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Original Article

Clinical and Histopathological Differences in Microsatellite Instable (MSI) and Microsatellite Stable (MSS) Colorectal Tumors

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Abstract

Introduction: Microsatellite instability (MSI) tumors represent an important molecular subtype of colorectal carcinoma with distinct clinicopathological features. This study aims to compare the clinical and histopathological characteristics of dMMR/MSI and microsatellite stable (MSS) colorectal tumors.

Methods: We retrospectively analyzed a total of 580 colorectal carcinoma cases resected between 2001 and 2018 and archived at the Department of Pathology, Manisa Celal Bayar University Faculty of Medicine. Tumors were classified as dMMR/MSI or MSS based on immunohistochemical analysis of MLH1, MSH2, MSH6, and PMS2 protein expression. Clinical and histopathological parameters were compared between the two groups.

Results: dMMR/MSI tumors accounted for 19.5% of cases. Compared with MSS tumors, dMMR/MSI tumors were significantly larger, more frequently right-sided, more commonly mucinous, and more poorly differentiated. Perineural invasion was more frequent in MSS tumors. No significant differences were found between the groups in terms of other parameters such as lymphovascular invasion, lymph node metastasis, tumor budding, or immune response.

Conclusion: dMMR/MSI colorectal tumors demonstrate distinct clinicopathological features compared with MSS tumors, particularly regarding tumor location, morphology, and differentiation.

Keywords: Colorectal carcinoma, Histopathology, Microsatellite instability, MSS, Prognostic factors

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Introduction

Colorectal cancer (CRC) is one of the leading causes of cancer-related morbidity and mortality worldwide.[1] Approximately 15–20% of CRCs develop through the microsatellite instability (MSI) pathway, which results from deficient mismatch repair (dMMR) function caused by alterations in the MLH1, MSH2, MSH6, or PMS2 genes.[2-4]

Compared with microsatellite stable (MSS) tumors, dMMR/MSI colorectal carcinomas exhibit distinct clinicopathological and therapeutic characteristics, including differences in tumor location, morphology, prognosis, and response to immunotherapy. The present study aimed to compare the clinical and histopathological features of dMMR/MSI and MSS colorectal tumors in a large regional cohort.

Materials and Methods

The study was conducted at the Department of Pathology, Manisa Celal Bayar University Hospital, a tertiary academic referral center serving the western Aegean region of Türkiye. The study population predominantly consisted of patients referred from Manisa and surrounding provinces, reflecting a regional colorectal cancer cohort.

Initially, 590 colorectal carcinoma cases diagnosed between 2001 and 2018 in resection specimens or consultation blocks archived at the Department of Pathology were included. Hematoxylin and eosin (H&E)-stained slides and corresponding paraffin blocks were retrieved from the archives. All slides were re-examined, and histopathological diagnoses, tumor grade, stage, and additional prognostic parameters were reassessed.

Among the initial 590 cases, six cases with complete pathological response following neoadjuvant therapy, three cases with familial adenomatous polyposis (FAP), and one case diagnosed as mixed adenoneuroendocrine carcinoma were excluded. The final study cohort consisted of 580 cases.

Representative tumor areas were selected for immunohistochemical evaluation. Histopathological parameters including tumor grade, lymphovascular invasion (LVI), venous invasion, perineural invasion (PNI), tumor budding (TB), poorly differentiated clusters (PDC), immune response patterns, focal mucinous differentiation, depth of invasion, tumor deposits, lymph node metastasis, TNM stage, and surgical margin status were reassessed in all cases.

Histopathological classification and grading were based on the 2019 WHO criteria. Tumor staging was performed according to the AJCC 8th edition (2017), and reporting was carried out in accordance with the CAP protocol

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(2021).

Cases were additionally categorized as mucinous and non-mucinous adenocarcinomas for statistical analysis.

Histopathological Evaluation

Depth of invasion was evaluated according to the AJCC 8th edition TNM classification and categorized as early invasion (Tis–T2) or advanced invasion (T3–T4) for statistical analysis.

Tumor location was categorized as right-sided or left-sided. Tumors located in the cecum, ascending colon, hepatic flexure, and transverse colon were classified as right-sided, whereas tumors located from the splenic flexure to the sigmoid colon were classified as left-sided. Rectal tumors were analyzed within the left-sided group according to the study design.

Tumor size was recorded in millimeters based on the largest macroscopic tumor diameter reported in the pathology records.

Tumor differentiation and focal mucinous differentiation were evaluated only in non-mucinous adenocarcinomas. Tumor differentiation was categorized as well/moderately differentiated or poorly differentiated.

Tumor budding was evaluated at the invasive front according to the ITBCC 2016 criteria and categorized as low, intermediate, or high budding. Poorly differentiated clusters (PDC) were defined as clusters of ≥ 5 tumor cells lacking glandular formation and categorized as low, intermediate, or high.

Intratumoral and peritumoral lymphocytic responses were semi-quantitatively assessed as absent, low, or high. Crohn-like inflammatory response was recorded as present or absent based on the presence of nodular lymphoid aggregates at the invasive tumor front.

Lymphovascular invasion was defined as the presence of tumor cells within endothelial-lined vascular or lymphatic spaces. Venous invasion was defined as tumor invasion into veins with identifiable smooth muscle wall. Perineural invasion was defined as tumor cell infiltration in, around, or through nerve structures.

Tumor deposits were defined according to AJCC criteria as discrete tumor nodules in the pericolorectal tissue without residual lymph node structure.

Surgical margins were considered positive when tumor cells were present at any resection margin.

Immunohistochemical Evaluation

Immunohistochemical evaluation was performed using normal colonic mucosa as an internal control. A 10% cutoff value was used to assess the retention or loss of DNA mismatch repair (MMR) protein expression in tumor cells. Cases with nuclear expression of MLH1, MSH2, MSH6, and PMS2 in more than 10% of tumor cells were classified as microsatellite stable (MSS). Cases showing complete loss of nuclear expression of at least one MMR protein were classified as deficient MMR (dMMR)/microsatellite instability (MSI).

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS), version 26. Pearson's chi-square test and Fisher's exact test were used to evaluate associations between categorical variables. A P-value < 0.05 was considered statistically significant.

Results

The study cohort consisted of 580 colorectal carcinoma cases, including 342 males (59%) and 238 females (41%). The mean age of the patients was 62.86 ± 12.10 years (range: 25–88 years), and the mean tumor size was 46.92 ± 20.27 mm (range: 0–140 mm). Most tumors were adenocarcinoma, NOS (88.3%), while mucinous adenocarcinoma accounted for 5.7% of cases.

Of the 580 cases, 113 (19.5%) were classified as dMMR/MSI, while 467 (80.5%) were MSS.

Mean age did not differ significantly between the groups (61.25 ± 13.73 vs 63.25 ± 11.66 years, $P = 0.120$). The mean tumor size was significantly larger in dMMR/MSI tumors compared to MSS tumors (57.30 ± 25.04 mm vs 44.49 ± 18.17 mm, $P < 0.001$). In addition, dMMR/MSI tumors were significantly more frequently located in the right colon compared with MSS tumors ($P < 0.001$).

Mucinous adenocarcinoma morphology was more frequent in dMMR/MSI tumors than MSS tumors (11.5% vs 4.3%, $P = 0.003$). Poor differentiation was observed in 27.4% of dMMR/MSI tumors and 7.9% of MSS tumors ($P < 0.001$).

Perineural invasion was identified in 28.3% of dMMR/MSI tumors and 39.0% of MSS tumors ($P = 0.035$). Advanced invasion depth (T3–T4) was more common in dMMR/MSI tumors (96.5% vs 88.4%, $P = 0.011$).

No significant differences were observed regarding lymphovascular invasion (LVI), lymph node metastasis, immune response, poorly differentiated clusters (PDC), tumor budding (TB), tumor deposits, venous invasion, or surgical margin positivity. The clinicopathological characteristics of the two tumor groups are presented in Table 1.

Discussion

In the present study, dMMR/MSI colorectal tumors demonstrated distinct clinicopathological characteristics compared with MSS tumors, particularly regarding tumor location, size, differentiation, and mucinous morphology.

Previous studies have shown that MSI tumors are more frequently right-sided, larger, and poorly differentiated.[5–9] Consistent with these findings, dMMR/MSI tumors in our cohort were significantly more frequently located in the right colon and demonstrated a significantly larger tumor size compared with MSS tumors. Kang et al. reported a 68% right-sided localization rate in MSI tumors,[5] while 52.8% of dMMR/MSI tumors in our cohort were right-sided compared with 23.9% of MSS tumors.

The reported frequency of MSI tumors in colorectal carcinoma ranges between 9% and 28% depending on study population and methodology.[6,7] The 19.5% MSI rate observed in our cohort is consistent with previously published data.

Table 1. Clinicopathological Characteristics of dMMR/MSI and MSS Colorectal Carcinomas.

Feature	Category	dMMR/MSI tumors (n = 113)	MSS tumors (n = 467)	*P* value
Age, years (mean ± SD)	—	61.25 ± 13.73	63.25 ± 11.66	0.120
Tumor size, mm (mean ± SD)	—	57.30 ± 25.04	44.49 ± 18.17	**< 0.001**
Sex	Male	65 (57.5)	277 (59.3)	0.728
	Female	48 (42.5)	190 (40.7)	
Tumor location	Right-sided	60 (53.1)	112 (24.0)	**< 0.001**
	Left-sided	53 (46.9)	355 (76.0)	
Mucinous morphology	Mucinous	13 (11.5)	20 (4.3)	**0.003**
	Non-mucinous	100 (88.5)	447 (95.7)	
Differentiation	Well/moderately differentiated	82 (72.6)	430 (92.1)	**< 0.001**
	Poorly differentiated	31 (27.4)	37 (7.9)	
Perineural invasion (PNI)	Present	32 (28.3)	182 (39.0)	**0.035**
	Absent	81 (71.7)	285 (61.0)	
Level of invasion	Early invasion (Tis–T2)	4 (3.5)	54 (11.6)	**0.011**
	Advanced invasion (T3–T4)	109 (96.5)	413 (88.4)	
Lymphovascular invasion (LVI)	Present	78 (69.0)	325 (69.6)	0.907
	Absent	35 (31.0)	142 (30.4)	
Lymph node metastasis	Present	38 (33.6)	194 (41.5)	0.125
	Absent	75 (66.4)	273 (58.5)	
Venous invasion	Present	7 (6.2)	55 (11.8)	0.085
	Absent	106 (93.8)	412 (88.2)	

Data are presented as n (%) unless otherwise indicated.
Tumor differentiation was evaluated only in non-mucinous adenocarcinomas.

Xiao et al. reported that MSI tumors were more frequently poorly differentiated than MSS tumors.[7] Similarly, poor differentiation was significantly more common in dMMR/MSI tumors in our study. In addition, mucinous morphology was significantly more frequent in dMMR/MSI tumors, consistent with previous studies demonstrating an association between MSI status and mucinous histology.[10]

Parc et al. reported no significant differences between MSI and MSS tumors regarding lymphovascular invasion, perineural invasion, or venous invasion.[11] In contrast, Wright et al. observed higher rates of perineural invasion in MSS tumors.[12] In our cohort, lymphovascular invasion did not differ significantly between the groups, whereas perineural invasion was significantly more frequent in MSS tumors.

Previous studies have reported increased lymphocytic response in MSI tumors.[13-15] Although Crohn-like inflammatory response tended to be more frequent in dMMR/MSI tumors in our cohort, no statistically significant differences were observed regarding intratumoral or peritumoral inflammatory response.

Tumor budding (TB) has been associated with advanced stage, lymphovascular invasion, and poor prognosis in colorectal carcinoma.[16,17] However, no significant differences in TB were observed between dMMR/MSI and MSS tumors in our study. Similarly, no significant differences were found regarding poorly differentiated clusters (PDC), despite previous studies suggesting an association between increased PDC and adverse clinicopathological features.[18]

Although lymph node metastasis was less frequent in dMMR/MSI tumors, the difference was not statistically significant. Previous studies have suggested that enhanced immune response in MSI tumors may contribute to lower lymph node involvement.[7]

This study has several limitations. First, its retrospective single-center design may limit the generalizability of the findings. In addition, detailed survival and treatment response data were not available for all patients. Despite these limitations, the relatively large cohort and comprehensive histopathological evaluation strengthen the findings of the study.

Overall, our findings support the presence of distinct clinicopathological differences between dMMR/MSI and MSS colorectal carcinomas, particularly regarding tumor location, morphology, and differentiation.

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Authors' Contribution
Conceptualization: Özgecan Hamdemir, Semin Ayhan
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Data Curation: Ömer Atmış, Özgecan Hamdemir
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Competing Interests
The authors declare no conflict of interest.

Ethical Approval

This study was approved by the Institutional Review Board of Kafkas University Training and Research Hospital (Approval No: KAÜ-TFEK 2025/07/16; Date: September 24/2025). Patient consent was waived due to the retrospective nature of the study. This work was previously presented as a poster at the 31st Turkish National Pathology Congress, İzmir, Turkey, October 2022.

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References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021;71(3):209-49. doi:10.3322/caac.21660
2. Yaraş S, Akkız H. Microsatellite instability screening and clinical efficacy in tumor tissue in patients with colorectal cancer. Mersin Univ Saglık Bilim Derg 2019;12(3):469-77. doi:10.26559/mersinsbd.562680
3. de'Angelis GL, Bottarelli L, Azzoni C, de'Angelis N, Leandro G, Di Mario F, et al. Microsatellite instability in colorectal cancer. Acta Biomed 2018;89(9-s):97-101. doi:10.23750/abm.v89i9-S.7960
4. Yamamoto H, Imai K. Microsatellite instability: an update. Arch Toxicol 2015;89(6):899-921. doi:10.1007/s00204-015-1474-0
5. Kang S, Na Y, Joung SY, Lee SI, Oh SC, Min BW. The significance of microsatellite instability in colorectal cancer after controlling for clinicopathological factors. Medicine (Baltimore) 2018;97(9): e0019. doi:10.1097/md.0000000000010019
6. Alexander J, Watanabe T, Wu TT, Rashid A, Li S, Hamilton SR. Histopathological identification of colon cancer with microsatellite instability. Am J Pathol 2001;158(2):527-35. doi:10.1016/s0002-9440(10)63994-6
7. Xiao H, Yoon YS, Hong SM, Roh SA, Cho DH, Yu CS, et al. Poorly differentiated colorectal cancers: correlation of microsatellite instability with clinicopathologic features and survival. Am J Clin Pathol 2013;140(3):341-7. doi:10.1309/ajcp8p2dynkgrbvi
8. Yan WY, Hu J, Xie L, Cheng L, Yang M, Li L, et al. Prediction of biological behavior and prognosis of colorectal cancer patients by tumor MSI/MMR in the Chinese population. Onco Targets Ther 2016;9:7415-24. doi:10.2147/ott.S117089
9. Saha S, Shaik M, Johnston G, Saha SK, Berbiglia L, Hicks M, et al. Tumor size predicts long-term survival in colon cancer: an analysis of the National Cancer Data Base. Am J Surg 2015;209(3):570-4. doi:10.1016/j.amjsurg.2014.12.008
10. Park JS, Huh JW, Park YA, Cho YB, Yun SH, Kim HC, et al. Prognostic comparison between mucinous and nonmucinous adenocarcinoma in colorectal cancer. Medicine (Baltimore) 2015;94(15): e658. doi:10.1097/md.0000000000000658
11. Parc Y, Gueroult S, Mourra N, Serfaty L, Fléjou JF, Tiret E, et al. Prognostic significance of microsatellite instability determined by immunohistochemical staining of MSH2 and MLH1 in sporadic T3N0M0 colon cancer. Gut 2004;53(3):371-5. doi:10.1136/gut.2003.019190
12. Wright CL, Stewart ID. Histopathology and mismatch repair status of 458 consecutive colorectal carcinomas. Am J Surg Pathol 2003;27(11):1393-406. doi:10.1097/00000478-200311000-00001
13. Jakubowska K, Kisielewski W, Kańczuga-Koda L, Koda M, Famulski W. Stromal and intraepithelial tumor-infiltrating lymphocytes in colorectal carcinoma. Oncol Lett 2017;14(6):6421-32. doi:10.3892/ol.2017.7013
14. Ward R, Meagher A, Tomlinson I, O'Connor T, Norrie M, Wu R, et al. Microsatellite instability and the clinicopathological features of sporadic colorectal cancer. Gut 2001;48(6):821-9. doi:10.1136/gut.48.6.821
15. Chapusot C, Martin L, Mungra N, Rageot D, Bouvier AM, Bonithon Kopp C, et al. Sporadic colorectal cancers with defective mismatch repair display a number of specific morphological characteristics: relationship between the expression of hMLH1 and hMSH2 proteins and clinicopathological features of 273 adenocarcinomas. Histopathology 2003;43(1):40-7. doi:10.1046/j.1365-2559.2003.01641.x
16. Ueno H, Murphy J, Jass JR, Mochizuki H, Talbot IC. Tumour 'budding' as an index to estimate the potential of aggressiveness in rectal cancer. Histopathology 2002;40(2):127-32. doi:10.1046/j.1365-2559.2002.01324.x
17. van Wyk HC, Roseweir A, Alexander P, Park JH, Horgan PG, McMillan DC, et al. The relationship between tumor budding, tumor microenvironment, and survival in patients with primary operable colorectal cancer. Ann Surg Oncol 2019;26(13):4397-404. doi:10.1245/s10434-019-07931-6
18. Reggiani Bonetti L, Barresi V, Bettelli S, Domati F, Palmiere C. Poorly differentiated clusters (PDC) in colorectal cancer: what is and ought to be known. Diagn Pathol 2016;11:31. doi:10.1186/s13000-016-0481-7