



PEER-REVIEW REPORT

Name of journal: World Journal of Gastrointestinal Oncology

Manuscript NO: 48710

Title: Clinical significance of MLH1/MSH2 for stage II and III sporadic colorectal cancer

Reviewer's code: 00043396

Reviewer's country: Singapore

Science editor: Jin-Lei Wang

Reviewer accepted review: 2019-06-18 05:08

Reviewer performed review: 2019-06-18 08:52

Review time: 3 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language	(High priority)	<input checked="" type="checkbox"/> Anonymous
<input type="checkbox"/> Grade C: Good	polishing	<input type="checkbox"/> Accept	<input type="checkbox"/> Onymous
<input checked="" type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of	(General priority)	Peer-reviewer's expertise on the
<input type="checkbox"/> Grade E: Do not	language polishing	<input type="checkbox"/> Minor revision	topic of the manuscript:
publish	<input type="checkbox"/> Grade D: Rejection	<input checked="" type="checkbox"/> Major revision	<input type="checkbox"/> Advanced
		<input type="checkbox"/> Rejection	<input checked="" type="checkbox"/> General
			<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

The manuscript is generally well written. However there are some grammatical errors which will need to be corrected. eg. However, patients with stage II or MLH1/MSH2-negative of stage III did not benefit from adjuvant chemotherapy. The following statements are confusing. Are there two pathways or three pathways. CRC



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is mainly associated with two distinct genetic pathways: microsatellite instability (MSI), chromosomal instability (CIN) and CpG Island methylator phenotype (CIMP) [2]. These three pathways are not mutually exclusive, and most tumors are characterized by multiple pathways. Where or which country do these figures refer to? The number of new cases of CRC in 2015 was 376 300, including 215 700 men and 160 600 women. There were 191 000 million deaths due to CRC, including 111 100 men and 80 000 women[13]. What do you mean by the word "otherwise"? Please rewrite clearly Mutations either on MLH1 or MSH2 are considered as MLH1/MSH2 negative, otherwise is defined as positive. The attached sentence from the abstract(first sentence below) and the first sentence in the following paragraph contradict the rest of the paragraph. A nonsignificant trend for survival benefit from adjuvant chemotherapy was observed for all stage II and MLH1/MSH2-positive stage III CRC. Patients with MLH1/MSH2-positive stage II or III CRC showed a favorable survival trend for OS (68.62 ± 0.83 vs 62.11 ± 1.07 mo, $P < 0.001$). Stratified analyses showed that patients with MLH1/MSH2-negative stage II CRC had longer OS than those with MLH1/MSH2-positive CRC (70.67 ± 0.65 vs 66.02 ± 1.01 mo, $P = 0.011$). Patients with MLH1/MSH2-negative stage III CRC also had longer OS than those with MLH1/MSH2-positive (66.05 ± 1.62 vs 63.40 ± 1.15 mo, $P = 0.023$). In patients who received adjuvant chemotherapy, those with MLH1/MSH2-negative CRC had OS of 64.02 ± 1.61 mo compared with 62.11 ± 1.07 mo in those with MLH1/MSH2-positive CRC ($P = 0.015$). In conclusion, the 5-year survival rate for patients with MLH1/MSH2-negative CRC was 86.9%, compared with 59.1% for patients with MLH1/MSH2-positive CRC. The data for OS are listed in Fig.2. Please check all statements carefully and ensure that conflicting statements are clarified.

INITIAL REVIEW OF THE MANUSCRIPT



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PEER-REVIEW REPORT

Name of journal: World Journal of Gastrointestinal Oncology

Manuscript NO: 48710

Title: Clinical significance of MLH1/MSH2 for stage II and III sporadic colorectal cancer

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Science editor: Jin-Lei Wang

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Reviewer performed review: 2019-06-20 09:03

Review time: 2 Days and 7 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
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SPECIFIC COMMENTS TO AUTHORS

The work was undertaken to evaluate the prognostic significance of MLH1/MSH2 status being determined by immunohistochemistry in a large cohort of patients with stage II and III colorectal cancer, as well as to detect for any relationship between MLH1/MSH2 and overall survival. The work is very interesting and the m/s is well-organized,



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however there are several points requiring correction or clarification in order to be suitable for publication. Major points 1. Lines 217-227: Revise the paragraph. It is difficult to be interpreted. What are being compared in the first sentence? 2. Discussion is extensive and should be revised. The authors should discuss their results regarding the longer overall survival of MLH1/MSH2-negative patients together with the relationship of MLH1/MSH2-negative with: a. poor cancer differentiation, b. marked lymphocyte infiltration, and c. positive mucin. Avoid also duplications (i.e., lines 315-316). 3. Legend of Fig. 2B should be corrected to "OS of patients with MLH1/MSH2-positive and MLH1/MSH2-negative stage II CRC". 4. Table 4 is better to be reconstructed. 5. Most of literature is outdated. Recent interesting studies should be included (i.e., Immunohistochemical Expression of MMR Proteins with Clinicopathological Correlation in Colorectal Cancer in Egypt. Soliman, et al. Open Access Maced J Med Sci. 2019;7(10):1608-1617; Microsatellite Instability and Adjuvant Chemotherapy in Stage II Colon Cancer. Koenig et al. Am J Clin Oncol. 2019, doi: 10.1097; Screening of MSI detection loci and their heterogeneity in East Asian colorectal cancer patients. Bai et al. Cancer Med. 2019;8(5):2157-2166; Study of histopathologic parameters to define the prognosis of stage II colon cancer. Romiti et al. Int J Colorectal Dis. 2019;34(5):905-913, and many others), as well as some other studies in the same field (i.e., Relationship between MLH-1, MSH-2, PMS-2, MSH-6 expression and clinicopathological features in colorectal cancer. Karahan et al. Int J Clin Exp Pathol. 2015;8(4):4044-53) and most of old literature may be discarded. Minor points 1. It seems there are two addresses for author Ju Wang, however information for only one is provided. 2. Line 81: Delete the word "million". 3. Line 85: Delete space. 4. Line 310: Replace "are" with "is". 5. Line 313: Replace "11100" with "111100".

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