

To the Editor,
World Journal of Clinical Oncology

Revisions to manuscript: Evaluating the influence of primary tumour location on oncological outcome in colorectal cancer liver metastases

Manuscript reference no: 53912

Dear Sir/Madam,

We welcome the insightful comments made by the reviewers and are very grateful for their advice and time invested in appraising the above submission. We have addressed the reviewer's suggestions in the following document (author responses in blue italic), which is accompanied by a revised version of the manuscript (with changes highlighted).

Reviewer #1: In this systematic review, the authors provided a summary of the available evidence on the impact of primary CRC location (PTL), right side versus left side, on oncological outcomes in patients with CRC liver metastases (CRCLM). The paper is well written overall. The methodology is reasonable, and the references are appropriate. This paper is worth publication. Minor comment 1) Page 7, Line 18; In addition, the authors reported enhanced 5-year OS (45.8% vs 44.5% $p=0.02$). Maybe this is the wrong number. Please correct.

We are grateful to the reviewer for having undertaken a detailed appraisal of our manuscript and welcome the largely positive comments. Thank you for making note of the typographical error. The original paper cited has been consulted and the error corrected with the statistics now quoted.

Reviewer #2: In this review, Bingham et al. examined the role of primary tumor location in overall (OS)/disease free (DFS)/ progression free (PFS) survival of metastatic colorectal cancer. The paper is interesting but some aspects need to be modified, as follows: 1. To be more conclusive, Discussion should be fragmented in subchapters: Anatomic location, therapeutic options, molecular profile, etc. 2. It is necessary mentioning the role of TACE in evolution of these patients. In some papers, amazing evolution was reported after TACE (see papers such PMID: 26496332; DOI: 10.1097/MD.0000000000001848). There is a role of tumor location in these patients? 3. The molecular profile was examined but no data about NRAS were added. There is a role of these gene in evolution? In most of the laboratories, NRAS profile is also detected, together with KRAS and BRAF....Moreover, there is an utility of of NGS for daily diagnosis? What about MSI/MSS status? 4. Therapy - in the NCCN guideline, it is mentioned taht, in aptients with liver metastases, if carcinoamtosis is associated, HYPEC might be a therapeutic alternative. What about this method? In such review, taking into account onl location, without the other parameters is not enough...all of the data should be examined. 5. A histolgical parameter which is recommend to be included in the histopathological reports is the budding degree. It is mandatory to mention data about this parameter (for definition see papers such PMID: 28780084; DOI: 10.1016/j.prp.2017.07.025) 6. No data bout antiangiogenic therapy was added, also ESMO guideline mention that therea are difference for answering in patients with right versus left-colon tumors. 7. The last data of literature search is October 2019. As it is March 2020, the paper should be updated and papers from 2020 should also be included.

We are grateful for the insightful suggestions made by the Reviewer. In response: (1) We have made extensive modifications to the discussion section of the manuscript (see revised manuscript); (2) We agree that TACE is showing significant promise in the management of selected patients with unresectable colorectal cancer liver metastases (CRCLM). This data is unfortunately not suitable for inclusion in the present review as we have not been able to identify any studies that evaluate and define oncological outcome according to primary tumour site following TACE in patients with CRCLM; (3) The revised discussion provides a more expanded description of known genetic mutational differences, the role of MMR and MSI, as well as the role of various adjuvant treatment modalities, with particular reference to biologics. The available data, where relevant to primary tumour location specifically, has been described. These additions are highlighted in blue; (4) Reviewing the potential for CRS + HIPEC in the context of CRC peritoneal metastases with concurrent liver metastases lies beyond the scope of the present manuscript. Metastatic patterns in general have shown some differences according to primary tumour sidedness^[1]. For example, it is believed that this exerts differences on lung metastatic burden and oncological outcome also^[2]. Our study has sought specifically to evaluate CRCLM and so these other issues are not discussed, but would be an interesting subject for a further article in the future. We are grateful to the reviewer for these suggestions; (5) A further section has been added to discuss histopathological findings as related to primary tumour location; (6) Additional text has been provided to cover molecular targeted

therapeutics; (7) We have updated the literature search and an additional 350 papers were reviewed for eligibility but none met our inclusion criteria.

Reviewer #3: This paper overviewed the influence of primary tumor location on the oncological outcome of colorectal cancer liver metastasis, which is an interesting topic.

We thank you for your positive comment.

Reviewer #4: Bingham et al. have written a review evaluating the influence of primary tumor location in overall (OS)/disease free (DFS)/ progression free (PFS) survival of metastatic colorectal cancer. They have done a literature search and narrowed down appropriate studies to be examined, and present consensus results that indicate patients with I-CRCLM have better OS, with DFP AND PFS being less clear. Twenty-one out of thirty-eight (55%) of studies provided the positive OS correlation (this uncomfortably close to a 50:50 outcome for the studies examined). The review is carried out and written very well, and the clinical data is well presented and considered. Title, abstract, key words, background, methods, results, ok. Discussion could be augmented. Illustrations, biostatistics, units, references, organization ok. The authors do begin to approach a discussion about the molecular mechanisms that could be responsible for the results in the 21 positive studies, it seems appropriate to mention that this could be better developed. The major focus of the review isn't molecular, but there is a great deal known that could be applied to the major observations of the report. The authors do not mention that almost all tumors with MMR alteration are found on the right side. It is suggested that they go over the TCGA paper on colorectal cancer (Nature 2012 vol 487:330-337). What might the molecular mechanism be that would lead to holding off DFP in r-CRCLM with lower OS? For instance, is the implication that MMR types of mutation take longer to accumulate the mutations that would lead to extravasation but harbored more mTOR/AKT/Pik3CA mutation and either a different proliferation or growth rate. Maybe not so paradoxical? None of these studies have molecular analysis associated with them but there is a lot known that could be integrated into the review. What does the PTL outcome mean in terms of what is already known/thought about the molecular differences between MMR tumors and CIN? It would make it a more interesting read.

Thank you for your shared expertise. We have clarified the number of patients in the group of studies with a statistically significant OS benefit in I-CRCLM, a total of 76% of the studied patients, and we feel this better communicates the findings of our review. As suggested, we have reviewed the TCGA paper and expanded our discussion to explore what is known about MMR, MSI, and various genetic alterations as related to PTL. These additions are highlighted in blue.

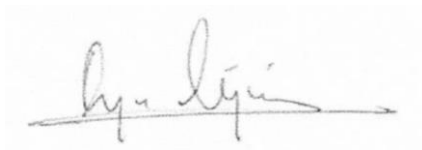
We feel that the manuscript has benefited significantly from the modifications made as advised by the reviewer and hope that it is deemed suitable for publication in its revised form.

We look forward to hearing from you in the near future with further news regarding the submission.

Yours Sincerely,

Mr Reza Mirnezami MB BS BSc FRCS PhD

(On behalf of the authors)

A handwritten signature in black ink, appearing to read 'Reza Mirnezami', with a long horizontal stroke extending to the right.

References:

1. **Prasanna T**, Karapetis CS, Roder D, Tie J, Padbury R, Price T, Wong R, Shapiro J, Nott L, Lee M, Chua YJ, Craft P, Piantadosi C, Sorich M, Gibbs P, Yip D. The survival outcome of patients with metastatic colorectal cancer based on the site of metastases and the impact of molecular markers and site of primary cancer on metastatic pattern. *Acta Oncol (Madr)* 2018;**57**:1438–44 [DOI: 10.1080/0284186X.2018.1487581]
2. **Byun JH**, Ahn JB, Kim SY, Kang JH, Zang DY, Kang SY, Kang MJ, Shim BY, Baek SK, Kim BS, Lee KH, Lee S Il, Cho SH, Sohn BS, Kim S, Hwang IG, Nam EM, Seo BG, Oh SC, Lee MA, Lee SC, Hong JH, Park YS. The impact of primary tumor location in patients with metastatic colorectal cancer: A korean cancer study group co12-04 study. *Korean J Intern Med* 2019;**34**:165–77 [DOI: 10.3904/kjim.2016.348]