

Dear Editor:

Thank you very much for your kind email of March 12, 2022 for the decision and comments to our submitted manuscript [Manuscript NO.: 73206]. We appreciate very much for the comments and criticisms by all three reviewers on our work.

The whole text has been revised based on the comments. We have very carefully repolished the language throughout the text. Furthermore, the manuscript has been reviewed by an English language editing service. The editing certificate has been uploaded as an attachment. As requested, all the amendments made to the manuscript text have been indicated in the text through the whole manuscript by highlighting (in blue paint and recorded by line and page number). The point by point revision for the manuscript was as follows.

Reviewer #1:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: The authors have conducted an interesting study to understand the clinical characteristics and outcomes of primary esophageal malignant melanoma. I have following comments regarding the manuscript.

1. How many patients underwent neoadjuvant therapy in this study? Is there any role of neoadjuvant therapy in this disease knowing that most patients have lymph nodal metastases at the time of diagnosis?

Reply:

Many thanks. None of the four patients who underwent treatment in our hospital were not received neoadjuvant therapy. For patients from literature review, there was only one patient who was documented received preoperative radiotherapy[ref. 25] As shown in Table 2, there were 16 patients who only underwent adjuvant therapy and only 4 patients were successfully followed up.

We described it in Table 4 and in the “Discussion” section (lines 477-492, page

16).

2. What does the high standard deviation in the overall and disease free survival indicate?

Reply:

Many thanks. The prognosis of patients with PMME was poor. About 60 percents patients were lived less than 12 months after diagnosed. We consulted statistician and re-calculated the data. It was not appropriate to use average \pm standard deviation to represent the overall and disease free survival time due to data were not normally distribution. We have revised it as median value in the manuscript.

3. Both figure 4 and table 4 provide the same information. One of them can be omitted.

Reply:

Thanks very much for your suggestion. We carefully rechecked the figure and the table. Figure 4 was retained and Table 4 was deleted.

4. Discussion section is too lengthy with repetition of results. It should be revised to make it more concise and comprehensive.

Reply:

Many thanks. We have revised the “Discussion” section to make it more concise and comprehensive.

5. How many patients underwent PETCT among the study patients? What is the role of PETCT in the management of this disease?

Reply:

Many thanks. None of the ten cases from our hospital underwent PET/CT. There was only one case enrolled from literature (Ref. 62) underwent PET/CT. The patients’ first symptom was pain on the right side of the head, and MRI revealed the possibility of multiple metastases. FDG-PET/CT showed lesions with high metabolic uptake in the

right frontal bone, bilateral acetabulum, bilateral cervical lymph nodes, and rectum, which were considered to be malignant lesions. PET/CT is currently considered to be the most sensitive method for the identification of metastatic lesions of solid tumors, which improves the diagnosis, staging, and treatment evaluation of tumors, and has a huge impact on patient management. We discussed it in detail in the “Discussion” section (lines 423-430, page 14).

Reviewer #2:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: Authors reported an article about the primary malignant melanoma of esophagus (PMME). The clinicopathological findings of ten cases with PMME treated in the Henan Provincial People’s Hospital were summarized. Moreover, English and Chinese literature that focused on Chinese patients with PMME from 1980 to September 2021 was reviewed and analyzed by univariate and multivariate analyses. STATUS: ACCETTABLE FOR PUBLICATION PENDING MINOR REVISIONS General considerations: This is an original article including a broad review of literature. The paper is well-written. The work is very interesting and the statistical analysis is good. There are only a few articles in literature about this topic, especially focusing on asian population. Although only 12 patients with PMME were retrieved in Henan Provincial Hospital from January 1990 to September 2021, the literature analysis is thorough and the teaching that can be learned from reading the article makes it extremely useful for spreading the concept of PMME.

1. However, more clarity is needed in the introductory phase on the type of article and how to set it up (original article + metanalysis or original article + review?). I recommend its publication, pending minor revisions.

Reply:

Thanks very much for your suggestion. The type of this present manuscript is “original article + literature review”. We described it clearly in the “title” and “Introduction” section ((lines 5-6, page 1; lines 131-135, page 5).

2. Abstract: In the abstract paragraph, the following concept is not clear: “A total of 290 Chinese patients with PMME were enrolled in the present study”. In the text I seem to understand that the records of only 12 patients with PMME were retrieved in Henan Provincial Hospital (from January 1990 to September 2021). Please, specify it better.

Reply:

Many thanks. There were 290 cases enrolled in the present study including ten from our hospital and 280 cases from literature. We described it in detail in the “Abstract” section (lines 76-77, page 3).

3. Paper On some aspects, the authors should address:

- 1) More clarity is needed in the introductory phase on the type of article and how to set it up (original article + metanalysis or original article + review?).

Reply:

Thanks very much for your suggestion. The type of this present article is “original article + literature review” We described it clearly in the “Introduction” section (lines 131-135, page 5).

- 2) In the Results paragraph you wrote: “Nine patients had an accurate preoperative diagnosis of PMME, and one was diagnosed with poor differentiated carcinoma”. If it is a poorly differentiated carcinoma, why is it included in the series?

Reply:

Many thanks. The remaining one diagnosed as poorly differentiated carcinoma by

biopsy pathology, was eventually diagnosed as PMME by postoperative pathology. We described it in the “Results” section (lines 215-217, page 8).

3) In the Discussion you wrote: “Even though some places in China are the high incidence area of esophageal cancer, there were fewer studies focused on Chinese patients with PMME compared with the Japanese and western populations”. Please, do not emphasize this aspect. I understand that the readers are predominantly asian, but WJCC is an international journal and would end up losing readers.

Reply:

Thanks very much for your suggestion. We have revised it in the manuscript.

4) It would be helpful if you briefly discuss about the melanoma involving mucosal surfaces other than the esophagus. You can refer to these two articles, which you need to cite: -Rectal melanoma presenting as a solitary complex cystic liver lesion: role of contrast-specific low-MI real-time ultrasound imaging. J Ultrasound. 2015 Oct 6;19(2):135-9. doi: 10.1007/s40477-015-0182-1. PMID: 27298643; PMCID: PMC4879010. -Anorectal mucosal melanoma. Oncotarget. 2018;9(9):8785-8800. Published 2018 Jan 2. doi:10.18632/oncotarget.23835.

Reply:

Many thanks. We have discussed mucosa malignant melanoma in the “Discussion” section (lines 370-372, page 13) and cited the two papers as ref. 128 and ref. 129.

5) Have you also investigated about the possibility of melanoma metastases? For example, to the liver. You could discuss this same article and do both at the same time: -Rectal melanoma presenting as a solitary complex cystic liver lesion: role of contrast-specific low-MI real-time ultrasound imaging. J Ultrasound. 2015 Oct 6;19(2):135-9. doi: 10.1007/s40477-015-0182-1. PMID: 27298643; PMCID: PMC4879010.

Reply:

Many thanks. Distant metastasis of PMME was not uncommon. There were 84 patients had local recurrence and distant metastasis documents. Both lung and liver were the most frequently organs involved. We described it in detail in the “Results” and “Discussion” sections (lines 322-332, page 11; lines 421-424, page 15) and Figure 4. The paper were cited the paper as ref. 128.

6) You need to discuss better about the role of imaging in the diagnosis of PMME.

Reply:

Many thanks. Multiple imaging diagnostic are used in PMME to evaluate primary cancer, metastasis and treatment responses. Endoscopic Ultrasound (EUS), computed Tomography (CT), magnetic Resonance (MRI) and positron emission tomography (PET) contribute to the information for diagnosis and management. We discussed it in detail in the “Discussion” section (lines 423-430, page 14).

7) Is this tumor histotype possibly associated with multiple primary malignancies? Discuss these articles and cite them. -Increased risk of second primary cancers after a diagnosis of melanoma. Arch Dermatol. 2010 Mar;146(3):265-72. doi: 10.1001/archdermatol.2010.2. PMID: 20231496; PMCID: PMC3076705. -Multiple primary tumours: challenges and approaches, a review. ESMO Open 2017; 2(2): e000172. doi: 10.1136/esmoopen-2017-000172. eCollection 2017.

Reply:

Many thanks. We discussed it in the “Discussion” section (lines 421-422, page 14) and cited the two papers as ref. 133 and ref.134.

8) A linguistic revision would be advisable. Try to search “Informoration” in the text.

Reply:

We apologize for this error. Our manuscript has been reviewed by Our manuscript has been reviewed by professional English language editing company.

9) Reference: please, add the ones that I suggested you.

Reply:

Many thanks. We have cited all those papers in the manuscript.

Reviewer #3:

Scientific Quality: Grade D (Fair)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: Primary malignant melanoma of the esophagus is a rare clinical entity, however, there are numerous case reports, case series and/or review papers published in current literature. Many of these papers are published by the research groups based in Asia. The assessed paper reviews 290 cases of Chinese patients with primary malignant melanoma of the esophagus. This indeed could be the largest study of the Chinese patients until now, which makes this manuscript more exclusive but mainly interesting only to the clinicians and/or researchers working in China and/or near by countries. Nevertheless, there are also some concerns regarding the scientific interest of the paper and quality of the manuscript:

1. - analysis reflects local clinical practices and provides little or no new information for the wider international circle of the readers;

Reply:

Many thanks. As discussed in the manuscript, PMME is a rare disease with aggressive behavior and poor prognosis. To date, majority of the existing studies were case reports. It is difficult to conduct a comprehensive retrospective study of patients with PMME. As we all known, some areas of China are the high incidence area of esophageal malignancy. The present manuscript is focused on Chinese patients with primary malignant melanoma of the esophagus (PMME). Previous studies[ref.130, ref.

131] were focused on Japanese and western population with PMME, respectively. Our results showed that the clinicopathological characteristics and prognosis of Chinese patients with PMME was similar with Japanese patients, but different from western population patients. We discussed it in detail in the “Discussion” (lines 382-388, page 13; lines 404-408, page 14; lines 439-445, 450-452, page 15).

2. - the title of the manuscript does not reflect that this is analysis is comprised of small case series (10 patients) and a literature review;

Reply:

Thanks very much for your suggestion. The type of this present article is “original article + literature review”, we revised the title to make it more clearly.

3. - case series itself is presented with very moderate quality and mainly serves the purpose of showing that the authors team have expertise in the field but the most interesting data comes from the literature review and combined analysis of all 290 cases;

Reply:

Many thanks. PMME is a rare disease. To date, majority of the existing studies were case reports. Our hospital is the second largest hospital in Henan province where is the high incidence area of esophageal malignancies. Case series might really limited, however, it represented the current situation of PMME in Henan province to a certain extent. The literature review focus on nationwide PMME patients, with the aim to investigate the clinic-pathological characteristics of this disease and try to provide some recommendation on the diagnosis and management of PMME.

4. - English language needs improvement.

Reply:

Many thanks. Our manuscript has been reviewed by professional English language editing company and revised to improve readability.

5. I would suggest include the cohort of 10 patients with the primary malignant melanoma of the esophagus (PMME) and present only the results of the whole pool of Chinese patients.

Reply:

Thanks very much for your suggestion. As reply to the question 3, PMME is a rare disease. To date, majority of the existing studies were case reports. Case series might really limited, however, it represented the current situation of PMME in Henan province to a certain extent. The literature review focus on patients with PMME nationwide , with the aim to investigate the clinic-pathological characteristics of this disease and try to provide some recommendation on the diagnosis and management of PMME.

6. Review all the tables and figures, and leave only essential and most informative because most of the information is extensively covered in text.

Reply:

Many thanks. We have revised the whole manuscript thoroughly to make it more concise and comprehensive.

7. Add some clinical tips & tricks, recommendation on the diagnosis and management of these patients in the context of international guidelines and local practices.

Reply:

Many thanks. The present study collected all Chinese PMME patients from literature, trying to investigate the clinic-pathological characteristics of this disease. Unlike esophageal cancer, PMME has its own unique clinical features.

The pathognomonic endoscopic finding of PMME is pigmentation. Our results showed that about thirty percents of PMME are amelanotic. The physician and endoscopist should enhance their awareness of rare diseases of the esophagus, particularly the early lesion, to avoid missed diagnosis and misdiagnosis. PMME prone to spread longitudinally, and recurrence is frequently soon after surgery. In addition, the frequency of LNM was as high as 45.3% even the primary tumor limited at the pT1b stage. Furthermore, the OS and DFS was poor, Both pT and LNM were the independent prognostic factors of PMME patients, pT stage was the independent DFS prognostic factor. Moreover, Our results showed that patients who received immunotherapy besides surgery and chemoradiotherapy tend to have better OS. These results suggested that PMME not only should be resection with adequate margins, but also extended lymph node dissection should be emphasized even the tumor at pT1b stage. Systemic treatment of PMME, including surgery, chemoradiotherapy, and immunotherapy, should be used to improve multidisciplinary treatments and outcomes for patients with PMME.

We discussed it in detail in the “Discussion” (lines 403-410, 431-436, page 13; 446-448, page 15 and 490-492, page 16).

8. Overall, the manuscript should be shortened significantly and more concentrated.

Reply:

Many thanks. We have revised the whole manuscript thoroughly to make it more concise and comprehensive.

EDITORIAL OFFICE’S COMMENTS

(1) Science editor:

Specific Comments To Authors: Primary esophageal malignant melanoma (PMME) is a rare disease. The authors explored the prognosis and related clinical features of the disease. The manuscript is well written and can be helpful for the readers to

ameliorate the diagnostic and therapeutic approach for this scenario. However, the author's own case data are few, most of which are second-hand data collected. Considering the impact of internationalization, I also suggest that the author briefly discuss melanoma involving the mucosal surface outside the esophagus. Scientific Quality:Grade C Language Quality:Grade B Recommendation:Conditional acceptance.

Reply:

Many thanks. We have discussed mucosa malignant melanoma in the “Discussion” section (lines 370-372, page 12).

(2) Company editor-in-chief:

I recommend the manuscript to be published in the World Journal of Gastrointestinal Oncology.

Reply:

Thanks very much for your suggestion.