

ANSWERING REVIEWERS

November 11, 2013

Dear Editor,



Please find enclosed the edited manuscript in Word format (file name: 5921-edited (Paschos et al.doc)).

Title: The natural history of hepatic metastases from colorectal cancer-pathobiological pathways with clinical significance

Authors: Konstantinos A. Paschos, Ali W. Majeed, Nigel C. Bird

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 5921

The manuscript has been improved according to the suggestions of the editor and the reviewers:

1 Format has been updated

1. the manuscript was typed in Book Antiqua font of size 10
2. all the authors' affiliations were rearranged with Department, University or Institute, City, Postcode, Country, etc.
3. the professional title of the corresponding author was provided
4. telephone and fax numbers were provided
5. the abstract was modified (147 words)
6. a core tip summary was provided (99 words)
7. the reference numbers were reformatted
8. heading 1 titles were reformatted
9. Figures were reformatted as decomposable ones and were saved at separate word documents
10. the reference list was reformatted and PMID and DOI numbers were provided

2 Revision has been made according to the suggestions of the reviewer

(1) Reviewer **00037998**

1. page numbers were rewritten
2. page 6, first line, last paragraph: may generate CRC

(2) Reviewer **02544402**

1. The manuscript length and reference list remained extended, as this is an invited review article with no word limit. The authors believe that the subject (natural history of colorectal hepatic metastases) attracts great scientific interest (from the molecular, genetic and clinical point of view) and a great number of scientific articles (especially the last decade) attempt to elucidate the various stages of the metastatic process. Therefore this review article should be rather long in order to present and analyze most of the recent knowledge.
2. Grammatical errors were corrected through proof reading

(3) Reviewer **00181023**

1. the semi colon in the title has been removed
2. no abbreviations are used in the abstract
3. Introduction, second paragraph: "during multiple metastatic stages" was removed
4. Introduction, third paragraph, first line: "cellular" was removed
5. page 6, third paragraph: "colorectal liver metastasis" was transformed to colorectal hepatic metastases (as well as in other parts of the manuscript)
6. Chapter "initial genetic alterations of epithelial cells in colorectal carcinogenesis":
 - 6a. "CRC's initial indication is certain cellular mutations" was altered to "Mutations in CRC include alterations in tumour suppressor genes..."
 - 6b. hMSLH1 was altered to hMLH1
 - 6c. Line 9 of this paragraph: "detach from the intestinal epithelium" was altered to "single cancer cells or small clusters of them may finally detach from the initial intestinal tumour and migrate"
 - 6d. Page 6, last paragraph: '80% of cancers follow the CIN pathway' was changed to 60%
 - 6e. Page 6, last paragraph: "FAP is the most common disease attributed to CIN pathway" was changed to "The role of APC gene is crucial in tumourigenesis as 100% of patients with the Familial Adenomatous Polyposis (FAP) syndrome who carry this mutation develop CRC if they receive no treatment."
 - 6f. Page 6, last paragraph: "Neoplastic cells in which genetic material has been mutated through MIN have aberrant DNA mismatch" was changed to "These neoplasms have aberrant DNA mismatch,"
 - 6g. Page 6, last paragraph: "The main genetic disorder caused by MIN is a sequence of mutations in DNA mismatch repair genes" was changed to "In HNPCC MIN is a consequence of mutations in DNA mismatch repair genes"
 - 6h. Page 6, last paragraph: "Notably, some colorectal tumours do not fall in either category, leading to the conclusion that other genetic pathways also exist..." was changed to "Notably, other genetic pathways also exist..."
7. Next chapter "Interactions of neoplastic...." 2nd line: "colorectal tissue stroma" was altered to stroma.
8. Chapter 2.2 macrophages, 1st line: "the development of tumour causes an inflammatory reaction to the intestinal tissue" was altered to "The development of a tumour causes an inflammatory reaction where immune cells may be implicated."
9. The reviewer states that he could not read any more because of the extremely poor quality of the article. Therefore, he failed to truly review this manuscript and we missed his crucial remarks.

3 References and typesetting were corrected as requested

Your invitation to us to send you a review article is an honor. Thank you very much for publishing our manuscript in the *World Journal of Gastroenterology*.

Yours faithfully,



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