Role of Prostate-Specific Membrane Antigen-Positron Emission Tomography in Metastatic Prostate Cancer: We have the answers

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Running head: PSMA: We have the answers
Then He said to Thomas “Put your finger here; see my hands. Reach out your hand and put it into my side. Stop doubting and believe.” John 20:27

A recent commentary from Sartor et al.(1) questions the use of PSMA-PET imaging for selection criteria for PSMA targeted therapy, commenting on the newly published outcome of patients with PSMA-PET/CT screen failure by VISION trial criteria(2). In addition, the comments by Hussain et al.(3) regarding the role of PSMA-PET in patients with metastatic hormone sensitive prostate cancer (mHSPC) have added to the controversy. Both commentaries require a response with our main points of concern below:

**Personalized Medicine**

Targeted therapy intends to selectively hit tumor cells expressing the specific target. In contrast to many novel targeted therapies that rely on a single tissue sample, PSMA-PET which serves as a companion diagnostic for PSMA radioligand therapy (RLT), displays *in vivo* the presence of PSMA expression in all detected tumor lesions. The likelihood to benefit from PSMA-RLT is clearly higher in patients with more PSMA-avid metastases(4). While careful investigation of the benefit of PSMA-RLT in PSMA-PET negative patients indeed warrants further formal testing, questioning the predictive value of PSMA-PET in mHSPC ridicules the concept of precision oncology.

**Misguided conclusions**

Many worthy points are made including an emphasis on patient quality of life and that medicine is an art where management decisions integrate physical exam, laboratory, imaging and other
data with clinical judgement. We also wholeheartedly agree with the statement that management discussions should be had with an interdisciplinary group, often including the image interpreting physician(3). However, this does not tally with Hussain and colleagues’ conclusions that,

“Outside clinical trials, our shared recommendation is that there is little utility currently for the routine use of PSMA-PET in patients with detectable metastases on CIM and recommendations regarding therapy should be based on CIM findings.” We do not see how this conclusion was drawn nor the methodology used to build this recommendation after citing works that demonstrate that PSMA-PET imaging is more sensitive compared to CIM(5) with fewer false-positive and equivocal findings at a lower radiation dose, which are the relevant measures for a diagnostic test. Additionally, PSMA-PET has a per node specificity of 99%(6) and has been convincing shown to lead to major patient management changes in the hands of experienced genitourinary oncologists(7–10). Furthermore, PSMA-PET is predictive of freedom from progression in men undergoing salvage radiation therapy for biochemical recurrence following radical prostatectomy(11). Given these advantages and regulatory approval, it seems bizarre to guide therapy decisions based on less accurate tests. This is akin to managing lung cancers using chest x-rays instead of computed tomography.

Fear of Overdiagnosis

One of the arguments made was that with a more sensitive imaging modality, more micrometastases will be found, leading to upstaging and over-treatment, with possible declines in quality of life, without a proven survival benefit(3). We agree that more long-term studies evaluating survival differences with PSMA-PET compared to CIM are needed, although not without challenges(12). However, one must consider that a higher specificity leads to fewer
harms caused by the false-positive results of CIM. In the ProPSMA study sensitivity analysis, when equivocal imaging findings were considered positive, the false-positive rate of CIM was an alarming 23%(9). Curiously, the authors then go on to contradict their first point of avoiding upstaging, by adding that despite the higher sensitivity of PSMA-PET, micrometastases could be missed (false-negatives) and that curative adjuvant therapy should not be withheld based on a negative PET(3). The claim therefore is that PSMA-PET is too sensitive and not sensitive enough!

*Stage Migration*

Hussain and colleagues’ state that replacing CIM with PSMA-PET/CT is likely to cause stage migration. However, we believe that stage migration and the study biases it may produce should be distinguished(13). Stage migration is a consequence of the introduction of any new (and usually better) classification technique due to higher sensitivity. This is counterbalanced by improved specificity with the overall impacts being unknown, requiring further study. The authors do not make this distinction or note that biases potentially caused by stage migration need to be considered in trial designs, instead suggesting that the Will Rogers effect is a reason against replacing CIM with new techniques(3).

To conclude, for the diagnosis of high-risk prostate cancer, localization of biochemical recurrence, and for PSMA treatment selection, the most accurate diagnostic method should be used— PSMA-PET/CT. This principle is accepted by multiple international guidelines. The opportunity to study both the benefits and detriments of PSMA-PET use remains open.
Bibliography

1. Sartor O. Invited Perspective, Outcome of patients with PSMA-PET/CT screen failure by VISION criteria treated with 177Lu-PSMA therapy: a multicenter retrospective analysis. 2022.


