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PEER-REVIEW REPORT

Name of journal: *World Journal of Gastrointestinal Oncology*

Manuscript NO: 78993

Title: Missed colorectal cancers in a fecal immunochemical test-based screening program: Molecular profiling of interval carcinomas

Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 03714297
Position: Peer Reviewer
Academic degree: MD, PhD
Professional title: Consultant Physician-Scientist
Reviewer's Country/Territory: Spain
Author's Country/Territory: Netherlands

Manuscript submission date: 2022-07-26
Reviewer chosen by: AI Technique
Reviewer accepted review: 2022-07-26 22:15
Reviewer performed review: 2022-08-04 08:23
Review time: 8 Days and 10 Hours

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [Y] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No

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Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

This is a retrospective study comparing molecular and genetic profiles of interval CRCs vs detected CRCs in a FIT-based CRC screening program. The authors identified 27 interval CRCs and randomly selected 54 detected CRCs (1:2 ratio). FIT-missed CRCs were more frequently CIMP+, MSI+ and showed an increased frequency of BRAF and PTEN mutations. The authors conclude that serrated molecular features are overrepresented in interval CRCs. This is an interesting study that, despite its low sample size, opens some working hypotheses for future research. Major comments: - The problem with this study, as the authors acknowledge, is the sample size. This is probably the underlying cause for the lack of significance of the described differences. Since the role of chance in the found differences cannot be ruled out, it seems a bit strong to say that "Serrated pathway associated molecular features are more common in FIT-interval CRCs". I would rephrase it to "seem to be" or "may be". - On the other hand, this lack of statistical significance does not automatically mean a lack of clinical significance. But we cannot figure this out because the confidence intervals are not provided. Knowing the upper and lower bound of the difference in proportion (e.g. 7% in MSI FIT-interval CRC vs SD-CRC) may give us information about how big or small the true difference might be. - In 14% (8/54) and 7% (2/27) of cases, DNA was not available. In other cases, the quality of reading for mutational analysis was not enough and they were excluded. In 22% of cases, DNA was not of enough quality. Despite using a manual extraction method these are quite high figures when dealing with low sample sizes and could have impacted the final results. This should be discussed in the "Discussion" section. - We do not know the familiar history of patients with cancers

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included in the study. Albeit rare, some of the interval CRCs might be related to some kind of familiar cancer. Minor comment: - Change the comma for a dot in the values of the last row in table 1, page 17.

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Academic degree: MD, MSc
Professional title: Associate Professor, Associate Specialist, Doctor
Reviewer's Country/Territory: China
Author's Country/Territory: Netherlands

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Reviewer performed review: 2022-08-04 15:43

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SPECIFIC COMMENTS TO AUTHORS

The authors studied the clinicopathological characteristics and gene mutation of colorectal cancer in the interval between fecal occult blood screening, which is closely related to the clinical practice and has clinical guiding significance. The research has certain innovation and practicality. The readability of the writing is good, and it is recommended to accept after modification.