

Answer to peer-reviewer

**Reviewer's code:** 00043396

1.Q:However, patients with stage II or MLH1/MSH2-negative of stage III did not benefit from adjuvant chemotherapy. The following statements are confusing.

A:We carefully checked the table of 4 and found the MLH1/MSH2 negative and positive labels made error in stage III, and correct it. So we correct the sentence as" patients with stage II or MLH1/MSH2-positive of stage III did not benefit from adjuvant chemotherapy". Thank you for your correction.

2. Q: Are there two pathways or three pathways. CRC is mainly associated with two distinct genetic pathways: microsatellite instability (MSI), chromosomal instability (CIN) and CpG Island methylator phenotype (CIMP) [2].

A: there are at least 3 pathways. Sorry, this is a clerical error and I have corrected it, thank you very much for your correction.

3. Q: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].

A: In China, the incidence of CRC has increased significantly in the last 10 years.... The number of new cases of CRC in 2015 was 376 300.....

So these sentences were described the data in China. And through the reference of **Chen W**, Zheng R, Baade PD, Zhang S, Zeng H, Bray F, Jemal A, Yu XQ, He J. Cancer statistics in China, 2015. *CA: A Cancer Journal for Clinicians*. 2016; **66**:115-132.

Attachment is the reference file, but if you think these descriptions are not important, we can delete all of these sentences about china's data.

4. Q: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.[19]

A: What I want to express is that if one of MLH1 or MSH2 is negative or all negative, it is defined as MLH1/MSH2-negative, otherwise both are positive are defined as MLH1/MSH2-positive

So I correct this sentence as” Mutations either on *MLH1* or *MSH2* or both of them are considered as *MLH1/MSH2* negative, and both are not mutated as *MLH1/MSH2* positive.”

5. Q:The attached sentence from the abstract(first sentence below) and the first sentence in the following paragraph contradict the rest of the paragraph.

A:We carefully checked the table of 4 and found the MLH1/MSH2 negative and positive labels made error, and correct it, thank you for your carefully review and correction.

**Reviewer’s code:** 02505493

1.Q: Lines 217-227: Revise the paragraph. It is difficult to be interpreted. What are being compared in the first sentence?

A: The sentences “In univariate analysis of all patients, MLH1/MSH2 positive had significantly worse OS than MLH1/MSH2 negative ( $P<0.001$ , HR 3.799, 95%CI 2.205-6.546)”

I want to express that MLH1/MSH2 positive patients have worse OS than MLH1/MSH2 negative patients. SO I revised this sentence, thank you.

2. Q: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).

A: Thank you very much for your constructive guidance. I have made a major revision to the discussion section. The molecular mechanism of MMR, the clinical features of MMR, the relationship between MMR and chemotherapy, and the current status of MMR and immunotherapy, and the prospects of later studies are described in each section.

3.Q: Legend of Fig. 2B should be corrected to "OS of patients with MLH1/MSH2-positive and MLH1/MSH2-negative stage II CRC"

A: yes I have found the mistake too, and corrected it, thanks

4.Q: Table 4 is better to be reconstructed

A: I have revised the order of the label of Table 4, thank you

5. Q: Most of literature is outdated.

A: I think your suggestions are very helpful for us, so I searched and read many new abstracts and which you recommend me in this field and modified most of references you listed.

6.Q: It seems there are two addresses for author Ju Wang, however information for only one is provided

A: I was studying in US and wrote this manuscript during the study in US, and got many help from university of Hawaii, so I add two addresses of me, I add the two addresses for author.

7.Q: 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".

A: I have checked all errors you found and corrected them, thank you again for your careful review!