

Dear Editors and Reviewers:

Thank you for your letter and for the reviewers' comments concerning our manuscript entitled "Relapsed Primary extraskeletal osteosarcoma of liver: A Case Report and Literature Review" (ID: 80668). Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. We have studied comments carefully and have made correction which we hope meet with approval. Revised portion are marked in red in the paper. The main corrections in the paper and the responds to the reviewer's comments are as following:

Responds to the reviewer's comments:

Reviewer #1:

In this article, Qiu-Yi Di and colleagues report a rare case of primary extraskeletal osteosarcoma of liver. However, several issues need to be addressed:

1. Response to comment: In the abstract, there is a similar phrase in BACKGROUND and CASE SUMMARY. Authors must eliminate one of the sentences.

Response: I have re-modified the BACKGROUND and CASE SUMMARY sections.

2. Response to comment: The initial part of the Core Tip is exactly the same as the abstract.

Response: I have modified the Core Tip.

3. Response to comment: Page 4: "A 76-year-old male readmitted to the hospital due to abdominal distension and pain.". Please correct the sentence: "A 76-year-old male was readmitted...".

Response: Page 4: the statements of "A 76-year-old male readmitted to the hospital on 14 September 2020 due to abdominal distension and pain.

" were corrected as "A 76-year-old male was readmitted to the hospital on September 14, 2020, due to abdominal distension and pain.

4. Response to comment: How long after hospital discharge was the patient readmitted?

Response: About half a month. The patient was discharged on 30 August 2020 and readmitted to the hospital on 14 September 2020.

5. Response to comment: Page 4: "The patient wanted the mass removed". Was the surgery performed just because the patient wanted it? Was the case discussed in a multidisciplinary cancer group meeting? Why was a biopsy of the lesion not performed?

Response: The case was discussed in a multidisciplinary cancer group meeting, and the doctors agreed that the treatment plan of surgical resection was more beneficial to the patients, as did the patients and their families. And about the patient's biopsy of the lesion, we also had described in the part of History of past illness.

6. Response to comment: Page 4: "The cystic fluid was already lost, and the grayish-red and grayish-yellow solid area of the tumor was soft with a cut-fish-like surface." This sentence is repeated twice in the manuscript.

Response: We apologize for our negligence, we have removed one of the sentences.

7. Response to comment: Was the lesion completely removed in surgery?

Response: The patient underwent surgery for right hemihepatectomy, and the tumor has been completely removed during surgery.

8. Response to comment: Laboratory examinations - Other analytical tests should be mentioned, such as blood count, liver profile, coagulation function and other tumor markers.

Response: Page 5: "Laboratory tests indicated that inflammatory indicators were elevated, and CA-125 was slightly increased, suggesting poor liver and coagulation functions. In addition, alpha-fetoprotein (AFP) was 7.86 ng/ml (normal value 8.0 ng/mL), a hepatitis B virus (HBV) surface antigen test and hepatitis C antibodies were negative, and HBV-DNA was $<1.00\text{E}+02$ IU/ml." was added.

9. Response to comment: "The patient received capecitabine monotherapy and was discharged 34 days after surgery." and "Seven days after surgery, the patient died of multiple organ failure." Authors should better clarify each of the temporal events.

Response: As suggested by the reviewers, we added dates to each event.

10. Response to comment: "Considering that the patient had inferior vena cava compression, stenosis, and a large amount of ascites, stent implantation in the inferior vena cava and transcatheter arterial chemoembolization were performed." - This sentence refers to TREATMENT and not FURTHER DIAGNOSTIC WORK-UP.

Response: We have made correction according to the Reviewer's comments.

11. Response to comment: Has a bone scan or other bone-directed examination been performed?

Response: Because the patient's course of disease is too short, no bone scan or other bone orientation tests were performed.

Reviewer #2:

1. Response to comment: Discussion. Suitable but needs some more information about ESOS in the literatures. Examples: Number of the reported case or clinical study ? Just liver. %?

Response: We have re-written this part according to the Reviewer's suggestion.

2. Response to comment: About the tumor free margin of the resected specimen. This may be the reason of early recurrence.

Response: The patient underwent surgery for right hemihepatectomy, and the tumor has been completely removed during surgery.

Reviewer #3:

Primary osteosarcoma of the liver is rare entity with a dozen of cases documented in the literature. While often found in the soft tissue of the limbs, Di et al. presents a new case of this rare neoplasm in the liver of a 76-year-old

male. A CT scan show a liver enlargement with a giant cystic-solid mass. Pathological examinations reveal fibroblastic malignant cells producing lace-like osteoid matrix. The authors conclude that diagnosis of ESOS requires pathology and immunohistochemistry for confirmation. Overall, the report is well-written and provide useful clinical information regarding this rare type of cancer. However, I have some questions/comments as described below to improve the manuscript.

1. Response to comment: This report lacks comprehensive discussion regarding how this presented case is different from or similar to other previous reports of primary hepatic osteosarcoma.

Response: We have re-written this part according to the Reviewer's suggestion.

2. Response to comment: Primary osteosarcoma of the liver is previously diagnosed with cirrhosis. Is there information regarding this issue?

Response: We have added to the Discussion section, " This study reports a primary osteosarcoma occurring on the liver....." was added.

3. Response to comment: While several markers were examined for immunohistochemistry, the authors show a weak staining result of SATB2 as a main figure (Figure 4). What is the significance of expression of SATB2 in the tumor? The authors should elaborate their rationale of presenting this specific piece of evidence.

Response: We had added to the Discussion section, "In this study, immunohistochemistry suggested SATB2 (partially weak+) " was added.

4. Response to comment: For Figure 3, arrows and insets could be very helpful for readers to understand the histological descriptions provided by the authors in the figure legends.

Response: Thank for your suggestion, we had described below the picture.

5. Response to comment: 5. Image(s) of macroscopic view of the tumor should be included in the report potentially along with Figure 3.

Response: We had added the macroscopic view of the tumor.

6. Response to comment: Is there an examination of the tumor tissue from the

ESOS recurrence in this patient? This information could be helpful for future studies of this neoplasm.

Response: Unfortunately, the tumor tissue of the patient with ESOS recurrence was not examined.

7. Response to comment: Please indicate the meaning of red arrows presented in all figures in the figure legends.

Response: We have explained the meaning of the red arrow below the picture.

8. Response to comment: "The cystic fluid was already lost, and the grayish-red and grayish-yellow solid area of the tumor was soft with a cut-fish-like surface." This sentence was repeated twice (pg. 4).

Response: We apologize for our negligence, we have removed one of the sentences.

9. Response to comment: Correct the verb tense (the word 'continue') under "Treatment" section pg. 5.

Response: We have made correction according to the Reviewer's comments.

We tried our best to improve the manuscript and made some changes in the manuscript. These changes will not influence the content and framework of the paper. And here we did not list the changes but marked in red in revised paper.

We appreciate for Editors/Reviewers' warm work earnestly, and hope that the correction will meet with approval.

Once again, thank you very much for your comments and suggestions.

Yours,

sincerely,

Qiuyi Di