Peer Review File

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Reviewer A

Comment 1:

The author has commented how presurgical PSMA PET/CT increases the accuracy in predicting biochemical recurrence based on the study. However, the author has not mentioned if the study compares PSMA PET/CT with conventional CT imaging in detecting lymph node or distant metastases. To rebut EAU's guideline - "Treatment should not be changed based on PSMA PET/CT findings", it is imperative to demonstrate that the survival benefit is purely due to added PSMA PET/CT. i.e., the patients all had false negative N/M staging on conventional CT.

In addition, the author could also mention that PSMA PET/CT is able to capture false positives reported by conventional CT, thus affecting treatment plan.

Reply 1:
We thank the reviewer for his suggestions for improvement, all of which we have taken into account in the manuscript.

We added some data and have modified our text as advised

Changes in the text:
Page 2, line 1-24
Page 3, line 34-48
Page 4, line 57-70
Page 5, line 71-94
Page 6, line 97-118
Page 7, line 119-124

Reviewer B

Comment 1:
Although the chain of arguments is clear and sound in this commentary it misses the major point made by Gelardi et al. (Source no. 2): Higher diagnostic accuracy and sensitivity leds to a higher survival rate in both groups without affecting overall survival rate known as the so-called Will-Rogers phenomenon.

Reply 1:

We thank the reviewer for his suggestions for improvement, which we have taken into account in the manuscript.

To explain to the reviewer why we hadn't detailed it before: the reason is that our editorial stated that miN1/miM1 patients had a higher risk of PSAR than patients with miN0/miM0.

Of course, we have now addressed the point raised by the reviewer in more detail.

We added some data and have modified our text as advised.

Changes in the text:
Page 2, line 17-24
Page 4, line 61-70
Page 5, line 71-94
Page 6, line 97-118
Page 7, line 119-124

Comment 2:

I recommend expanding the section on the two mentioned trials on source 7 and 8 while shortening the section on the case reports. Both studies have significant higher level of evidence, are published in higher ranked journals, while listing case-reports could be seen as cherry-picking.

Reply 2:

We thank the reviewer for this suggestion, which we implemented in the manuscript.

We added some data and have modified our text as advised.

Changes in the text:
Page 6, line 97-104 / 105-114

Reviewer C

Comment 1:
The editorial commentary is concise and question the therapeutic decision based on PSMA PET imaging for primary staging of patients diagnosed with Prostate Cancer.

The authors start the text citing proPSMA trial that showed the PSMA superiority over conventional imaging to assess prostate cancer staging. I suggest adding a brief explanation about why PET PSMA is superior to conventional exams and what was the main staging modification: downstaging or upstaging.

Reply 1:

No response is required for this comment.

We thank the reviewer for his suggestions for improvement, which we have taken into account in the manuscript.

The main staging modification – from our point of view – is upstaging.

We added some data and have modified our text as advised

Changes in the text:
Page 2, line 3-9 / 17-21
Page 4, line 57-70
Page 5, line 71-94
Page 6, Line 97-104

Comment 2:

The EUA and also the AUA inquire about the influence of PSMA PET on the decision making based on the lack of prospective data about the patient's outcome.

Reply 2:

We thank the reviewer for the comment, which we have now incorporated into the manuscript by citing and commenting on three recent (one of them ongoing) prospective randomized trials (RCTs) for staging with PSMA PET/CT. Additionally, we cited and commented a prospective randomized controlled multicenter study.

We added some data and have modified our text as advised

Changes in the text:
Page 5, line 86-4
Page 6, line 97-118
Page 7, line 119-124

Comment 3:

The Djaïleb and coworkers objective study was "to assess the added prognostic value of presurgical PSMA-PET for BCR-FS compared with the presurgical Cancer of the Prostate Risk Assessment (CAPRA) and postsurgical CAPRA-Surgery (CAPRA-S) scores in patients with intermediate- to high-risk PCa treated with radical prostatectomy (RP) and pelvic lymph node dissection." It was not totally clear if the decision was based on PET imaging, although I believe

so, and the BCR incidence was 38% after a median follow-up of 2,5 years. This find agrees with the data before the molecular era when BCR were expected in up to 40% with prostate cancer treated with curative intent. Also, Djaileb and coworkers did not assess overall survival nor BCR free survival.

Reply 3:

We thank the reviewer for his suggestions.

The comparison given fits with the PSMA PET/CT findings were not used in decisions of treatment.

The authors focused on presurgical PSMA PET/CT for BCR risk assessment. As the reviewer notes, overall survival and BCR free survival were not considered in their (Djaileb et al.) study.

Comment 4:
My point is that if the authors intend to favor PMSA influence on the management decision other prospective studies that showed an increase on the BCR free survival should be pointed out otherwise the text would agree with the EUA and AUA orientation. So, another suggestion is to search and cite these prospective studies.

Reply 4:
We thank the reviewer for the suggestions for improvement, which we have now incorporated into the manuscript by citing and commenting on three recent prospective randomized trials (RCTs) for staging with PSMA PET/CT. In particular, an RCT, which is still ongoing, was also included in the work.

Additionally, we cited and commented a prospective randomized controlled multicenter study.

We added some data and have modified our text as advised.

Changes in the text:
Page 5, line 86-94
Page 6, line 105-118
Page 7, line 119-124

Comment 5:
Regarding the end of the title “To see clearly is not enough”, it seems that the reader may be confused about what the authors are standing for or are questioning.

Reply 5:
We thank the reviewer for this comment and have taken it as an opportunity to expand the title to provide more clarity for the reader (please see Page 1, Title).

(Background for the beginning "To see clearly is not enough": It was our intention to arouse interest in the topic with the title).

Changes in the text:

Page 1, Title

Comment 6:
The PSMA superiority over conventional exams may be ascertained in comprehensive guidelines such as NCCN where the panel does not feel that conventional imaging is a necessary prerequisite to PET since 2020. Also, the PSMA influence over management decisions is not discouraged, although they make it clear that we still need strong data about the outcome changing.

Reply 6:
We thank the reviewer for the suggestions. We conclude that PSMA PET/CT is the best imaging modality to point to positive sites of prostate cancer and that this information should be used for patient management.

To take the reviewer's suggestions into account, we included three recent prospective randomized trials (RCTs) for staging with PSMA PET/CT in the manuscript. Three RCTs are published and one registered RCT is ongoing.

Changes in the text:
Page 5, line 86-94
Page 6, line 105-118
Page 7, line 119-124

Comment 7:
So, maybe "too see clearly is still not enough" but it may be a matter of time.

Reply 7:
We thank the reviewer for this suggestion.

However, we relied on a corresponding statement in the manuscript by Gelardi et al. based. In this context, it would not be appropriate to change these words. As an addition, we have now added the words “It is the choice of action that counts” to the title (please see Page 1, Title).

Changes in the text:

Page 1, Title

Comment 8:
The authors end the text attesting that PET PSMA is the best imaging modality to evaluate prostate cancer patients, however, recommend caution during the therapeutic choice regarding the consequences of PSMA influence. This is a healthy exercise that all physicians should do before ordering an exam or procedure, but towards the strong data published about PSMA until today it seems that, in real life, as the authors pointed out in the text, there is no turning back from the molecular information influence.

Reply 8:
We thank the reviewer for his positive assessment of the value of PSMA imaging.

Comment 9:
With all that being said, I suggest reviewing the specific points cited above and clarify what the authors stand concerning the decision making based on PET PSMA findings.

Reply 9:
We implemented the reviewer's suggestions and examined all of his suggested changes and incorporated them into the manuscript.

Changes in the text:

Please see above

Reviewer D

Comment 1:

A commentary piece - opinion is a little unclear however I assume the authors are of the opinion that management decisions should be based on PSMA PET findings not conventional imaging.

I agree with the authors opinion.

Reply 1:

We thank the reviewer for his suggestions for improvement. We have now specified it in the manuscript.

The authors are of the opinion that management decisions should be based on PSMA PET findings not ONLY on conventional imaging.

The authors conclude, that PSMA PET/CT is the best imaging modality to point to positive sites of prostate cancer.

We added some data and have modified our text as advised.

Changes in the text:

Page 2, line 17-24
Page 4, line 61-65 / 68-70
Page 5, line 71-74 / 75-79 / 86-87
Page 6, line 97-116
Page 8, line 149-158

Comment 2:

I agree with the authors opinion. I think the conclusion should also talk about further studies to optimise treatment options:

- PSMA PET as a biomarker for timing of salvage rtx or systemic therapy

- PSMA PET for metastasis directed therapy.

Reply 2:

We thank the reviewer for the kind words and for his suggestions for improvement, which we have taken into account in the manuscript.

We added some data and have modified our text as advised.

Changes in the text:

Page 4, line 61-70
Page 5, line 71-94
Page 6, line 97-118
Page 7, line 119-124
Page 8, line 156-158
