Editorial: assessment of ⁶⁸Ga-PSMA-11 PET accuracy in localizing recurrent prostate cancer, a prospective single arm clinical study: California shows the way!

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The article by Fendler *et al.* published in *JAMA Oncology* (1) confirms many previous studies of the prostate cancer imaging agent, ⁶⁸Ga-PSMA-11 PET in the setting of biochemical recurrence (BCR). Like many before it, this study demonstrates the high sensitivity of PSMA PET/CT and PET/MR for detecting sites of disease in the post-treatment BCR setting. However, unlike almost all previous papers it is a large prospective study (n=635) conducted at two US centers (UCSF and UCLA) with carefully controlled eligibility and quality controls. Even with these enhancements, it suffers from the inability to histologically validate most of the PET findings but it provides the highest-level evidence to date for ⁶⁸Ga PSMA-11 PET. In spite of all the care that went into this study and the strict adherence to modern guidelines for prospective trials compared to trials before it, the results largely reproduce those of far-less controlled studies published over 4 years ago at multiple German centers. While much criticism has been leveled at the anecdotal nature of these first studies, in fact, the field of prostate cancer imaging owes a huge debt of gratitude to these early pioneers of PSMA imaging at numerous German and Australian academic centers who demonstrated the spectacular results that we have all come to expect from PSMA PET and directly led to this study in two California academic centers. Nonetheless, in order for PSMA PET imaging to proceed in the United States, studies of this quality will be necessary to secure FDA approval.

What do we learn from this study? One facet of PSMA PET imaging that makes it different from the validation of PET imaging in other cancers where no reliable serum biomarker exists, is that prostate specific antigen (PSA) is routinely used as a stand-in for disease recurrence. Indeed, the existence of PSA gives rise to a distinct subcategory of disease in prostate cancer, BCR. It is well accepted that PSA levels above 0.2 ng/mL constitute BCR, however, routine imaging like bone scan and CT are almost always negative at low PSA values. However, PSMA PET is highly sensitive to recurrence even at these levels. In previous large studies the range of detection rates using PSMA PET/CT for patients with PSA in the range 0.2–0.5 ng/mL was from 46–57% (2-4). The Fendler study had a slightly lower detection rate of 38%. Similarly, for the next PSA strata, 0.5–1.0 ng/mL, detection rates have varied from 58–73%, with this study coming in at 57%, again slightly lower than previously reported. In the group with PSA values between 1.1–2.0 ng/mL the range is 72–93% and this study comes in comfortably in the middle of that range at 84% and for patients with PSA >2.0 previous studies report detection rates of >85–96% and this study comes in at 86%. Why might the detection rates be lower for the same PSA strata in California *vs.* Germany? One possibility is the rigid criteria applied to the prospective trial *vs.* the more flexible rules of a retrospective trial particularly with regard to the multi-reader nature of the study. Also, differences in the timing of surgery relative to the natural history of the

cancer in two different medical systems could play a role. Although this is purely speculative it is possible that patients in the US are operated on at a slightly earlier point in the course of their disease than in Germany with the result being slightly lower detection rates at recurrence.

Of course, these differences raise the very interesting question: why do PSMA PET detection rates vary with PSA? PSA likely reflects tumor burden and lower PSA would indicate a lower (sub-detectable?) volume of disease. But there is also a wide range of PSMA expression across a range of tumors. Some tumors that are high expressors of PSMA may be detected at lower PSA values whereas low expressors may require larger volumes of tumor (and higher PSAs) to be detected. Why PSMA is expressed in prostate cancers is unknown but there are several threads of data emerging that PSMA expression may reflect tumors with growing metabolic demands (5). Moreover, PSMA is negatively controlled by androgen receptor (AR). The expression of PSMA in Gleason 6 and many Gleason 7 tumors is lower than tumors of higher grade. Very low grade tumors tend not to express it (6) but also very high grade tumors, or tumors suppressed by androgen deprivation therapy (ADT) also do not express PSMA. Thus, slight changes in the severity of disease at the time of surgery in the study population could influence outcomes for cancer detection when using PSMA PET.

There is another interesting and potentially problematic finding from this and several other prior studies that will require further study. Why is it that PSA doubling time appears to make no difference in terms of cancer detection on PSMA PET? PSA doubling time has proven to be an excellent prognostic marker for patients with BCR with shorter doubling times strongly implying a worse prognosis, specifically progression to metastatic disease. The lack of correlation between PSMA uptake and PSA doubling time suggests PSMA uptake alone will not be prognostic for outcome. Instead, the combination of tumor burden seen on PSMA PET and other biochemical factors like PSA doubling time may be necessary to predict outcomes. Currently, when the recurrence site is discovered on PSMA PET there is usually a rush to treat. However, some caution is warranted since PSMA uptake per se may not predict poor outcomes.

Does PSMA PET provide insight into the way prostate cancer metastasizes? This is one of the first imaging methods that gives a whole-body view of disease progression in prostate cancer. At first glance the occurrence of nodal and bone disease at various PSA strata shows no defined pattern. On further reflection one can discern that nodal disease tends to appear earlier than bone disease and as PSA increases there is a steady increase in bone and node + bone disease. Although this is not the first study to report this pattern it raises interesting biologic questions regarding how prostate cancer spreads. Bone disease appears later than nodal disease. Is this because bone disease is simply slower to materialize or is it that nodal disease should precede bone disease? Most oncologists agree that bone disease is more lethal than nodal disease. As the disease progresses, nodal disease rarely becomes a predominant feature of the disease whereas bone disease often relentlessly progresses. Is nodal disease self-limiting? Is nodal disease a precursor for bone disease or is nodal disease a completely separate process with different lineage from bone metastases? These questions are important as they bear on how vigorously the PSMA findings should be pursued from a treatment perspective. Now that PSMA is becoming available and the location of these lesions can be reliably ascertained it should be possible to address whether nodal and bone disease are clonal or independent. If nodal disease leads to bone disease, then it is important to treat to the maximal extent possible nodal disease as it appears. If nodal disease is independent of bone disease than the focus should be on preventing bone metastases and if that is not possible, limiting them. The answers to these questions will require much more analysis of biological tissue than is currently being done but the greater availability of PSMA PET may lead to such studies in the future.

This study is also of note because of the unusually large number of readers (n=9) that took part. It should be noted that the readers are among the luminaries in the field and are far from neophytes but it is comforting to see that the degree of inter-reader agreement was good to excellent and far exceeds what is seen with multiparametric MRI of the prostate (7). Detection rates varied from 70–91% with PPVs of 0.82–0.97. This is a very acceptable range and bodes well for the reliability of PSMA PET outside of highly specialized academic centers, but of course, this needs to be tested with novice readers as well.

PSMA ligands can be labeled with ^{68}Ga or ^{18}F. ^{18}F-DCFPyl is the most commonly used of the ^{18}F labeled compounds. Few studies have compared the two different types of agents (8). The most important difference is the half-life of the two isotopes with ^{68}Ga having a 68-min half-life and ^{18}F having a 110-min half-life. The shorter half-life makes ^{68}Ga-labelled compounds more difficult to deliver from a central facility due to loss of activity. As a result,

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[68]Ga-labelled compounds are often made on-site requiring a ^{68}Ga generator and a radiopharmacist, whereas ^{18}F-labeled compounds can be delivered ready to inject. It will be interesting to see whether one or another or both of these two "flavors" of PSMA PET prevails. Although, the two types of agents are generally considered equivalent, several trials have suggested that ^{18}F-DCFPyl has a higher cancer detection rate in BCR especially for low PSA patients than has been reported for ^{68}Ga-PSMA-11 (8,9).

Finally, a number of false positives and negative PSMA PET findings were discovered. For local recurrences, a common false positive was midline urethral urine activity simulating a lesion. Since PSMA-11 is excreted into the bladder and because urinary continence can be an issue in post-operative patients, this is not unexpected. Care should be used when interpreting local recurrence in the midline of the prostate bed. Among 635 patients there were 8 false negative cases. It's likely the true number is higher but false negatives, by their nature, are very hard to detect. Interestingly, about half of the false negatives showed PSMA uptake >3.3 SUV and therefore, may constitute interpretive errors that are potentially correctable. Local recurrences and seminal vesicle recurrences accounted for about half the false negatives with nodes accounting for only 2/8 false negatives. However, a good dose of humility is always warranted when interpreting medical imaging especially one based on a new agent. In one case of a 1.3 cm lung metastasis, the PSMA scan was negative. Although an unusual occurrence, it is important that we always leave open the possibility that as the disease advances, PSMA expression may decrease or be absent. This may not occur uniformly across all metastases but could reflect tumor heterogeneity across metastases. The absence of uptake in many cases of neuroendocrine phenotypic prostate cancer suggests that AR independent disease may pose challenges for PSMA PET. This opens the possibility of additional PET agent to detect lesions not detectable by PSMA PET.

Thus, this study confirms that PSMA PET is an excellent tool for detecting the sites of disease in patients with biochemical recurrence. PSMA PET far exceeds the performance of bone scan and CT and hopefully, as PSMA is introduced more widely, it will replace conventional imaging. The study shows excellent interobserver variation at least among expert readers and a small false negative rate some of which may be interpretative. Nonetheless, PSMA PET is not a perfect imaging tool and false positive and negative results were found. Hopefully, this study and others to follow will reach the necessary benchmarks for speedy approval of PSMA PET imaging by the FDA in the United States and around the world and encourage more work on understanding what PSMA uptake is trying to tell us about prostate cancer biology.

Acknowledgments

Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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