

Peer Review File

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Reviewer A

In the 2018 NCCN guidelines, it was already recommended to perform MMR/MSI testing for all newly diagnosed CRC patients. Clinically, from the mid-2010s, MSI testing has been routinely performed on all patients worldwide. Selecting candidates for MSI testing based solely on family history has been considered an old-fashioned method for over a decade.

If the purpose of this study is to change the German colorectal cancer treatment guidelines, then I believe it is a paper of sufficient value. However, considering the current global trend in treatment, it's hard to say that it contributes to colorectal cancer treatment.

Reply A:

The reviewer is absolutely correct. A major purpose of this study is to indicate this shortcoming in the German colorectal cancer guidelines with the hope that a systematic approach would be adopted. We owe this to our patients.

Reviewer B

A retrospective study on the incidence of MSI-H tumors in a cohort of patients with CLR cancer. These are my comments:

Introduction and aim:

- the authors mention the main aim of this study is to validate if the amsterdam/revised bethesda criteria is a good screening tool for MSI screening.
- however, these guidelines are outdated, and the current gold standard is for routine MSI testing for all newly diagnosed colorectal cancers. The authors can refer to the latest version of the NCCN guidelines "principles of pathologic and molecular review" for more information. Many institutions have already adopted routine MSI testing for all tumors, as such this study adds minimal value to the literature.

Results:

- when comparing both groups, the authors should present their findings in a table with the P values
- this will make for easier comparison
- there is a significant portion of missing data (approximately 20%) - this may significantly affect the reproducibility / interpretation of data.

Conclusion:

- I think the authors conclusion that MSI testing should be routine is already practiced in most institutions

Reply B:

Introduction and aim:

We thank the reviewer for his fair minded comments. As the reviewer correctly commented, the main reason for this manuscript was to indicate a relevant shortcoming in the current german guidelines and argue for systematic MSI screening as recommended in the NCCN guidelines. With that in mind, there is need to convince decision-makers by presenting local data to argue for a change in approach.

Results and Conclusion:

We have added the p-value as advised (page 5, li 148 – 150). The sentence now reads “Equally, significantly more cases of MSI-H CRC were found in the group with family history for MSI – tumors compared to the group without any family history of MSI – tumors, 27.1 % vs. 16.5 %, $p = 0.04$ ”

We agree with the review’s comment regarding missing data. This was discussed as a serious limitation and simultaneously reiterates the meaningfulness of such an investigation as an argumentation tool to convince decision-makings about the need of a change in protocol.