
Letter

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Samowitz et al. (1) described recently that MSI2 in sporadic CRC is associated with an improved prognosis at the population level. These findings well agree with most (2–4) but not all (5, 6) of the previous studies on the prognostic value of MSI in this setting. In particular, Samowitz et al. (1) emphasize that their study is the largest to date and the first population-based study of sporadic CRC including the most frequent ages at diagnosis demonstrating that MSI is associated with improved prognosis independent of tumor stage. On these grounds, they propose that these findings are directly applicable and clinically relevant to the population at large. We fully agree with this conclusion, although we believe that standardized criteria should be adopted for a better assessment of MSI. Moreover, we have recently obtained evidence indicating that additional factors may help improve the prognostic resolution of MSI in CRC patients (7). In fact, besides confirming the favorable clinical outcome of MSI-H CRC, we also demonstrated that the prognostic value of the MSI status alone is significantly enhanced by the combined evaluation of the number of intratumoral activated cytotoxic lymphocytes (7). This supports the hypothesis that MSI-H tumors may continuously produce new immunogenic epitopes as a consequence of the inherent defective DNA mismatch repair and may explain why patients with MSI-H CRC able to mount effective antitumor immune responses have a particularly favorable clinical outcome.

As pointed out by Samowitz et al. (1), MSI could also have clinically relevant implications for the selection of CRC patients to receive adjuvant chemotherapy. Nevertheless, the putative role of MSI as a predictor of response to chemotherapy is still controversial (3, 8, 9). Our recent findings do not seem to support such a generalized role, because the large majority (79.8%) of patients from our series did not receive any additional therapy besides radical surgery, suggesting that adjuvant treatment could be useless in cases showing both MSI-H and high numbers of activated cytotoxic lymphocytes (7). On the other hand, adjuvant chemotherapy could be beneficial to those MSI-H cases (24% in our series of proximal CRC) showing no evidence of local antitumor immune responses. Conclusive assessment of the predictive value of MSI would require large prospective clinical trials including adjuvant treatment and nontreatment arms. Nevertheless, because of the widespread acceptance of 5-fluorouracil-based regimens in the treatment of stage III CRC, it will be more and more difficult to include nontreatment arms in future trials. Therefore, as a first approach, we would favor the re-evaluation of large retrospective studies comprising both treated and nontreated arms, using standardized MSI assessment criteria, as well as defined tumor stage, patient characteristics, and adjuvant therapy. In this respect we strongly recommend considering also the number of activated cytotoxic lymphocytes infiltrating CRC, which may allow a more precise assessment of the prognostic value of MSI.

References

Reply

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We are pleased that Dolcetti et al. (1) agree with our conclusions and that their previous work supports our findings regarding the improved prognosis associated with MSI.1 Their results

1 The abbreviations used are: MSI, microsatellite instability.

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with intratumoral lymphocytes are of interest. As noted by these authors (1), this feature correlates strongly with MSI, and it would be of great interest if other groups can corroborate their finding that the number of intratumoral lymphocytes has an effect on prognosis over and above that seen with MSI alone. However, the findings reported by Dolcetti et al. (1) should be evaluated carefully. In their study 43% of right-sided colon cancers exhibited MSI. As noted by others (2), this is a very high percentage, even for right-sided cancers, where the reported percentage of MSI is typically closer to 25% (3, 4). This suggests that their group of cancers may not be representative of sporadic colon cancers in general and, therefore, raises questions as to whether their results can be extrapolated to colon cancer at the population level.

We would also take issue with the criticism of the authors that “standardized criteria should be adopted for a better assessment of MSI.” The measures of instability we utilized in our study showed statistically significant relationships with age, gender, tumor site, stage, differentiation, prognosis, and, in a previous study, Ki-ras and p53 status, and the Bethesda consensus panel (4, 5). If the authors are suggesting that the Bethesda consensus panel is the only appropriate way to measure instability, then we would emphasize that this runs counter to the recommendations of the National Cancer Institute workshop which developed this panel. That workshop stressed that the Bethesda consensus panel was not meant to replace other validated panels—and our instability measures have been amply validated by us and others—and acknowledged that in different situations other panels might be more appropriate (6).

It would be unfortunate if rigorous adherence to one panel or another would cause investigators to miss clinically important findings such as the suggestion in our study that instability in TGFβRII is a favorable prognostic finding in stage IV colon cancer (4).

References

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