Response to the editor and reviewer

We would like to express our sincere gratitude for the constructive and positive comments about our manuscript. In this point-by-point letter we shall try to answer the reviewer's suggestions and requirements. In light of these comments, certain changes have been made in the revised version of the manuscript. Corrections have been highlighted using the "Track Changes" function in Microsoft Word, making them easily visible. The suggested references have been included at the end of the revised version of the manuscript. A careful revision of the text for English-related aspects has also been performed by a native speaker (a professional scientific language editor). A certificate of this language revision has been submitted with the revised version of the manuscript.

Answer to reviewer:

"It is an interesting study. The authors should add and discuss also their findings with other studies present the KRAS mutation in cfDNA as an also non-invasive method. The studies ie PLoS One. 2015 Apr 22;10(4):e0123902, Anticancer Res. 2017 Feb;37(2):651-657 should be added".

We thank the reviewer for this valuable suggestion. The following paragraph has been added to the Discussion in the revised version of the manuscript (lines 337-351):

"In a previous study, using ddPCR we detected the *KRAS* G12V mutation in plasma cfDNA from 9 of 10 patients whose tumors were also mutated[20]. In this study, we found that metastatic patients had a significantly higher number of mutated copies in circulating cfDNA than M0 patients. The only negative sample was obtained from a T1N0M0 patient. These results are in line with other studies: Bettegowda *et al.* also reported that ctDNA in plasma increases with disease stage, and only 47% of early-stage patients with a wide variety of cancers had

detectable levels of ctDNA[21]. Similarly, Galanopoulos *et al.* recently described that the *KRAS* codon 12 mutation rate in cfDNA is significantly higher in CRC patients compared to healthy subjects, though this methodology seems to have limited potential for predicting the existence of premalignant lesions (neoplastic colonic polyps)[26]. Taken together, these findings suggest that at early disease stages, levels of mutated copies in circulating cfDNA may be, in some cases, too low for detection. Thus, alternative non-invasive methods are still needed".

The references suggested by the reviewer have been included in the Discussion and now appear in the following sentence (lines 331-333):

"In CRC, *KRAS* mutations have been analyzed in blood, both in DNA obtained from circulating tumor cells (PLoS One. 2015 Apr 22;10(4):e0123902)[25] and in cfDNA (Anticancer Res. 2017 Feb;37(2):651-657)[26]".

Reference 26 (Anticancer Res. 2017 Feb;37(2):651-657) has also been cited in lines 345-349, corresponding to the above-mentioned paragraph added to the Discussion.

Thank you once again for considering our manuscript for publication in the *World Journal of Gastroenterology*.

Sincerely yours,

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