Editorial

# What is the significance of mismatch repair deficiency in stage IV colon cancer?

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Colorectal cancer (CRC) is the second most common cause of cancer-related death in the United States (1). The 5-year survival rate for patients in the early stage is over 90%; however, the 5-year survival rate drops to 65% in patients initially diagnosed with regional lymph node metastases and is less than 10% in patients with distant metastases (2). Distant metastatic disease is present in approximately 25% of CRC patients at initial diagnosis, and half of CRC patients develop metastatic disease (3). Metastatic CRC (mCRC) is primarily treated with surgery, systemic therapies (i.e., cytotoxic chemotherapy, biologics such as growth factor antibodies), locoregional treatments (such as radiotherapy and hepatic artery infusion), and combinations of these treatments. Over the past decades, the development of effective treatments has extended survival for mCRC patients. However, the prognosis of mCRC remains poor at 2–3 years (4,5).

The discovery of mismatch repair deficiency (MMR-D) and the invention of immune checkpoint inhibitors have led to progress in the treatment of mCRC. The KEYNOTE-177 randomized phase 3 study evaluated the programmed cell death 1 protein inhibitor pembrolizumab compared with standard of care in patients with microsatellite instability-high (MSI-H)/MMR-D mCRC in the first-line setting (6-8). During the >5 years of follow-up, pembrolizumab showed robust clinical efficacy, with a median overall survival of 77.5 months compared with 36.7 months with chemotherapy [hazard ratio (HR), 0.73; 95% confidence interval (CI), 0.53–0.99] (8). Another phase 3 trial examined first-line nivolumab plus ipilimumab compared with chemotherapy (9). In patients with MSI-H or MMR-D mCRC who had not previously received systemic treatment, progression-free survival was 19.2 months (95% CI: 17.9–20.5) with nivolumab plus ipilimumab compared with 8.6 months (95% CI: 6.7–10.4) with chemotherapy, indicating a difference of 10.6 months (95% CI: 8.4–12.9). These trials demonstrated the favorable prognosis for mCRC with MMR-D treated with immunotherapy and have opened new possibilities for the effective treatment of patients with mCRC.

Colon cancer (CC) with MMR-D is associated with genomic characteristics such as MSI and *BRAF* gene mutation (10). CC with MMR-D also exhibits distinct pathologic and epidemiologic features such as the tendency to localize in the proximal colon, poor differentiation, and mucinous histology. MMR-D may also play a critical role in the progression and metastatic spread of CC, and treatment strategies targeting MMR-D may improve the unfavorable prognosis of metastatic colon cancer (mCC) patients. Nevertheless, because of the low tendency of CC with MMR-D to exhibit lymph node and distant organ metastasis, there are few studies on mCC with MMR-D (11).

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Therefore, targeted analysis of MMR status among patients with mCC is an unexplored and urgent need.

In the article, Schaub *et al.* made noteworthy work of researching the characteristics of mCC with MMR-D (12). With a large sample, the authors identified detailed associations between mCC and MMR-D. The study included 10,922 mCC cases, including 8,796 (80.53%) MMR-proficient (MMR-P) cases and 2,126 (19.47%) MMR-D cases. The frequency of MMR-D cases was higher than would be anticipated from previous studies, which reported that mCRC with MSI-H or MMR-D constituted 3.5–6.5% of total mCRC cases (13,14), supporting the value of this study. The authors found that MMR-D was associated with worse mortality at 180 days, 1 year, and 2 years. This result suggested that mCC patients with MMR-D disease are a specific subgroup with poor prognosis that would benefit from more intense treatment. Additionally, the authors highlight the significance of the findings given that MMR-D is considered a positive prognostic factor in non-metastatic CC (stages I–III) (15-20). This seemingly contradictory result also makes this study noteworthy. One possible explanation for this discrepancy discussed in the study is the difference in sociodemographic comorbidities, such as right-sided colonic predominance, older age at diagnosis, female sex, and white race that were associated with MMR-D status. An alternative explanation is the chemotherapy-resistant nature of mCC with MMR-D compared with MMR-P (21). Given the retrospective observational nature of this study, whether the relationship is causal or correlates with unknown confounding factors could not be addressed. Future studies should investigate the relationship and etiology between mCC and MMR-D.

In summary, mCC is challenging to treat, and MMR-D status appears to have a significant impact on prognosis, as demonstrated in the article. Despite guideline recommendations and significant therapeutic implications, overall biomarker testing rates in mCC remain approximately 40–50% (10). As reported in Schaub *et al.*'s article, MMR-D in mCC has a prognostic value, and it is recommended that all cases of mCC undergo genomic testing to determine candidates for immunotherapy or other potential treatment options. MMR-D in mCC warrants further investigation.

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