

## Answering Reviewers

Dear Editors and Reviewers,

Thank you very much for your letter and for the reviewers' comments concerning our manuscript entitled "Perioperative mortality of metastatic spinal disease with unknown primary: A case report" (Manuscript NO.: 57036, Case Report). The 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. Based on the instructions provided in your letter, we uploaded the file of the revised manuscript and a copy of the original manuscript with all the changes highlighted by using the track changes mode in MS Word.

Appended to this letter is our point-by-point response to the comments raised by the reviewers. The comments are reproduced and our responses are given directly afterward in a different color (red).

### **Responds to the comments of Reviewer #1:**

*The authors have reported a rare case of spinal metastases with unknown origin. This study not only provides a detailed analysis of the case, but also summarize a series of literatures describing this disease, which is very helpful for clinicians to understand this disease. The reviewer has three specific comments to the authors:*

#### **Response to Reviewer #1:**

Thank you very much for your review and your kind comments. We have answered each of your points below.

#### **Comment 1:**

*It's better to summarize clinical features of spinal metastases with unknown origin, these data can be retrieved from the reported literatures.*

#### **Response to Comment 1:**

Thank you for pointing out this weakness of our manuscript. According to previous studies, metastatic tumors from unknown sources are likely to retain the characteristics of their putative primary origin. Therefore, due to the large differences in the manifestations of tumors from different sources, as well as the low incidence and the lack of relevant research, it is difficult to summarize a set of precise clinical features for spinal metastases with unknown origin. After carefully reading of the reported literatures, we have summarized several gross signatures that are possible to depict this peculiar group of metastatic spinal diseases.

These summaries have been added in the discussion section of our manuscript. The revised text reads as follows: "Metastatic tumors from unknown sources are likely to retain the characteristics of their putative primary origins, therefore large differences in clinical manifestations are usually observed among patients with spinal metastases

from UPT[24]. Nonetheless, several common signatures can be retrieved from the reported literatures to depict this peculiar group of diseases: i) Rapid progression and early dissemination, which contribute to the unidentified origin and aggressive presentation[24]; ii) diversity of clinical and biological profiles due to the difference in origin[25]; iii) relatively poor prognosis as non-selective empirical therapy rather than targeted management is conducted[26]; iv) traditional diagnostic indicators including tumor markers and immunohistochemical activity may raise without any diagnostic or predictive value, and new methods such as NGS (next generation sequencing) may be suggested to improve diagnosis and prognosis[27].”

Comment 2:

*The reviewer suggested that the pathological images, CT-Imaging results and PET-CT Imaging results could be present in different figure, respectively.*

**Response to Comment 2:**

We appreciate your insightful suggestion. The original Figure 2 has been split into three figures (revised “Figure 1, 2 and 3”) according to your suggestion to present the CT-Imaging results, PET-CT Imaging results and pathological images, respectively.

Comment 3:

*Other important results, such as laboratory and immunohistochemical staining results, could be present as a table.*

**Response to Comment 3:**

Thank you very much for your kind advice. We have added an additional table (revised “Table 1”) to present the abnormal findings from laboratory and pathological examination according to your suggestion.

In addition, we have checked the content and format of our manuscript based on the Guidelines. Furthermore, according to the two issues raised by the Editorial Office, we have prepared and uploaded the approval document for the National Natural Science Foundation of China (No. 81702662) and the original figures in PowerPoint file.

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 highlighted by using the track changes mode in MS Word. We appreciate for Editors and Reviewers’ warm work earnestly, and hope that the correction will meet with approval.

Once again, we would like to thank you for taking the time to review our manuscript and look forward to meeting your expectations.

Sincerely yours,

Xiumao LI on behalf of the authors

Address: Department of Orthopedics, The Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang 310009, China.

Email: [simonzju@zju.edu.cn](mailto:simonzju@zju.edu.cn), [simonleepku@163.com](mailto:simonleepku@163.com)  
Tel: 86-571-87783533