89.1 months). The estimated three-year disease-free survival (DFS) and overall survival (OS) rates were 90.0% and 93.6%, respectively. During the follow-up period, disease progression occurred in 15 patients (10.7%), and 12 patients (8.6%) died. Among patients with pathological stage T4, 10 experienced recurrence or metastasis, compared with 5 in the T3 stage group. The mean age at recurrence or metastasis was 78.13 years. Only two of these patients had received postoperative adjuvant oxaliplatin-based chemotherapy (Table 2). Patients who received adjuvant chemotherapy had significantly prolonged DFS ($P = 0.011$) and OS ($P = 0.022$) compared to those who did not (Figure 1).

Univariate Cox regression analysis identified several factors associated with poorer disease-free survival (DFS), including age >65 years, no adjuvant chemotherapy, dissection of <12 lymph nodes, and BRAF mutation; similar associations were observed for overall survival (OS). Multivariate analysis incorporating these factors demonstrated that age >65 years remained an independent risk factor for worse DFS (HR=18.509, 95% CI: 2.251–152.206, P=0.007) (Table 3).

Table 2. Characteristics of Clinicopathological Factors

Characteristic	Levels	Non-ACT (67)	ACT (73)	P value
Age				< 0.01
	< 65	28 (41.8)	60 (82.2)	
	≥65	39 (58.2)	13 (17.8)	
Sex				0.104
	Male	35 (52.2)	48 (65.8)	
	female	32 (47.8)	25 (34.2)	
Size				0.669
	≥5cm	38 (56.7)	44 (60.3)	
	< 5cm	29 (43.3)	29 (39.7)	
T stage				0.470
	3	25 (37.30)	23 (31.50)	

	4	42 (62.70)	50 (68.50)	
LN				0.888
	< 12	5 (7.5)	5 (6.8)	
	≥12	62 (92.5)	68 (93.2)	
PNI				0.554
	Yes	12 (17.9)	16 (21.9)	
	No	55 (82.1)	57 (78.1)	
VNI				0.032
	Yes	4 (6.0)	13 (17.8)	
	No	63 (94.0)	60 (82.2)	
CEA≥5ng/mL				0.860
	Yes	22 (32.8)	25 (34.2)	
	No	45 (67.2)	48 (65.8)	
BRAF				0.097
	Yes	13 (19.4)	7 (9.6)	
	No	54 (80.6)	66 (90.4)	

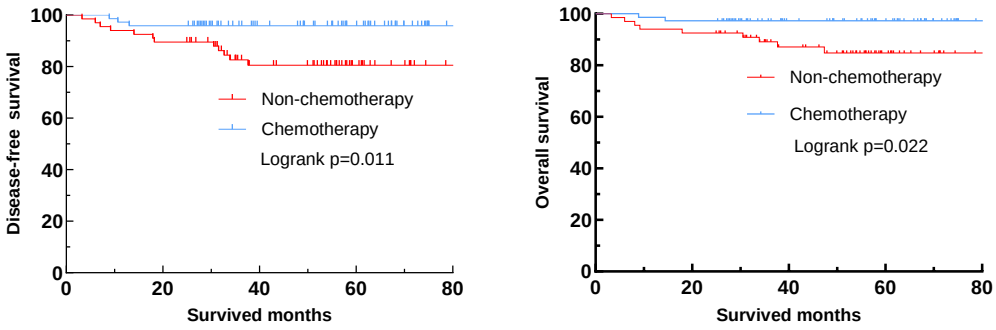

Figure 1. Kaplan-Miere Curves Analysis of the Non-chemotherapy Group and the Chemotherapy Group

Table 3. Cox Univariate and Multivariate Analyses of Phase II DFS

	Univariate DFS		P value	Multivariate DFS		P value
	HR	95%CI		HR	95%CI	
Age≥65	27.667	(3.635 210.539)	< 0.01	18.509	(2.251 152.206)	0.007
Male Gender	0.237	(0.075 0.745)	0.014			
Tumor Size	0.825	(0.299 2.275)	0.710			
T stage	1.123	(0.384 3.288)	0.832			
Location	1.004	(0.357 2.822)	0.944			
ACT	0.224	(0.063 0.793)	0.020	0.547	(0.141 2.118)	0.382

< 12 LNS	4.026 (1.132 14.323)	0.031	3.178 (0.855 11.812)	0.084
PIN	1.289 (0.357 4.649)	0.699		
VIN	0.041 (0.000 72.157)	0.403		
BRAF	3.025 (1.034 8.854)	0.043	1.597 (0.533 4.785)	0.403
CEA≥5ng/mL	0.985 (0.336 2.881)	0.977		

3. Discussion

A consensus has been reached that postoperative adjuvant chemotherapy provides a clear survival benefit for stage II colorectal cancer patients exhibiting high-risk features. These high-risk factors include T4-stage tumors (T4a/T4b), poorly differentiated or undifferentiated histology, examination of fewer than 12 lymph nodes, lymphovascular invasion (LVI), perineural invasion (PNI), high-grade tumor budding, intestinal obstruction, perforation, and positive or uncertain surgical margins. For patients with stage II tumors above, three months of adjuvant therapy with oxaliplatin combined with fluorouracil should be considered after surgery (Baxter, Kennedy, Bergsland, et al., 2022). The MOSAIC trial and a subsequent multicenter study by Silvia et al. demonstrated that patients with stage II colorectal cancer exhibiting mismatch repair deficiency (dMMR) derived no significant benefit from fluorouracil-based monotherapy (Sargent, Marsoni, Monges, et al., 2010; Andre, Boni, Mounedji-Boudia, et al., 2004); A meta-analysis demonstrated that the addition of oxaliplatin to fluoropyrimidine-based adjuvant chemotherapy significantly improved overall survival (OS) in patients with stage III MSI-H/dMMR colorectal cancer. These findings suggest that MSI-H/dMMR status should be considered a significant predictor of benefit from adjuvant chemotherapy in lymph node-positive colorectal cancer patients who have undergone radical resection, particularly those with high-risk features such as pT4 stage and/or pN2 disease (Tomasello, Ghidini, Galassi, et al., 2022). Another large, multicenter retrospective study of AGEO also affirmed the efficacy of oxaliplatin combined with fluorouracil in postoperative adjuvant therapy for patients with stage III dMMR colorectal cancer (Tougeron, Mouillet, Trouilloud, et al., 2016). The role of adjuvant chemotherapy in stage II, high-risk dMMR/MSI-H colorectal cancer remains controversial. However, our findings indicate that for this patient group, particularly those with T4 disease, postoperative adjuvant therapy was associated with prolonged 3-year disease-free survival (DFS) and overall survival (OS). A key confounding factor was age, as patients aged ≥65 years demonstrated lower compliance and acceptance of adjuvant chemotherapy compared to younger patients (<65 years). In this study, 68.9% (60/87) of patients under 65 completed at least 3 months of oxaliplatin-based adjuvant therapy. Furthermore, older patients exhibited a higher prevalence of comorbidities such as hypertension, diabetes, and cardiovascular/cerebrovascular diseases (Wang, Yuan, Zheng, et al., 2020), and both oxaliplatin and fluorouracil could induce vascular endothelial cell damage and cardiotoxicity (Peng, Dong, Wang, et al., 2018; Du, Sudlow, Shahverdi, et al., 2023). Furthermore, oxaliplatin-induced peripheral neuropathy and microvascular dysfunction are particularly distressing for elderly patients. These adverse effects

can significantly compromise their quality of life and are likely to have a negative impact on overall survival prognosis (Peipert, Roydhouse, Tighiouart, et al., 2024; Taib, Durand, Dehais, et al., 2025). Therefore, although patients with stage II MSI-H have a better prognosis, age should play an important reference role in the clinical decision-making of such patients.

Additionally, our study included a statistical analysis of patients with BRAF mutations. Current evidence indicates that BRAF-mutated colorectal cancer is strongly associated with advanced TNM stage, poor differentiation, mucinous histology, and proximal tumor location, collectively contributing to a poorer prognosis (Clarke, & Kopetz, 2015; Chen, Huang, Liu, et al., 2014). Compared to BRAF-mutated microsatellite stable (MSS) tumors, those with co-occurring BRAF mutation and MSI-H demonstrate a less aggressive clinical phenotype and are associated with significantly improved overall survival (OS) (Grothey, Fakih, & Tabernero, 2021). Relatively speaking, MSI-H status is a favorable prognostic indicator for patients with BRAF-mutated colorectal cancer. In our cohort of 140 stage II MSI-H patients, BRAF mutations were identified in only 20 cases (14.29%). This incidence is notably lower than the 35-45% prevalence reported by Sabine et al. in MSI-H populations (Venderbosch, Nagtegaal, Maughan, et al., 2014). This discrepancy is related to the small sample size of this study and the possible results of molecular tests from different institutions. There were 5 cases of disease progression during follow-up, including 1 (1/7) in the chemotherapy group and 4 (4/13) in the non-chemotherapy group. The Cox univariate regression analysis showed a risk HR=3.025, 95%CI(1.034-8.854), P=0.043 < 0.05, compared with patients without BRAF mutation. Although postoperative adjuvant chemotherapy may not be sensitive to BRAF-mutated patients, BRAF-mutated patients in the MSI-H group may benefit from this study, but the defect of insufficient sample size and the important confounding factor of age require a larger sample size for validation.

Patients with MSI-H/dMMR tumors exhibit a lower propensity for lymph node metastasis compared to their MSS/pMMR counterparts. However, significant discrepancies are frequently observed among preoperative imaging, intraoperative assessment, and final pathological lymph node staging. This often results in a final pathological node stage that is higher than initially anticipated based on preoperative evaluations (Hong, Chalabi, Landolfi, et al., 2022; Kim, Min, Choi, et al., 2022). Compared with microsatellite-stable (MSS) colorectal cancer, MSI-H tumors are characterized by a higher tumor mutational burden (TMB) and greater neoantigen load, which enhances immune recognition and promotes antitumor cytotoxicity (Sui, Zhang, Chen, et al., 2022). Consequently, the robust anti-tumor immune response in MSI-H patients can induce reactive lymph node hyperplasia. This inflammatory response may lead to significant discrepancies between the lymph node enlargement observed on preoperative imaging or during surgery and the final pathological findings, which often show an absence of actual metastasis. Xuan Dai et al. identified the number of negative lymph nodes as an independent prognostic factor for MSI-H tumors, noting that a lower count was significantly associated with increased tumor recurrence and poorer overall survival (Dai, Dai, Fu, et al., 2024). Univariate Cox analysis indicated that the dissection of fewer than 12 lymph nodes may be associated with poorer

prognosis. Disease progression was observed in 3 of the 10 patients in this subgroup, a rate (30.0%) substantially higher than the overall progression rate of 10.7% (15/140) in the cohort. Consequently, greater clinical vigilance regarding postoperative recurrence and progression is warranted for such patients.

The present study has several limitations. First, as a single-center retrospective analysis, it is subject to potential biases in patient selection, diagnostic testing, treatment approaches, and data completeness. Second, the relatively small sample size of 140 patients may limit the statistical power and generalizability of the findings. Third, the advanced age of the included cohort may have introduced confounding, as older patients tend to have a higher prevalence of comorbidities that could influence both treatment tolerance and oncologic outcomes.

Despite these limitations, this study provides valuable insights into the clinically debated management of stage II MSI-H colorectal cancer. Our findings indicate that patient age significantly influences the administration of postoperative adjuvant chemotherapy, and that such treatment can confer a survival benefit in this population. However, the role of the T4 stage as an independent risk factor warrants further investigation.

4. Conclusion

In conclusion, this study suggests that patients with stage II MSI-H colorectal cancer may derive benefit from oxaliplatin-based adjuvant chemotherapy following surgery, with patient age identified as a significant independent prognostic factor. However, these findings should be interpreted with caution due to the limitations of the present study and require validation through larger-scale, multicenter randomized controlled trials. Furthermore, the growing influence of immunotherapy is expected to substantially reshape traditional treatment paradigms for this patient subgroup, underscoring the continued need for further research to refine and expand clinical guidelines.

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