Dear Editor,

Thank you very much for considering our manuscript titled “Revised Hepatocellular carcinoma with Biliary and Neuroendocrine Differentiation- A Case Report and Review of the Literature” by Yiannis Petros Dimopoulos et al as a “Case report” to the World Journal of Clinical Oncology for publication. We have revised our manuscript, addressing all the comments and suggestions of the expert reviewers. We thank the reviewers and the editorial team for reviewing our manuscript for their valuable comments and constructive suggestions which have enhanced the readability of our manuscript. We hope that the revised manuscript (with changes appearing in bold) will be acceptable for the publication in your journal.

Yours sincerely,

Yiannis Petros Dimopoulos

Response to reviewer #1

1. The content of the manuscript does not fully reflect the title as the authors did not include a "Review Literature" section. I recommend that the authors summarize in a table similar cases published so far, even if their number was small.

We have provided a table summarizing previous reported cases, including references to the original articles.

2. History of past illness (neuroendocrine tumors in the rectum, detected on routine colonoscopies and removed endoscopically in 2012 and 2017), requires more explanations and clarifications.

The patient’s previous neuroendocrine tumors were typical low grade carcinoid tumors and have been reviewed in our department and are morphologically totally different from the liver tumor. This is clarified in the manuscript.

3. The link between previous history of hepatitis C and history of low grade well differentiated neuroendocrine tumor, on the one hand, and current tumors detected, requires a detailed approach.

HCC is often associated with hepatitis C as seen in this patient. However, to our best knowledge, carcinoid tumor has no known associations with hepatitis C. This is emphasized in the discussion.

Response to reviewer #2

Specific Comments to Authors: This is a case report of a very rare liver tumor presenting with differentiation to HCC/CCC/NEC. As the authors described in the discussion, only few similar cases have been reported so far, and this is a very rare case report. It's very well written, but it's necessary to add a few more points. Please refer to the following points for correction and resubmit. Major point 1) The final histopathological diagnosis in this case was a mixed tumor in which the lesion in segment 4 was

differentiated into hepatocellular carcinoma (HCC), cholangiocellular carcinoma (CCC), and neuroendocrine carcinoma (NEC). And, the lesion of Segment 7 was mANEC which mixed cholangiocelluar carcinoma and neuroendocrine carcinoma. Although this is a very rare and interesting case, imaging is not well described. In these 2 lesions, details on contrast-enhanced dynamic CT and imaging on MRI (T1-weighted, T2-weighted, DWI, etc.) should be described in detail. Please explain the CT/MRI findings while comparing with the lesion distribution in the postoperative specimen as well.

We have included more detailed description of CT and MRI findings of the liver lesions, as well as PET/CT, chest CT, and Gallium-68 dotatate PET in the imaging examinations and discussion sections. Briefly, peripheral enhancement was seen on CT, and peripheral rim like enhancement on the arterial phase and persistent enhancement on the venous phase.

2) The patient underwent endoscopic resection for rectal carcinoids in 2012 and 2017. It cannot be denied that the origin of the present hepatic lesion is metastasis from rectal carcinoid. Therefore, the size of the endoscopically resected lesion and the presence or absence of vascular/lymphatic invasion should be described.

We have added more detailed history of patient's previous neuroendocrine tumors and interventions in history of past illness section. The patient's neuroendocrine tumor of the rectum was 1 cm, and there was no lymphovascular invasion noted.

3) The authors describe this case is intra-hepatic metastatic case. Please discuss in more detail about the mechanism of tumor and explain why the final diagnosis was metastasis rather than simultaneous occurrence or collision tumor.

We have summarized our thought process of why we believed the smaller tumor to represent a metastasis rather than simultaneous occurring tumor in the final diagnosis and discussion segments. Given the propensity of HCC to metastasize intra-hepatically, the relative size of the two masses (with the left lobe segment 4 mass being larger than the right lobe segment 7 mass), and findings of metastatic HCC to the portacaval lymph node, and the fact that both had neuroendocrine differentiation, the right lobe segment 7 mass was favored to represent an intra-hepatic metastatic focus of the larger segment 4 mass.

4) The authors describe that NEC has a worse prognosis than HCC, CCC, or mixed HCC-CCC. Why did they choose to treat CCC rather than NEC in postoperative chemotherapy? Since the histological diagnosis of lymph node metastasis that recurred after surgery was based on the CCC component, did they select GEM/CDDP therapy as adjuvant chemotherapy? Please mention which disease (HCC, CCC, NEC) was dominant in the resected specimen. Postoperative chemotherapy for NEC may have been the choice in terms of prognostic factors. Therefore, selection of chemo regimen for postoperative chemotherapy should be discussed in more detail.

We have added a more detailed discussion about the decision of palliative chemotherapy after detection of disease recurrence/spread following surgery in the discussion section, as well as included next generation sequencing results in the outcome and follow up section showing that no specific

targetable mutations were seen. In brief, palliative systemic therapy with cisplatin and gemcitabine was favored after disease recurrence and additional metastasis was detected.

4) Please create a table that summarizes the case reports so far after adding the following case. Clin J Gastroenterol 2014 Oct;7(5):449-54. doi: 10.1007/s12328-014-0521-3. Epub 2014 Aug 13. Primary hepatic neuroendocrine carcinoma with a cholangiocellular carcinoma component in one nodule Yoshihito Kano 1, Sei Kakinuma, Fumio Goto, Seishin Azuma, Yuki Nishimura-Sakurai, Yasuhiro Itsui, Mina Nakagawa, Atsushi Kudo, Minoru Tanabe, Susumu Kirimura, Tomonori Amano, Takashi Ito, Takumi Akashi, Yasuhiro Asahina, Mamoru Watanabe.

We have provided a table summarizing previous reported cases, including references to the original articles.

Response to reviewer #3

Specific Comments to Authors: Interesting case report. Some clarifications are however needed: 1) did the patient underwent octreoscan before or after surgery? If no explain why. If yes indicate the findings.

We have included the Gallium-68 dotatate PET scan that was performed in place of an octreotide scan in the imaging examinations and discussion sections. Gallium-68 dotatate PET scan is a widely accepted method for the detection of neuroendocrine tumors and their metastases, with higher reported sensitivity and specificity compared to octreotide scans.

2) was HCV eradicated?

HCV was not treated due to absence of fibrosis of the liver. We have included plans to start treating hepatitis C following surgical intervention in the further diagnostic work-up section.

3) How rectal neuroendocrine tumor was classified and managed? Did the patient receive adjuvant therapeutics after endoscopic resection?

We have added more detailed history of patient's previous neuroendocrine tumors and interventions in history of past illness section. Specifically, in a screening colonoscopy performed in 2012, a 1-centimeter polypoid lesion was seen in the rectum. This was removed endoscopically with saline injection and hot snare cautery. Review of the slides revealed a low grade, well differentiated neuroendocrine tumor ("carcinoid") with no evidence of lymphatic or vascular invasion. Resection margins were not able to be assessed on this excision pathologically. On subsequent colonoscopy in 2017, a more extensive endoscopic mucosal resection was performed in the region of the previously identified carcinoid, with final margins negative on pathologic examination.

The case report is poorly written. The titles of paragraphs are useless and confusing. CT scan results are never detailed. MRI result are incomplete: whether tumor washout was observed at the portal phase is not indicated.

The case report was formatted according to the requirements detailed in the World Journal of Clinical Oncology for case reports. We have included more detailed description of CT and MRI findings of the liver lesions, as well as PET/CT, chest CT, and Gallium-68 dotatate PET in the imaging examinations

and discussion sections. Briefly, peripheral enhcancement was seen on CT, and peripheral rim like enhancement on the arterial phase and persistent enhancement on the venous phase.

Management is intriguing: authors indicate that 'pathologic findings raised the possibility of metastatic disease at the time' but hepatic surgery was however decided and only staging laparoscopy was performed. What about extraabdominal metastases? FDG and Gallium-68 PET-scan are inadequate for that purpose.

We have included more points about the main differential diagnosis (HCC) in the further diagnostic work-up and discussion sections and included PET/CT, chest CT, and Gallium-68 dotatate PET in the imaging examinations and discussion sections that, in addition to the staging laparoscopy and a chest CT, were against any extra-abdominal metastases and would advocate for regional resection of the patient's liver lesions.

Finally the discussion is somewhat poor. Hypothesis regarding common molecular mechanisms involved in the 3 observed tumor differenciations, for instance, would have been interesting.

We have included **a more detailed discussion about molecular heterogeneity observed in similar cases, the next-generation sequencing results from our patient, and literature supporting a hepatic stem cell origin of cases of mixed hepatic tumors in the outcome and follow-up and discussion sections.**

A complete discussion regarding imaging would also have been interesting by explaining why the diagnisis of HCC, NET or cholangiocarcinoma monodifferenciated tumors could have been challenged.

We have included a more detailed imaging profile and a discussion of varying imaging findings in cases of mixed liver tumors in the imaging examinations and discussion sections.

4 LANGUAGE QUALITY

Please resolve all language issues in the manuscript based on the peer review report. Please be sure to have a native-English speaker edit the manuscript for grammar, sentence structure, word usage, spelling, capitalization, punctuation, format, and general readability, so that the manuscript's language will meet our direct publishing needs.

5 EDITORIAL OFFICE'S COMMENTS

Authors must revise the manuscript according to the Editorial Office's comments and suggestions, which are listed below:

(1) Science editor: 1 Scientific quality: The manuscript describes a case report of the hepatocellular carcinoma with biliary and neuroendocrine differentiation. The topic is within the scope of the WJCO. (1) Classification: Grade B, Grade C and Grade D; (2) Summary of the Peer-Review Report: This is a case report of a very rare liver tumor presenting with differentiation to HCC/CCC/NEC. As the authors described in the discussion, only few similar cases have been reported so far, and this is a very rare case report. It's very well written, but it's necessary to add a few more points. The questions raised by the

reviewers should be answered; and (3) Format: There are 1 table and 4 figures. A total of 15 references are cited, including 4 references published in the last 3 years. There are no self-citations. 2 Language evaluation: Classification: Two Grades B and Grade C. The authors are native English speakers. 3 Academic norms and rules: The written informed consent of treatment was not provided. No academic misconduct was found in the Bing search. 4 Supplementary comments: This is an unsolicited manuscript. No financial support was obtained for the study. The topic has not previously been published in the WJCO. 5 Issues raised: (1) The authors did not provide original pictures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor. 6 Recommendation: Conditional acceptance.

(2) Editorial office director:

(3) Company editor-in-chief: I have reviewed the Peer-Review Report, the full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Clinical Oncology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. Before its final acceptance, the author(s) must provide the Signed Informed Consent Form(s) or Document(s). For example, authors from China should upload the Chinese version of the document, authors from Italy should upload the Italian version of the document, authors from Germany should upload the Deutsch version of the document, and authors from the United States and the United Kingdom should upload the English version of the document, etc.

At time of preparation of case report, patient had passed away. However, utmost care was shown during the preparation of the case report to not reveal any personally identifiable protected health information. Also per the MedStar Office of Research integrity, case reports including 3 or fewer individuals do not meet the U.S. Department of Health and Human Services (DHHS) definition of research and therefore do not require Institutional Review Board (IRB) review but are still subject to Health Insurance Portability and Accountability Act of 1996 (HIPAA) requirements. No Protected Health Information (PHI) was disclosed during the preparation of the case report.