

Dear editor,

Enclosed is a manuscript by Jin-Song Zhang et al. entitled “**Small-cell carcinoma of the prostate with negative CD56, NSE, Syn, and CgA indicators: A case report**”. We greatly appreciate the feedback and constructive comments from the editor and reviewers.

In our attempt to revise our manuscript, we believe that we have clarified all of the technical concerns raised by reviewers. We responded to the reviewer’s comments point-by-point. We strongly feel that the manuscript has improved with this revision following the critical, yet helpful suggestions offered by the editor and reviewers. Please find attached the revision, which we hope and believe meets the high standards of *World Journal of Clinical Cases*.

We hope that you are satisfied with our manuscript and will consider it for publication in *World Journal of Clinical Cases*. Thank you very much again for aiding in improving the overall quality of the paper and considering our paper for *World Journal of Clinical Cases*.

Sincerely,

Jin-Song Zhang

Reviewer #1:

Comment 1. These days, using the ^{68}Ga -PSMA PET is highly recommended for rare cases in initial stages for finding small lesions around the prostate bed or extra-prostate LN metastasis. Therefore, conventional imaging such as CT or MRI is not recommended only for initial imaging or staging of the patients. In your case, however; you provided the historical info about the patient but it seems that medical imaging for this case is not under updated scans (PET/CT).

AUTHOR RESPONSE: Good point, thank you for this suggestion. According to the Urological guidelines of China, CT, MRI, and whole-body bone imaging are allowed for prostate cancer staging, and ^{68}Ga -PSMA PET/CT is also recommended. We suggest that the patient receive ^{68}Ga -PSMA PET/CT to further detect small metastasies, but the patient and his family refused due to the high cost. Because PET/CT has not been covered by medical insurance in China. We also added this statement in the case presentation section. (also pasted below).

(please see “We strongly recommend that the patient use ^{68}Ga -PSMA PET/CT to look for small lesions around the prostate bed or extra-prostatic lymph node metastases. However, the patient and his family declined our offer due to the high cost.” in the case presentation-laboratory and imaging examinations section).

Comment 2. Regarding the developing of ^{177}Lu -PSMA-617 for treatment planning of metastatic prostate cancer patients, I think you have to focus on the new tracers which are FDA approved. Please check the below link for checking the results about the same case that the authors prepared it very perfectly not only for the initial imaging but for following under ^{177}Lu -PSMA-617 therapy (three or four cycle); <https://tech.snmjournals.org/content/jnmt/47/1/85.full.pdf>

AUTHOR RESPONSE: Thank you for providing such a good case as a reference. I have carefully read the literature provided by you, and also reviewed other literature related to the new tracers and ^{177}Lu -PSMA-617 therapy. We have added this

statement in the discussion section. (also pasted below).

(please see “The application of ^{68}Ga -PSMA PET/CT in the whole diagnosis of prostate cancer has developed rapidly, which plays a vital role in assisting clinical tumor staging. It can accurately detect local lesions, lymph node metastasis, and distant metastasis in prostate cancer, with high sensitivity and specificity. It can be found that the advantage is especially significant at a low PSA value ($< 0.5 \text{ ng/mL}$)^[21]. The patient described in this article refuses to undergo ^{68}Ga -PSMA PET/CT examination, when the patient's CT scan finds the lesions in the lung as a metastatic site, but we do not know about the function of the lesion. Rahul Parghane et al. used Dual-tracer (^{68}Ga -PSMA and ^{18}F -FDG) PET/CT in the case of metastatic SCCP, Interestingly, whereas metastatic SCCP transformed pelvic and penile lesions were nonavid with ^{68}Ga -PSMA but avid with ^{18}F -FDG. Therefore, the role of new tracer ^{18}F -FDG in metastatic SCCP should not be underestimated. The bone and pelvic lesions demonstrated a favorable response to a multimodal therapeutic approach (^{177}Lu -PSMA radioligand therapy and radiotherapy), a trend toward a decrease in PSA level^[22]. ^{177}Lu -PSMA radioligand therapy shows promising prospects for metastatic SCCP patients who progress after conventional therapy. For patients with metastatic SCCP patients that progress after chemotherapy, ^{177}Lu -PSMA radioligand therapy is expected to change the status quo of patients with short survival and poor quality of life ^[23]. ^{68}Ga -PSMA PET/CT is used to screen patients suitable for ^{177}Lu -PSMA radioligand therapy, and then ^{177}Lu -PSMA radioligand therapy for the suitable patients for targeted therapy, can intuitively and visually dynamic evaluation of efficacy. Tumor staging is carried out to realize the integration of diagnosis and treatment, which embodies the precision and personalized diagnosis and treatment concept of nuclear medicine. Despite urgent clinical needs, ^{177}Lu -PSMA radioligand therapy for metastatic SCCP has yet to be approved by FDA and the European Medicines Agency.

However, with the accumulation of global research data, it is expected to become an extension and complement to the clinical routine treatment of metastatic SCCP.” in the discussion section).

Comment 3. With no specific symptoms in the early stage, CT scan or another conventional imaging cannot find active masses from the body. It seems sometimes you find the lesions in the lung as a metastatic site but you do not know about function of the lesion. So it is not perfect for only focusing on the structural imaging for final decision on the interpretation.

AUTHOR RESPONSE: Good point, thank you for this suggestion. The patient's previous health examination did not find any pulmonary nodules. Combined with the patient's medical history and the prone to metastasis characteristics of small cell carcinoma of the prostate, we suspect that the newly emerging lung lesions may be tumor metastases, but we really cannot know about function of the lesion. Therefore in light of the reviewer's pertinent comments, we also added this statement in the discussion section.

(please see “The patient described in this article refuses to undergo 68Ga-PSMA PET/CT examination when the patient's CT scan finds the lesions in the lung as a metastatic site, but we do not know about the function of the lesion.” in the discussion section).

Comment 4. The images do not provide with good resolution and also the name of the patients must remove from the images without consent from patients. As an another point, please use the lung window for showing the involved masses. I kindly ask you please provide the more imaging data from the patient regarding the comments and then transfer to me for more discussion.

AUTHOR RESPONSE: Thank you for this suggestion. We have adjusted the resolution of the image, changed the image of the lungs to the lung window, and deleted the patient's information from the image. In addition, I added whole-body bone imaging, lung CT, abdominal CT, and prostate multi-parameter magnetic resonance images at different levels in the paper.

Thank you again for your contribution to improving the quality of the manuscript.