Author’s response to reviews

Title: Risk Factors Affecting Prognosis in Metachronous Liver Metastases from WHO Classification G1 and G2 Gastroenteropancreatic Neuroendocrine Tumors after Initial R0 Surgical Resection

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Author’s response to reviews:

Dear Editor,

Thank you very much for this opportunity to revise our manuscript "Risk Factors Affecting Prognosis in Metachronous Liver Metastases from WHO Classification G1 and G2 Gastroenteropancreatic Neuroendocrine Tumors after Initial R0 Surgical Resection", of which the previous submission code is BCAN-D-18-03462.

As mentioned in the earlier cover letter, in this study we found that elevation of the Ki-67 index between the metastatic and primary lesions was an independent predictive factor for a poor prognosis. Local treatment was associated with prolonged survival of Metachronous hepatic
metastatic GEP-NET patients. We really appreciate the chance for you to re-evaluate this revised version and hope it will be finally accepted for publication of your magazine.

A point-by-point response letter is as follows:

Editor Comments:

BMC Cancer operates a policy of open peer review, which means that you will be able to see the names of the reviewers who provided the reports via the online peer review system. We encourage you to also view the reports there, via the action links on the left-hand side of the page, to see the names of the reviewers.

Reviewer reports:

Ming Lu (Reviewer 2): This study retrospectively analyzed the clinico-pathology and prognosis of 108 patients with GEP-NET metachronous liver metastases from 2003 to 2014. It is suggested that increased Ki67 index of liver metastases compared with the primary tumors is an important prognostic factor. The phenomenon is relatively common in tumors originated from gastrointestinal tract. The author proposed a prognostic risk model using multi-factor analysis, which was instructive for clinical practice. It's noted that the time span of the study was relatively long (2003-2014), during which the treatment modalities had changed over time. More novel strategies have been approved in the disease, including somatostatin analogues, everolimus and other target therapy. Such changes also exerted impact on the prognosis. Did the author take these factors into consideration?

Response: Your comments are very helpful and instructive. Thank you for your kind comments and questions. First of all, Gastroenteropancreatic Neuroendocrine tumors is a group of rare tumor and the volume of selected cases (108) is not easy to accumulate; in this study, specially, we aim to investigate the clinical-pathological characteristics of WHO G1 and G2 GEP-NET metachronous liver metastases, of which included criteria of the patients is strict. That is the why it tooks 11 years to collect 108 cases’. Besides, as we demonstrated in the manuscript, only 7 patients with pNETs were treated with everolimus, 15 patients with pNETs and 24 patients with GI-NETs received the treatment of somatostatin analogues. We admitted that during 11 years more novel treatment strategies have been approved in the disease, however, our main finding is that the elevation of ki-67 index between liver metastases compared with the primary tumors is an independent predictive factor of dismal prognosis and the prognostic significance of local hepatic resection (intervention) on these patients. To address the main research object of this study, we finally focus in analyzing the treatment modalities instead of analyzing such a small volume of treatment data solely. Thus through the analysis of our data, we found that local
treatment is necessary and beneficial for these patients’ prognosis, which is also in accordance with current study conclusion. Finally, we have also added these considerations into the “discussion” section, which is marked in red ink. Thank you for your kind comments, we hope our response could address your kind and valuable comments.

Bhawna Sirohi (Reviewer 3): the authors have addressed the points raised previously.

Response: Thank you for your kind review.

We hope our present version can address your kind and valuable comments. If you have any further comments and reviews, please do not hesitate to contact us.

Thank you very much

Best regards,

Cheng Huang and Wenhui Lou

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