



# Is prognosis uniformly excellent in patients with stage II MSI-high colon cancer?

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The genomic subtyping of colon cancer groups tumors into microsatellite stable (MSS) and unstable (MSI). Although the MSI-high (MSI-H) subtype is found in only 15% of tumors (of which 12% are sporadic and 3% hereditary), it has attracted much interest because of its association with favorable outcomes. However, the prognosis of patients with MSI-H may in reality be heterogenous. This is clinically important, especially in stage II colon cancer, because the subset of patients with less favorable prognosis may need adjuvant chemotherapy to prevent disease recurrence after surgery. High-risk features such as a T4 primary, obstructed or perforated colon cancer, <12 nodes in the surgical specimen, and lymphovascular invasion (LVI) or perineural invasion (PNI) may be associated with the subset of MSI-H patients with poor prognosis. In fact, the updated consensus based National Comprehensive Cancer Network (NCCN) guidelines have acknowledged this possibility and recommend weighing risks and benefits of adjuvant therapy. To further complicate matters, the response to chemotherapy may also be influenced by MSI status. Specifically, the MSI-H subtype is associated with lower response to chemotherapy, and it has been suggested that fluoropyrimidines alone may even worsen outcomes in these patients.

The study by Zhang *et al.* is important because only a few studies to date have assessed whether prognosis is uniformly excellent in the MSI-H group (1). First, the authors defined the high-risk features of stage II colon cancer as the presence of any of the following: pathologic stage T4, poor differentiation (grade 3/4, excluding MSI-H), vascular invasion, PNI, initial bowel obstruction or perforation of

tumor site, positive or unknown margins, insufficient surgical margin, and <12 excised lymph nodes. Next, the authors estimated the prognosis of MSS and MSI-H groups with and without the presence of high-risk features. The MSS group with high-risk features had significantly worse disease-free survival (DFS) than the other three groups. In contrast, there was no significant difference in DFS among MSI-H patients without high-risk features, MSI-H patients with high-risk features, and MSS patients without high-risk features. These results suggest that the presence of high-risk features alone cannot be used to select patients for adjuvant chemotherapy.

Of note, in a recent analysis of the National Cancer Database, Mohamed *et al.* reported that in patients who received no adjuvant chemotherapy, the high-risk MSI-H patients had worse 5-year overall survival (OS) than their counterparts with no “high-risk features” [5-year survival and 95% CI: 69.8% (62.6–75.9%) vs. 78.4% (74.3–81.9%), respectively,  $P < 0.0001$ ] (2). Of note, they did not assess DFS. In addition, this study defined high-risk features as <12 lymph nodes examined, LVI, positive surgical margin, and pT4 tumor. No data were available for obstruction or perforation at diagnosis, and poor or undifferentiated histology was not included as a high-risk feature. Thus, the definition of high-risk features differed between the two studies, with PNI and initial bowel obstruction or perforation of tumor site only considered high-risk features in the Zhang study. This may explain the disparate results.

Indeed, another recent study by Cavallaro *et al.* found that some but not all high-risk features are associated with worse survival in patients with stage II MSI-H colon

cancer (3). Specifically, they showed that certain high-risk features (LVI, PNI, and high-grade histology) were not associated with worse survival, and obstructing or perforating disease was not considered a high-risk feature in this study. In contrast, other high-risk features (T4 stage, positive resection margins, and inadequate nodal sampling) were associated with worse survival. This may explain why Zhang *et al.*, who considered PNI, high-grade histology, and obstructive or perforating disease as high-risk features, found comparable survival between patients with and without high-risk features. Interestingly, Cavallaro *et al.* showed that these features were all prognostic in patients with MSS tumors. Another study by Fleming *et al.* corroborated the finding that poor differentiation and LVI do not independently worsen outcomes in patients with MSI-H stage II colon cancer (4). Instead, they showed that the presence of multiple high-risk features has an additive effect leading to worse outcomes.

Ultimately, the study by Zhang *et al.* is an important contribution because only a few studies to date have assessed whether prognosis is uniformly excellent in MSI-H patients. However, more studies are needed as current studies have produced contradicting results. Future studies should also investigate whether other novel factors can delineate subsets of stage II MSI-H patients with unfavorable outcomes. For example, Williams *et al.* has recently proposed the tumor infiltrating lymphocyte (TIL)/mismatch repair (MMR)-based classification (5). Specifically, they reported that TIL-low/MSI-H patients not only have distinctly worse DFS compared to other MSI-H patients, but that their DFS is also comparable to that of MSS tumors. Thus, traditional and novel features may need to be combined to define a subset of stage II MSI-H patients who have distinctly worse DFS. While such prognostic stratification cannot directly predict treatment benefit, it can direct interventions towards appropriate high-risk groups and maximize the likelihood of a clinically meaningful trial.

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