Peer Review File

Article Information: https://dx.doi.org/10.21037/tau-22-708

Reviewer A

The study design is interesting. However, the study would benefit from randomization into conventional AS and PET-guided AS. This would certainly add significant value to the clinical significance.

Is stratification according to favorable intermediate risk and low risk planned?

REPLY

Thank you for your insights into our protocol paper. When we perform the analysis for this study, we will stratify according to risk to identify if PSMA-PET/CT has greater value in the higher risk group.

Please see changes in lines 254-255 to reflect this.

The inclusion criteria describe that patients who have an indication for AS can be included. How should patients who have only received a systematic biopsy be handled?

REPLY

Patients who have only undergone a systematic biopsy may still be enrolled in the trial as long as they fit the inclusion criteria. For these patients they will undergo a mpMRI and PSMA-PET within 3 months of confirmatory biopsy as per protocol as well as follow-up imaging at year 3-4.

The planned multicenter study is certainly interesting. However, randomization would be desirable, and stratification according to risk groups would also make sense.

REPLY

Thank you for your comments. We agree that randomization would be the most desirable study design, however given the relative prompt uptake of PSMA PET CT imaging in Australia, it would be difficult to accrue patients to the control arm as more and more patients are undergoing PET imaging within active surveillance (without prospective data to support it).

Reviewer B

This is a protocol of prospective study for adding PSMA-PET for initial screening of prostate cancer patients on active surveillance. PSMA is an emerging tool for prostate cancer diagnosis and staging, the authors aim to evaluate the additive value of PSMA to mpMRI.

The manuscript is well written and clear. However, I have minor comments on the protocol:

Exclusion criteria: should add cribriform pattern in the pathology details (as these are not typically eligible for active surveillance).

REPLY

Thank you for your comments. We have added cribiform pattern as an exclusion criteria. Please see lines 150-151

I suggest to do analysis for PSA level as well, for patients on active surveillance and correlate it with imaging findings.

REPLY

We plan to perform an analysis of PSA and correlate it with imaging findings. This will be performed as part of a multivariate nomogram we plan to develop which will aid in predicting the likelihood of pathologic progression. Please see lines 266-269

PSA level should be added to active surveillance eligibility criteria as well.

REPLY

Thank you for you comment. In initial drafts of our protocol we included a PSA level for eligibility criteria. However, we decided to remove these as we believe that PSA alone could exclude some patients who would be suitable for active surveillance such as a PSA of 10-15 with a large prostate with a volume of >100cc. Moreover, extensive baseline evaluation (biopsy, mri and PET) might open the door to patients with high PSA levels (PSA density levels) being enrolled to a period of active surivellance as we are nowadays better to rule out significant disease outside the standard biopsy template.

In the discussion authors should address the accuracy of biopsy and impact of this on the results of the study.

REPLY

We agree that the accuracy of prostate biopsy will impact the results of this study. Biopsy only samples a small proportion of the prostate and thus there is a possibility to miss progression of cancer. As part of the study, we will provide surgeons with PSMA-PET/CT images to allow for targeting of possible lesions and encourage MRI targeting of lesions to further improve the accuracy of biopsy and detection of progression.

Please lines 358-362.

Cost effectiveness study is planned per study protocol. But I prefer to add it to the discussion too. Adding PSMA to mpMRI for patients on surveillance will add significant cost for the patients and insurance.

REPLY

We have added discussion regarding the need to assess the cost effectiveness of PSMA. PSMA may incur significant costs to patients and healthcare systems and thus the benefits must outweigh the cost to make PSMA viable.

Please see lines 367-369