

Response Letter

Dear Editor and Reviewers,

Thank you for your letter and for the reviewers' comments concerning our manuscript entitled "Research progress on reactive oxygen species production mechanisms in tumor sonodynamic therapy" (Manuscript ID:84498). Those comments are valuable for revising our manuscript. We studied comments carefully and made correction which we hope to meet with approval. Revised sentences are marked in red in the revised manuscript. 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:

1. The paper could be improved by including an oncologist in the author team, there are several points in the paper that could be improved.

Response: Thanks to your suggestion. Thank you very much for your advice. The corresponding author of this review is Professor Zhu Jiang, one of the leaders of the Zhejiang Provincial Key Laboratory of Precision Diagnosis and Therapy for Major Gynecological Diseases, who has profound research in ultrasound diagnosis and interventional treatment of gynaecological tumours, and currently has two National Natural Science projects related to the treatment of ovarian cancers. If you still think we need to add a specialist in oncology, we can also do that.

2. Please add more recent cancer statistics, we are already in 2023.

Response: We thank the reviewer for pointing out this issue. We have updated the cancer data and made changes in introduction to Cancer statistics, 2023 published in "CA: A cancer Journal for Clinicians" on January 12, 2023 and the National Cancer Center published the latest issue of national cancer statistics in "Zhonghua Zhong Liu Za Zhi" on March 22, 2023.

3. It would be advisable to state that cancer treatment requires various combinations of surgery, chemotherapy and/or radiotherapy rather than saying most cancers are treated by surgery followed by chemo&radiotherapy.

Response: Thank you very much for your advice and we agree with your views. Most malignant tumours are not treated by surgery followed by radiotherapy and chemotherapy, it can be said that the common treatment modalities for malignant tumours are different combinations of surgery, chemotherapy and/or radiotherapy. So in this article we introduced treatment of ovarian cancer, a common malignancy in women.

4. I think failure of cancer treatment arises from tumor recurrence and refractory disease or late presentations of patients with advanced disease rather than side effects of therapy.

Response: I strongly agree with you and have found the relevant literature to support this. Early symptoms of malignant tumours are atypical and detected late, tumour recurrence, resistance to therapeutic agents and systemic toxicity of treatment are all reasons for the failure of cancer treatment in patients.

5. Nitric oxide does not pertain to the ROS class, but to the reactive nitrogen species one

Response: Thank you very much for pointing out this error, we have corrected it in the article.

6. Have you obtained permission to reuse the figures? I did not see any agreement forms uploaded. Be aware that some publishers might require you ask for permission even if the papers are published in an open access format.

Response: Thank you very much for your advice, the figures were licensed and the agreement has been re-uploaded.

7. I think the content can be improved by preparing a table with all the cancers in which SDT was employed and the main findings.

Response: Thank you very much for your suggestions. I have added a table to the article to demonstrate the use of sonodynamic therapy in cancer.

8. Are there any ongoing/planned/previous clinical trials exploring the use of SDT in solid cancers?

Response: There are already applications of SDT in clinical solid cancers, with references to SDT in combination with PDT for advanced refractory breast cancer and SDT in combination with gemcitabine for advanced breast cancer in the review.

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 your warm work earnestly, and hope that the correction will meet with approval.

Sincerely yours

Prof. Zhu

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