*Original Article*

# Comparison of Clinicopathological Features and Survival Outcomes between MSI-H and MSS Status in Stage II Colorectal Cancer: A Retrospective Single-center Study

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***Key Words***
Stage II colorectal cancer;
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Mismatch repair (MMR)

***Purpose.*** Microsatellite instability (MSI) is an important biomarker in stage II colorectal cancer where representative tumors are associated with distinct pathological features and favorable prognosis. This study aimed to compare clinical features and outcomes between tumors with high microsatellite instability (MSI-H) and microsatellite stability (MSS).

***Methods.*** This retrospective study included patients with pathological stage II colorectal cancer (CRC) who underwent curative surgery between January 2015 and December 2021 at a single tertiary hospital. Patients were classified as having MSI-H or MSS based on mismatch repair protein expression by immunohistochemistry. Clinical features, recurrence patterns and survival outcomes were analyzed.

***Results.*** A total of 162 patients were included, with 14 patients classified as MSI-H (8.6%). High microsatellite instability tumors were more frequently right-sided, larger than 5 centimeters, and less likely to meet high-risk criteria. Fewer patients received adjuvant chemotherapy in the MSI-H group. No early recurrence occurred in the MSI-H group, compared to 6.1% in the MSS group. After a median follow-up of 65 months, the median disease-free survival (DFS) rates and median overall survival (OS) rates were not reached. The five-year recurrence-free survival rate was 92.9% for high microsatellite instability and 81.8% for stable cases ($p$ = 0.332). Overall survival was similar between groups.

***Conclusion.*** Although we demonstrated that stage II colorectal cancer with MSI-H shows distinct clinical features and a favorable trend in DFS, our findings support guidelines that do not recommend routine adjuvant chemotherapy for these patients who are stage II with MSI-H and in the absence of high-risk factors.

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Colorectal cancer (CRC) remains one of the leading causes of cancer-related morbidity and mortality worldwide. Among patients with non-metastatic disease, approximately 20% are diagnosed with stage II CRC, which is typically managed with surgical resection alone, although the decision to administer ad-

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juvant chemotherapy in stage II CRC remains complex and controversial.[1,2]

Microsatellite instability (MSI), a hallmark of defective mismatch repair (dMMR), is present in approximately 15-20% of stage II CRCs and has emerged as a key molecular biomarker with both prognostic and predictive significance.[3,4] Microsatellite instability-high (MSI-H) tumors are characterized by right-sided predominance, larger tumor size, mucinous histology and increased immune cell infiltration.[5-7] Importantly, multiple studies have demonstrated that MSI-H status is associated with a favorable prognosis and limited benefit from fluoropyrimidine-based adjuvant chemotherapy.[1,4,8]

Despite these insights, the clinical behavior of MSI-H versus microsatellite stability (MSS) tumors in stage II CRC remains an area of ongoing investigation, particularly in real-world, population-specific cohorts.[9] In addition, the interaction between MSI status and other clinicopathological features such as tumor size, location, *B-Raf proto-oncogene* (*BRAF*)/*rat sarcoma viral oncogene homolog* (*RAS*) mutation, and high-risk factors warrants further evaluation.[10,11]

The aim of this study is to compare the clinicopathological characteristics and oncologic outcomes, including disease-free survival (DFS) and overall survival (OS) between MSI-H and MSS tumors in patients with stage II colorectal cancer treated in a single center and to better understand the prognostic value of MSI status.

# Materials and Methods

## Patients and study design

This retrospective cohort study included patients diagnosed with pathological stage II colorectal cancer who underwent curative surgical resection between January 2015 and December 2021 at Kaohsiung Medical University Chung-Ho Memorial Hospital. We followed up the enrolled patients till January 2025. Patients were categorized into two groups based on MSI status: the MSI-H group and the MSS group. Inclusion criteria were histologically confirmed stage II colorectal adenocarcinoma (American Joint Committee on Cancer 8th edition), while exclusion criteria included unknown MSI status and incomplete follow-up.

## Data collection

Clinical, pathological, and oncologic data were retrospectively extracted from institutional medical records. The variables collected for analysis included patient demographics (age categorized as ≥ 65 years or < 65 years, and sex), tumor characteristics (location, histological type, differentiation, tumor size with a cutoff at 5 cm, presence of lymphovascular invasion or perineural invasion, and the number of lymph nodes retrieved), and performance status based on the Eastern Cooperative Oncology Group (ECOG) score (grouped as 0-1 or ≥ 2). Tumor location was defined anatomically, with right-sided tumors encompassing the cecum to the transverse colon, and left-sided tumors including the descending colon to the rectum.

Laboratory data included preoperative and 1-month postoperative carcinoembryonic antigen (CEA) levels, using 5 ng/mL as the cutoff value. Molecular profiles such as *BRAF* and *RAS* mutation status were also recorded when available. High-risk features of stage II colorectal cancer were identified according to the NCCN guidelines, including factors such as T4 lesions, poor differentiation, lymphovascular invasion, perineural invasion, bowel obstruction or perforation, positive surgical margins, and retrieval of fewer than 12 lymph nodes. Treatment-related variables included whether patients received adjuvant chemotherapy. In addition to recurrence status, we specifically documented early recurrence, defined as tumor recurrence occurring within 12 months after surgery.

Oncologic outcomes of interest were DFS defined as the time from randomization to recurrence of tumor or death, and OS defined as the time from the date of randomization until the date of death or the last date of follow-up.

## MSI testing

MSI status was determined using immunohisto-

chemistry (IHC) for the four mismatch repair (MMR) proteins: MutL Homolog 1 (MLH1), MutS Homolog 2 (MSH2), MutS Homolog 6 (MSH6), and Postmeiotic Segregation Increased 2 (PMS2). Tumors were classified as MSI-H if there was a loss of expression of at least one of these proteins, while tumors with intact expression of all four proteins were considered MSS.

### Statistical analysis

Categorical variables were compared using the chi-square test; survival analyses were conducted using the Kaplan-Meier method; and group comparisons were assessed using the log-rank test. All statistical analyses were performed using SPSS version 27 (IBM Corp., Armonk, NY, USA), with a $p$ value < 0.05 considered statistically significant.

### Ethical considerations

The study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. The study protocol was reviewed and approved by the Institutional Review Board of Kaohsiung Medical University Hospital (IRB No. KMUHIRB-E(I)-20200036).

## Results

### Study population and disposition

A total of 265 patients were initially identified. Seventeen patients were excluded due to lack of MSI testing, and of the remaining 248 patients, 21 were identified as having MSI-H tumors and 227 as having MSS tumors. Among these, 7 patients from the MSI-H group and 79 patients from the MSS group were excluded due to loss of follow-up for more than one year. After exclusions, 14 patients with MSI-H and 148 patients with MSS tumors were included in the final analysis. The CONSORT diagram is presented in Fig. 1.

### Clinicopathological characteristics

A total of 162 patients with stage II colorectal cancer were included in this study, comprising 14 patients (8.6%) with MSI-H tumors and 148 patients (91.4%) with MSS tumors. The comparison of clinicopathological features between the two groups is summarized in Table 1.

No statistically significant differences were observed between MSI-H and MSS groups regarding gender ($p$ = 0.130), age group (≥ 65 vs. < 65 years, $p$ = 0.750), ECOG performance status ($p$ = 0.533), preop-

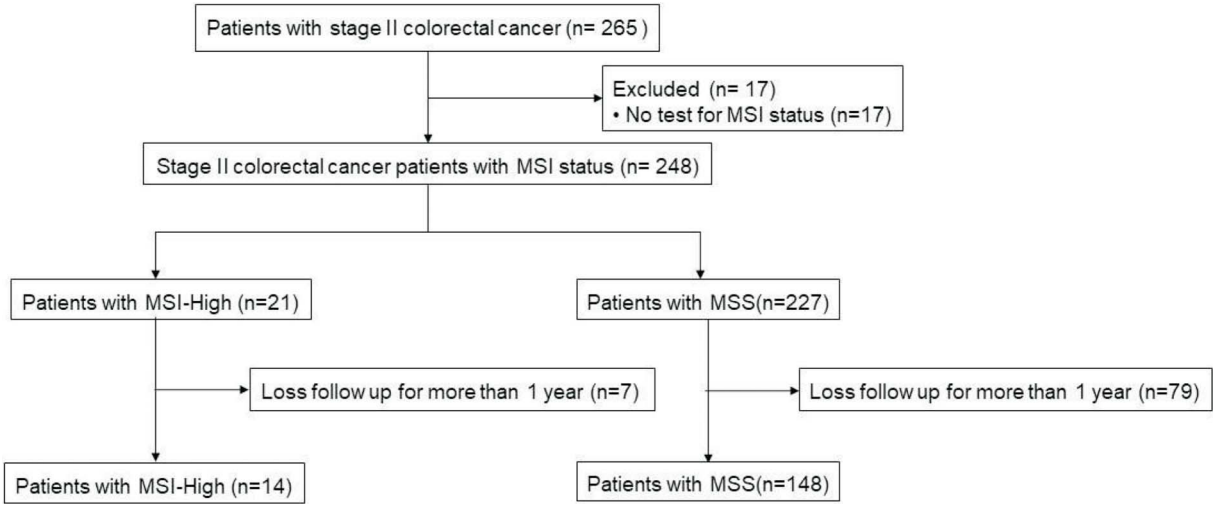


**Fig. 1.** CONSORT diagram of this study. The final enrolled patients for analysis were 162 patients. Collection was from January 2015 to December 2021, and database was locked for final analysis on January 2025. Median follow-up time was 65.0 months (range 4 to 119 months).

**Table 1.** Clinicopathological features of the 162 enrolled stage II colorectal cancer patients

| | Total (n = 162) | MSI-H[1] (n = 14) | MSI-L[2] (n = 148) | *p*-value |
|---|---|---|---|---|
| Baseline | n | n (%) | n (%) | |
| Gender | | | | 0.130 |
| Male | 89 | 5 (35.7) | 84 (56.8) | |
| Female | 73 | 9 (64.3) | 64 (43.2) | |
| Age (y/o) | | | | 0.750 |
| ≥ 65 | 76 | 6 (42.9) | 70 (47.3) | |
| < 65 | 86 | 8 (57.1) | 78 (52.7) | |
| ECOG[3] | | | | 0.533 |
| 0-1 | 158 | 14 (100) | 144 (97.3) | |
| ≥ 2 | 4 | 0 (0) | 4 (2.7) | |
| Clinical features | | | | |
| Pre-operation CEA[4] | | | | 0.583 |
| ≥ 5 (ng/mL) | 40 | 2 (14.3) | 38 (25.7) | |
| < 5 (ng/mL) | 115 | 11 (78.6) | 104 (70.3) | |
| Missing data | 7 | 1 (7.1) | 6 (4.1) | |
| Post-operation CEA[5] | | | | 0.823 |
| ≥ 5 (ng/mL) | 11 | 1 (7.1) | 10 (6.8) | |
| < 5 (ng/mL) | 147 | 13 (92.8) | 134 (90.5) | |
| Missing data | 4 | 0 (0) | 4 (2.7) | |
| Location | | | | < 0.001* |
| Right-sided colon[6] | 45 | 12 (85.7) | 33 (22.3) | |
| Left-sided colon[7] | 117 | 2 (14.3) | 115 (77.7) | |
| Adjuvant chemotherapy | | | | < 0.001* |
| Yes | 151 | 9 (64.3) | 142 (95.9) | |
| No | 11 | 5 (35.7) | 6 (4.1) | |
| Early recurrence[8] | | | | 0.342 |
| Yes | 9 | 0 (0) | 9 (6.1) | |
| No | 153 | 14 (100) | 139 (93.9) | |
| Recurrence | | | | 0.294 |
| Yes | 28 | 1 (7.1) | 27 (18.2) | |
| No | 134 | 13 (92.9) | 121 (81.8) | |
| Pathological features | | | | |
| Stage | | | | 0.604 |
| IIA | 152 | 14 (100) | 138 (93.2) | |
| IIB | 8 | 0 (0) | 8 (5.4) | |
| IIC | 2 | 0 (0) | 2 (1.4) | |
| Tumor size | | | | < 0.001* |
| ≥ 5 cm | 51 | 11 (78.6) | 40 (27.0) | |
| < 5 cm | 109 | 3 (21.4) | 106 (71.6) | |
| Missing data | 2 | 0 (0) | 2 (1.4) | |
| LVI[9] | | | | 0.384 |
| Yes | 17 | 0 (0) | 17 (11.5) | |
| No | 144 | 14 (100) | 130 (87.8) | |
| Missing data | 1 | 0 (0) | 1 (0.7) | |
| PNI[10] | | | | 0.435 |
| Yes | 32 | 1 (7.1) | 31 (20.9) | |
| No | 129 | 13 (92.9) | 116 (78.4) | |
| Missing data | 1 | 0 (0) | 1 (0.7) | |
| Type | | | | 0.662 |
| Adenocarcinoma | 160 | 14 (100) | 146 (98.6) | |
| Mucinous carcinoma | 2 | 0 (0) | 2 (1.4) | |

**Table 1.** Continued

| | Total (n = 162) | MSI-H[1] (n = 14) | MSI-L[2] (n = 148) | *p*-value |
|---|---|---|---|---|
| High/low risk group | | | | 0.017* |
| High | 84 | 3 (21.4) | 81 (54.7) | |
| Low | 78 | 11 (78.6) | 67 (45.3) | |
| *BRAF*[11] mutation | | | | < 0.001* |
| Wild type | 21 | 5 (35.7) | 16 (10.8) | |
| Mutation | 2 | 2 (14.3) | 0 (0) | |
| No test | 139 | 7 (50.0) | 132 (89.2) | |
| *RAS*[12] mutation | | | | 0.496 |
| Wild type | 13 | 2 (14.3) | 11 (7.4) | |
| Mutation | 6 | 1 (7.1) | 5 (3.4) | |
| No test | 143 | 11 (88.6) | 132 (89.2) | |

***Note.*** Data are given as no. (%) except where otherwise noted.
[†] *p*-value was calculated by the Chi-square test for the categorical data. * Statistical significance.
[1] MSI-H, microsatellite instability-high; [2] MSI-L, microsatellite instability-low; [3] ECOG, Eastern Cooperative Oncology Group; [4] CEA, carcinoembryonic antigen; [5] Post-operative CEA, 1-month postoperative carcinoembryonic antigen; [6] right-sided colon, cecum + ascending colon + transverse colon; [7] left-sided colon, descending colon + sigmoid colon + rectosigmoid junction + rectum; [8] Early recurrence, recurrence within 12 months after the curative operation; [9] LVI, lymphovascular invasion; [10] PNI, perineural invasion; [11] *BRAF*, v-Raf murine sarcoma viral oncogene homolog B; [12] *RAS*, rat sarcoma virus.

erative CEA level ($p = 0.583$), postoperative 1-month CEA level ($p = 0.823$), lymphovascular invasion ($p = 0.384$), perineural invasion ($p = 0.435$), histological subtype ($p = 0.662$) or *RAS* mutation status ($p = 0.496$). A significantly higher proportion of MSI-H tumors were located in the right-sided colon (85.7%) compared to MSS tumors (22.3%) ($p < 0.001$) while being more likely larger with 78.6% measuring ≥ 5 cm, in contrast to 27.0% in the MSS group ($p < 0.001$).

Adjuvant chemotherapy was administered less frequently in the MSI-H group (64.3%) than in the MSS group (95.9%) ($p < 0.001$). In the MSI-H group (n = 14), 9 patients (64.3%) received adjuvant chemotherapy. Among them, 7 received oral Uracil-Tegafur (UFUR) and 2 received oxaliplatin, leucovorin, and fluorouracil (FOLFOX6). When stratified by risk, of the 3 high-risk patients, 2 received UFUR and 1 did not receive chemotherapy. Among the 11 low-risk patients, 5 received UFUR, 2 received FOLFOX6, and 4 did not receive chemotherapy. In the MSS group (n = 148), 142 patients (95.9%) received adjuvant chemotherapy. Of these, 99 received single-agent oral chemotherapy and 43 received fluorouracil-based combination chemotherapy. Among the 83 high-risk patients, 31 received combination therapy, while among the 67 low-risk patients, 12 received combination therapy and the rest received single-agent oral chemotherapy.

Regarding risk stratification, only 21.4% of MSI-H patients met the high-risk criteria defined by the NCCN, compared to 54.7% in the MSS group ($p = 0.017$). Furthermore, *BRAF* mutations were found exclusively in the MSI-H group (14.3%), with none detected in the MSS group ($p < 0.001$). No early recurrence was observed in the MSI-H group, while 6.1% of the MSS group experienced early recurrence ($p = 0.342$).

Similarly, overall recurrence did not differ significantly between the groups (7.1% in MSI-H vs. 18.2% in MSS, $p = 0.294$). In the MSI-H group, only one patient experienced disease recurrence, which manifested as peritoneal carcinomatosis. In contrast, among the 27 patients with recurrence in the MSS group, a wider spectrum of metastatic patterns was observed. Specifically, there were 4 cases of local recurrence, 9 cases of peritoneal carcinomatosis, 8 cases of liver metastasis, 6 cases of lung metastasis, 4 cases of distant lymph node involvement, and 1 case of ovarian metastasis. It is important to note that several patients had metastases involving multiple sites; therefore, the total count of metastatic locations exceeds the number of recurrent cases.

### Survival analysis

At the cut-off time (January 2025), the median time of follow-up was 65 months (range 4 to 119). The medians for both DFS and OS were not reached during the study period, reflecting the overall favorable prognosis of this stage II colorectal cancer cohort. Although the 5-year DFS rate appeared numerically higher in the MSI-H group compared to the MSS group, the difference was not statistically significant ($p = 0.332$). Notably, the DFS curves appeared stable beyond 60 months, with a 5-year DFS rate of 92.9% in the MSI-H group and 81.8% in the MSS group, further suggesting durable disease control in both subgroups. The number of patients at risk at each time point is shown in the corresponding Kaplan-Meier survival curve (Fig. 2A). Similarly, no significant difference in overall survival was observed between the MSI-H and MSS groups ($p = 0.178$). The OS curve and number at risk are illustrated in Fig. 2B.

## Discussion

In this retrospective analysis of 162 patients with pathological stage II colorectal cancer, we compared clinicopathological features and survival outcomes between patients with MSI-H and MSS tumors. Our findings support the well-established molecular and clinical distinction between these two subtypes and offer further insight into their implications for treatment strategies. The MSI-H group exhibited a strong predilection for the right-sided colon, larger tumor size (≥ 5 cm), and lower frequency of high-risk features as defined by NCCN guidelines. These findings are consistent with prior reports that highlight the unique phenotype of MSI-H tumors where they are more commonly found in the proximal colon and exhibit poor differentiation, mucinous histology and lymphocytic infiltration.[12-14] Several large-scale studies also report that MSI-H is associated with a higher tumor burden yet paradoxically better prognosis due to an activated immune microenvironment.[3,8,15] The exclusive presence of *BRAF* mutations in the MSI-H group in our study is also consistent with previous literature, particularly among sporadic MSI-H cases, which are often driven by MLH1 promoter hypermethylation and $BRAF^{V600E}$ mutations.[16-18] In addition, *KRAS* mutations have been shown to coexist with MSI-H status and are associated with poorer outcomes in certain molecular contexts.[19-21]

One of the significant findings in our study was the markedly lower rate of adjuvant chemotherapy administration in the MSI-H group (64.3% vs. 95.9%, $p < 0.001$). This reflects the current clinical consensus that MSI-H status, especially in the absence of high-risk features, is not benefited from 5-fluorouracil-based adjuvant therapy. The ASCO guideline update

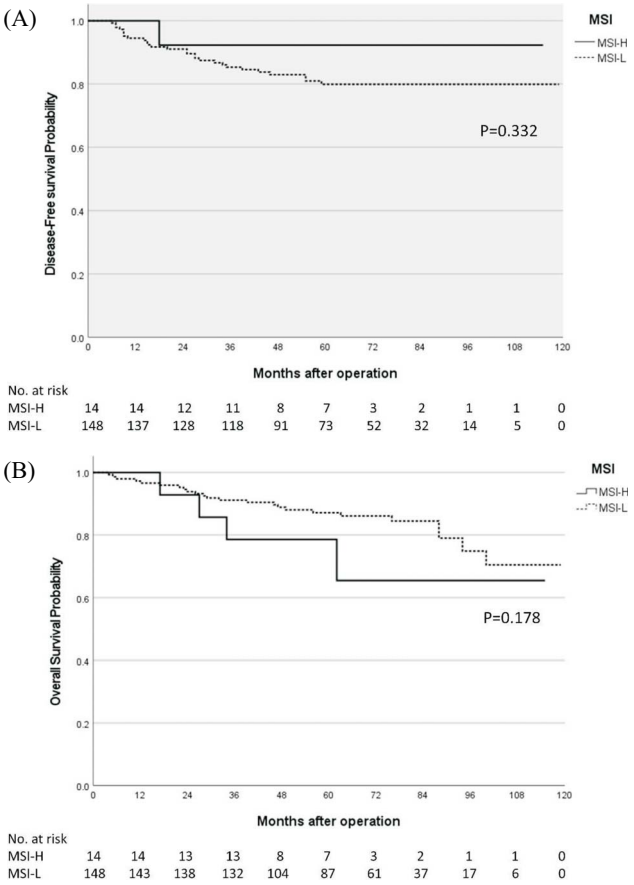


**Fig. 2.** Cumulative disease-free survival (DFS) rates and overall survival (OS) rates of the 162 enrolled patients with stage II CRC, obtained using the Kaplan-Meier method. Difference in DFS and OS were analyzed using the log-rank test. The results demonstrated that (A) DFS did not significantly differ between the two groups ($p = 0.332$); (B) OS did not significantly differ between the two groups ($p = 0.178$).

explicitly recommends against routine adjuvant chemotherapy in stage II MSI-H patients due to lack of efficacy and potential for harm.[1] Similarly, our study observed no significant improvement in disease-free or overall survival with chemotherapy in MSI-H patients, which is aligned with data from previous meta-analyses and national database studies.[2,4,22,23] The difference in adjuvant chemotherapy used between the MSI-H and MSS groups in our study reflects both molecular-guided decision-making and adherence to clinical guidelines. The lower chemotherapy rate in MSI-H patients aligns with current evidence suggesting limited benefit of fluoropyrimidine-based therapy in this subgroup. Additionally, the more frequent use of combination chemotherapy in high-risk MSS patients underscores risk-adapted treatment intensification. Nevertheless, a subset of low-risk MSI-H patients still received oral chemotherapy, which may indicate physician discretion or patient preference. These findings highlight the evolving role of molecular profiling in treatment decisions and the importance of personalized care in stage II colorectal cancer. Additionally, despite MSS patients receiving adjuvant chemotherapy more frequently, survival benefit was not significantly superior. This underscores the growing need for additional predictive markers beyond MSI status, such as circulating tumor DNA (ctDNA).[24]

In our cohort, the MSI-H group demonstrated a trend toward improved disease-free survival (DFS) compared to the MSS group, although the difference did not reach statistical significance ($p = 0.332$). This favorable trend is consistent with previous studies reporting that MSI-H tumors in stage II colorectal cancer are associated with a lower risk of recurrence. Notably, in our cohort, all observed early recurrence events occurred in the MSS group, while no early recurrence was recorded in patients with MSI-H tumors. This recurrence pattern, although not statistically significant, further supports the trend of improved disease-free survival in the MSI-H population. The MSS group showed a more aggressive and widespread recurrence pattern, in contrast to the limited recurrence observed in MSI-H patients. This observation supports existing evidence that microsatellite stable tumors may exhibit a more invasive biological behavior, while high microsatellite instability tumors tend to follow a more indolent clinical course. Meta-analyses and population-based studies have shown that MSI-H status serves as a positive prognostic factor, particularly in early-stage disease.[2-4]

The lack of statistical significance in our data could be attributed to the small sample size in the MSI-H group (n = 14), which limits the power of survival analysis. Nonetheless, our findings are biologically reasonable given the established immunogenicity of MSI-H tumors, which might enhance tumor surveillance and reduce recurrence despite the presence of adverse features such as larger tumor size.[3,8] There was also no statistically significant difference in overall survival (OS) between the MSI-H and MSS groups ($p = 0.178$), and no clear directional trend was observed. This result aligns with several reports suggesting that while MSI-H status might influence recurrence risk, its impact on overall survival — particularly in the context of stage II disease — is less definitive.[5] The lack of OS difference could also reflect effective salvage therapies at recurrence and the overall favorable prognosis associated with stage II CRC.

Several limitations should be acknowledged in the interpretation of our findings. The retrospective and single-institution design introduces potential selection and information biases, despite standardized MSI testing protocols and consistent follow-up, while the relatively small number of MSI-H patients (n = 14) significantly limits statistical power to detect differences in survival outcomes, particularly for disease-free and overall survival analyses, contributing to the lack of statistically significant findings despite observable trends.

## Conclusion

In this retrospective study of stage II colorectal cancer, MSI-H tumors were more frequently located in the right-sided colon, exhibited larger tumor size, and were less likely to present with NCCN-defined high-risk features compared to MSS tumors. Although no statistically significant differences were observed in DFS and OS, the patients with MSI-H demonstrated a favorable DFS trend, consistent with existing

literature. These findings reinforce the distinct biological behavior and prognostic implications of MSI-H tumors and support current clinical guidelines that discourage routine use of adjuvant chemotherapy in stage II MSI-H patients without high-risk features. Further prospective studies with larger cohorts are warranted to validate these observations and refine treatment strategies, particularly for molecularly defined subgroups.

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## Authors' Contributions

All authors contributed equally to the writing of the manuscript, reviewed any revisions that were made, and provided their final approval of the manuscript.

## Consent for Publication

Written informed consent was obtained from the patients for the treatment. In addition, written informed consent was obtained from the patients' families for publication of this case report and any accompanying images.

## Competing Interests

The authors declare that they have no competing interests.

## Sources of Financial Support

Nil.

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原　著

# 第二期大腸直腸癌中高微衛星不穩定性與微衛星穩定型狀態之臨床病理特徵與存活結果比較：單一中心回顧性研究

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**研究目的**　微衛星不穩定性是第二期大腸直腸癌中重要的分子預後指標。具高微衛星不穩定性之腫瘤常呈現特異的病理特徵，並與較佳的臨床預後相關。本研究旨在比較第二期大腸直腸癌中高微衛星不穩定性與微衛星穩定腫瘤之臨床病理特徵與治療結果。

**研究方法**　本回顧性研究納入 2015 年 1 月至 2021 年 12 月間於單一醫學中心接受根除性手術之第二期大腸直腸癌病患。根據免疫組織化學染色檢測錯配修復蛋白，將病人分類為高微衛星不穩定性與微衛星穩定兩組，並比較其臨床特徵、復發情形與存活結果。

**研究結果**　共 162 位病患納入分析，其中 14 位為高微衛星不穩定性。此類腫瘤多位於右側結腸、腫瘤大於 5 公分，且較不符合 NCCN 定義的高風險標準。高微衛星不穩定性組接受輔助化學治療的比例亦較低。未觀察到此組病患有早期復發，反觀微衛星穩定組早期復發率為 6.1%。追蹤中位數時間為 65 個月，期間未達到無病存活中位數與總存活中位數時間。五年無病存活率分別為 92.9% (高微衛星不穩定性) 與 81.8% (微衛星穩定) ($p$ = 0.332)，兩組總存活率無顯著差異。

**結論**　第二期大腸直腸癌中，高微衛星不穩定性腫瘤展現較佳的無病存活趨勢。研究結果支持針對第二期病人且具高微衛星不穩定性及無高風險因子的病患，可不常規使用輔助化學治療之臨床建議。

**關鍵詞**　第二期大腸直腸癌、微衛星不穩定性、高微衛星不穩定性、微衛星穩定型、錯配修復系統。