

Dear Prof. Wang,

Thank you very much for allowing us to revise our manuscript (Manuscript ID: 73012) entitled "Simultaneous multiple primary malignancies diagnosed by endoscopic ultrasound-guided fine-needle aspiration: A case report." We greatly appreciate editors and reviewers for their comments and suggestions. These comments and suggestions are valuable for improving our manuscript. All authors approve the revised manuscript for publication.

**Response to the reviewer's comments was as follows:**

**Reviewer #1:**

**1. Response to comment:** (In the text, you wrote "synchronized liver and pancreatic MPMs." According to the Warren and Gates definition, I would prefer that you use the word "synchronous.")

**Response:** Thank you for your suggestion. The word "synchronized" has been replaced by "synchronous" throughout the text.

**2. Response to comment:** (You defined: "Multiple primary malignancies (MPMs) refers to more than one primary malignancy in the same or separate organs of the same patient, and MPMs are considered when different histological or morphological characteristics are detected." I believe that the word "morphological" is misleading. I would propose to eliminate it.)

**Response:** Thank you for your suggestion. The word "morphological" has been eliminated.

**3. Response to comment:** (Was a preliminary transabdominal US examination performed? If so, please insert the images.)

**Response:** A transabdominal US examination was not performed.

**4. Response to comment:** (In the text, you never specify how exactly EUS-FNA was carried out. Was it FNAB (biopsy) or a FNAC (cytology)? Please specify carefully.)

**Response:** Thank you for your suggestion. It was FNAB (biopsy), and "EUS-FNA biopsy (EUS-FNAB) was performed" has been added in the "Imaging examinations" section.

**5. Response to comment:** (You wrote: "Three senior pathologists in our medical university confirmed that the considerable differences in immunohistochemical results indicated that the pancreatic mass and multiple liver nodules were not metastatic lesions from the other. The final diagnoses were listed as follows: 1. Simultaneous liver and

pancreatic MPMs; 2. Pancreatic pseudocyst". Why don't you specify the definitive histopathological diagnoses? Was it a pancreatic adenocarcinoma? or a NET? Please, specify it.)

**Response:** Thank you for your suggestion. "(Hepatic signet ring cell adenocarcinoma and pancreatic neuroendocrine tumor)" has been added following "Simultaneous liver and pancreatic MPMs."

**6. Response to comment:** (It should be mentioned how often MPMs metastasize to the liver, most commonly in colon tumors. This can be found in an article similar to the one proposed, which you must cite, emphasizing above all the aspect that liver lesions are more often considered metastases rather than primary tumors. -Corvino A, Corvino F, Radice L, Catalano O. Synchronous mucinous colonic adenocarcinoma and multiple small intestinal adenocarcinomas: report of a case and review of literature. Clin Imaging. 2015 May-Jun;39(3):538-42. DOI: 10.1016/j.clinimag.2014.12.019. Epub 2015 Jan 7. Reference: please, add the ones that I suggested you.)

**Response:** Thank you for your suggestion. "Liver lesions are more often considered metastases than primary tumors" has been added in the last paragraph of the discussion section, and the mentioned reference has also been added.

## **Reviewer #2:**

**1. Response to comment:** (Imaging showed multiple liver tumors. Authors need to describe the type of liver resection performed)

**Response:** Thank you for your suggestion. "Left liver resection" has been added in the treatment section.

**2. Response to comment:** (What was the final histopathology of the liver tumor as preoperative FNAC showed signet ring cells. If it is signet ring cell adenocarcinoma, whether a colorectal primary was ruled out)

**Response:** Thank you for your suggestion. The final histopathology of the liver tumor was signet ring cell adenocarcinoma, and his colonoscopy was negative. Both "the patient's colonoscopy was negative" and "hepatic signet ring cell adenocarcinoma and pancreatic neuroendocrine tumor" have been added in the text.

**3. Response to comment:** (What was the neoadjuvant chemotherapy given as the patient had different types of tumors in the pancreas and liver)

**Response:** Thank you for your question. Since the patient's liver lesions have a higher Ki-67 positive rate than pancreatic lesions, his liver lesions were considered his major problem, and his local doctors chose apatinib (500 mg, once per day). "Apatinib, 500 mg, once per day" has been added in the treatment section.

**4. Response to comment:** (Whether EUS-FNA of the liver had any advantage over percutaneous FNAC. The proposed advantage of EUS-FNA of the pancreatic lesion may not be applicable to the liver lesion)

**Response:** Thank you for your question. The diagnostic quality of EUS-FNA and percutaneous procedures were comparable for liver tumors, while EUS-FNA was often associated with fewer adverse events, including bleeding and pain. (**1.** Takano Y, Noda J, Yamawaki M, Azami T, Kobayashi T, Niiya F, Maruoka N, Norose T, Ohike N, Wakabayashi T, Matsuo K, Tanaka K, Nagahama M. Comparative Study of an Ultrasound-guided Percutaneous Biopsy and Endoscopic Ultrasound-guided Fine-needle Aspiration for Liver Tumors. *Intern Med.* 2021;60(11):1657-1664. DOI: 10.2169/internalmedicine.6183-20; **2.** Shuja A, Alkhasawneh A, Fialho A, Fialho A, Shukri A, Harris C, Smotherman C, Malespin M, de Melo SW Jr. Comparison of EUS-guided versus percutaneous and transjugular approaches for the performance of liver biopsies. *Dig Liver Dis.* 2019;51(6):826-830. DOI: 10.1016/j.dld.2019.01.006. )

**Response to the editorial comments was as follows:**

**Science editor:**

**Response to comment:** (Please add the type of hepatectomy, explain how EUS-FNA is performed, and specify a clear histopathological diagnosis of pancreatic pseudocyst.)

**Response:** Thank you for your suggestion.

(1) "Left liver resection" has been added in the treatment section.

(2) "A linear Pentax echoendoscope (Hoya co., Tokyo, Japan) and the color Doppler flow imaging were employed to determine the puncture site" and "EUS-FNA biopsy (EUS-FNAB) was performed with two 19-gauge needles (Boston Scientific co., Natick, American), respectively." have been added in the second paragraph of the "imaging examinations" section.

(3) The histopathological examination of the pancreatic pseudocyst revealed no tumor cells but lots of inflammatory cells and necrotic materials, and "post-necrotic pancreatic pseudocyst" has been added in the treatment section.

***Company editor-in-chief***

**Response to comment:** (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 Cases, 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 final acceptance, uniform presentation should be used for figures showing the same or similar contents; for example, "Figure 1 Pathological changes of atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: ...". 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.)

**Response:** Thank you for your comment. All figures have been prepared in PowerPoint as requested.

Once again, we would like to express our great appreciation to editors and reviewers for their comments and suggestions and hope that the revised manuscript will meet with approval. We sincerely appreciate your kind consideration of our manuscript, and we look forward to hearing from you at your convenience.

Best regards,

Jun-Wen Zhang