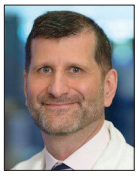
PROSTATE CANCER IN FOCUS

Current Developments in the Management of Prostate Cancer

Section Editor: Andrew J. Armstrong, MD

The Use of PSMA PET/CT Imaging as an Endpoint in Clinical Trials of Prostate Cancer



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H&O In what clinical situations is the use of prostate-specific membrane antigen positron emission tomography/computed tomography (PSMA PET/CT) imaging well established?

MM There are 3 approved indications for PSMA PET/CT. First, it can be used as a routine staging study for men with newly diagnosed prostate cancer who are at elevated risk of having metastatic disease. Second, it is approved to establish the extent and location of disease in patients who have relapsed disease as evidenced by a rising prostate-specific antigen (PSA) level. This is especially relevant in men who have had primary therapy with surgery or radiation, and now have a rising PSA level. PSMA PET/CT is frequently the only imaging modality that can detect disease in this circumstance, when the PSA can be quite low, and there is a window of curability if the clinician knows where the disease is and can apply the appropriate treatments. Indeed, in both indications PSMA PET/CT is the most accurate radiologic study for illuminating disease extent and location relative to any other single imaging modality. As a result, PSMA PET/CT has largely supplanted the previous methods used to assess disease extent and location, such as CT and bone scans.

The final routine use of PSMA PET/CT is to establish which patients with metastatic disease are candidates for treatment using the theranostic agent lutetium 177 (^{177}Lu)-PSMA-617 (Pluvicto, Novartis). ^{177}Lu-PSMA-617 is presently approved for men with metastatic castration-resistant prostate cancer that has progressed through androgen deprivation therapy and an androgen receptor pathway inhibitor in both the prechemotherapy and postchemotherapy settings. PSMA PET/CT is used to establish that these patients' cancers express PSMA and is a highly useful biomarker to indicate the likelihood of benefiting from therapy.

What has not yet been established is the use of PSMA PET/CT to assess response to treatment. We do not know how to use PSMA PET/CT in the context of demonstrating the anticancer effects of therapy, or of demonstrating treatment failure. We also do not know what component of PSMA PET/CT is the most closely associated with clinical benefit. For example, it could be the intensity of the PET/CT component, including some measure of the standardized uptake value (SUV; in which case we do not know what threshold of change should best define response), or it could be the total avid tumor volume (in which case we do not know the degree of change that represents a response). By the same token, these same measures could be used to define progression, and the same questions would stand. Or perhaps something simpler, such as new lesions, would represent progression rather than a change in SUV or tumor volume. These are all open questions.

H&O How might PSMA PET/CT imaging response or progression be used as an endpoint in clinical trials?

MM PSMA PET/CT is the most accurate single imaging modality for assessing prostate cancer. It also can directly assess the tumor in bone, the primary site of metastatic disease, and has the potential to reflect changes resulting from treatment—whether favorable or unfavorable—much earlier and more accurately than traditional imaging modalities such as bone scintigraphy because it is a direct measure of the cancer. Plus, because it fuses information about disease biology in the PET, and disease dimensionality in the CT, it contains more information about soft tissue disease than changes in size alone. The technology represents untapped potential to assess whether a drug is having an effect on disease or not.

The challenge that we face as a field is how to recognize this potential. We need to identify candidate biomarkers that are features of PSMA PET/CT, such as SUV changes or changes in disease volume or burden. We then need to credential those biomarkers by incorporating serial PSMA PET/CT studies into clinical trials and comparing these endpoints with clinical endpoints. Clinical endpoints are generally clinically meaningful events, such as longevity, how patients feel, or how patients function.

We conducted this credentialing process for bone scintigraphy as part of the Prostate Cancer Clinical Trials Working Group (PCWG) 2 and 3 guidelines.[1,2] We proposed a semiquantitative biomarker for defining disease progression by bone scan (which is based on developing 2 new lesions on a bone scan) and tested that endpoint in large phase 3 trials involving thousands of patients, showing that the PCWG definition correlated with overall survival. We now need to repeat that same process using PSMA PET/CT as an imaging technique.

H&O What are the potential advantages of using PSMA PET/CT over conventional imaging for measuring treatment response in prostate cancer?

MM Prostate cancer metastasizes primarily to the axial skeleton. Bone scans are not as accurate as we would like them to be because they do not visualize the disease directly—they look only at the changes in surrounding bone rather than the tumor itself. They change slowly and often yield spurious results. For example, when a patient responds well to a therapy, the bone scan can worsen (or "pseudoprogress") because of increased bone metabolism due to healing bone. Cross-sectional imaging techniques such as CT and magnetic resonance imaging tend to work poorly in metastatic prostate cancer because much of the disease occurs in the bone rather than in the soft tissues. As a result, Response Evaluation Criteria in Solid Tumors (RECIST) does not apply to most prostate cancers, and when the criteria do apply, it is generally to a small component of a patient's overall disease.

We developed the PCWG3 recommendations[2] to standardize a definition of progression for bone metastases and to credential that definition as an intermediate endpoint for regulatory approval of drugs. This effort was conducted using imaging technology far inferior to PSMA PET/CT. We are now developing PCWG4 guidelines to address this medical need, to standardize how PSMA PET/CT will be utilized, and to start asking the questions needed to credential it as an imaging endpoint. PSMA PET/CT provides a good opportunity to improve this imaging because it can directly visualize prostate cancer in bone, nodes, and viscera, and reflects changes that can be measured fully quantitatively.

> Physicians are beginning to order PSMA PET/CT scans when patient PSA levels begin to rise, so it makes sense to incorporate those scans into clinical trials.

PCWG4 will propose preliminary definitions regarding which posttreatment changes seen on PSMA PET/CT might be candidates for development as endpoints in clinical trials. This document should be published shortly. We then need for scans to be piggybacked onto clinical trials, so we can compare the results of conventional imaging with those of PSMA PET/CT and see how they correlate with outcomes. As soon as we can get to a true credentialed PSMA PET/CT–specific definition of progression and response, we can dispense with the use of older technology, such as bone scans.

H&O What are the challenges with using PSMA PET/CT imaging as an endpoint for the approval of new therapies?

MM The challenges are both scientific and practical. The scientific challenge, as I have described, is that we do not yet have a definition of what defines progression and response. The practical challenge is getting PSMA PET/CT incorporated into clinical trials, embraced by sponsors, and paid for as part of the research costs of a given clinical trial. This is a somewhat different scenario from when we

were developing the use of bone scans and CT, both of which were simple to build into clinical trials because they were standard imaging modalities that were reimbursed.

H&O Do scenarios exist where PSMA PET/CT might not be an appropriate endpoint?

MM PSMA PET/CT has the potential to be used across the full spectrum of prostate cancer. It is very good at detecting early and late disease, both of which involve PSMA expression. However, not all lesions within a patient are PSMA-avid, and not all patients have PSMA-avid disease. In particular, patients who have neuroendocrine differentiation tend to have lesser degrees of PSMA avidity and greater heterogeneity. Neuroendocrine disease historically has been imaged with ^{18}F-fluorodeoxyglucose PET but new modalities that are far more specific for neuroendocrine features such as Delta-like ligand 3 (DLL3) are now in development for both imaging and theranostic radioligand therapy.

H&O Can you comment on the recent Standardised PSMA PET/CT Analysis and Reporting Consensus (SPARC) publication?

MM Many groups have been working on various aspects of PSMA PET/CT reporting across the globe, such as how to report the routine findings on a PSMA PET/CT scan. Another example is how to use PSMA PET/CT to describe staging, because sometimes PSMA PET/CT can pick up findings not otherwise seen on other imaging modalities. These discrepant findings need to be incorporated into tumor, node, metastasis (TNM) staging schema in a way that is appropriate for the imaging modality. SPARC is an effort of international experts representing a variety of disciplines—radiation oncology, medical oncology, nuclear medicine, and radiology, among others—to create criteria for reporting results.[3] The goal is to bring some uniformity to what otherwise has been a heterogeneous, unconnected group of efforts.

H&O Are any ongoing studies looking at some of the questions you have been asking?

MM Many studies have begun to incorporate PSMA PET/CT into the standard imaging algorithms for clinical trials, and discussions with regulatory agencies have already begun in terms of thinking about how those scans should inform the results of the clinical trials. For example, studies of localized disease are starting to use PSMA PET/CT to detect the development of metastatic disease. Physicians are beginning to order PSMA PET/CT scans when patient PSA levels begin to rise, so it makes sense to incorporate those scans into clinical trials.

H&O Could PSMA PET/CT imaging be used to select patients for clinical trials beyond ^{177}Lu-PSMA-617 therapy?

MM There are an increasing number of PSMA-directed therapies. Some are in the radioligand family of therapeutics. These include the alpha-emitting radioligand therapies, commonly using Actinium-225 or Lead-212. New Auger emitters that are PSMA-directed are under development as well. PSMA T-cell engagers and PSMA-directed chimeric antigen receptor T-cell therapeutics are also being developed. Finally, PSMA-directed antibody-drug conjugates are being tested. Some or all of these trials may benefit from patient selection using PSMA PET/CT.

Even beyond clinical trials of PSMA-directed therapies, PSMA PET/CT will play a key role in eligibility criteria for future trials, as it can detect otherwise occult metastatic disease in patients who have localized or biochemically relapsed prostate cancers. These patients represent a new kind of trial candidate. New treatment paradigms will need to be developed for patients who have metastatic disease by PSMA PET/CT that is otherwise undetectable.

Disclosures

Dr Morris is a paid consultant for Lantheus, AstraZeneca, Daiichi, Convergent Therapeutics, Pfizer, ITM Isotope Technologies, Clarity Pharmaceuticals, Blue Earth Diagnostics, POINT Biopharma, Telix Pharmaceuticals, Progenics Pharmaceuticals, Z-Alpha Therapeutics, Ambrx, Flare Therapeutics, Fusion Pharmaceuticals, Curium, TransThera Biosciences, Bristol Myers Squibb/Celgene, Arvinas, Wren Laboratories, Isotopia, Actinium Pharmaceuticals, AdvanCell, and Artbio. He receives institutional research funding from Corcept Therapeutics, Janssen, and Novartis.

References

1. Scher HI, Halabi S, Tannock I, Morris M, Sternberg CN, Carducci MA, et al. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. *J Clin Oncol.* 2008;26(7):1148-1159.

2. Scher HI, Morris MJ, Stadler WM, et al; Prostate Cancer Clinical Trials Working Group 3. Trial design and objectives for castration-resistant prostate cancer: updated recommendations from the prostate cancer clinical trials working group 3. *J Clin Oncol.* 2016;34(12):1402-1418.

3. Herrmann K, Walz J, MacLennan S, et al. SPARC: The standardised prostate-specific membrane antigen positron emission tomography/computed tomography analysis and reporting consensus: a Delphi analysis [published online September 12, 2025]. *Eur Urol.* doi:10.1016/j.eururo.2025.08.005.