

PROSTATE CANCER IN FOCUS

Current Developments in the Management of Prostate Cancer

Section Editor: Andrew J. Armstrong, MD

PSMA PET/CT for Staging and Treatment of Prostate Cancer



Michael Hofman, MBBS, FRACP, FAANMS, FICIS
Professor of Molecular Imaging
Peter MacCallum Cancer Centre
The University of Melbourne
Melbourne, Australia

H&O What is prostate-specific membrane antigen (PSMA), and what makes it a good target for staging and treatment in prostate cancer?

MH PSMA is a glycoprotein that sits on the surface of prostate cells and is heavily upregulated in prostate cancer, especially in metastatic and castration-resistant disease. PSMA expression also occurs in the gut and kidneys, but at very low levels. It was first identified as a neurotransmitter in the brain, so it does have a signaling function. It is also a folate hydrolase receptor, so in the gut, for example, it allows folate to be transported into the circulation after ingestion of food.

Although the exact function of PSMA in prostate cancer is not well elucidated, it is a good target for staging and treatment because it is highly overexpressed in this cancer compared with normal tissues—an increase of 1000-fold or even 10,000-fold.

H&O What types of PSMA tracers are currently being used in clinical research and practice?

MH PSMA tracers are small molecules that bind to the PSMA receptor. The one that is in most widespread use around the world is ^{68}Ga -PSMA-11, in which gallium-68 is the radioactive carrier and PSMA-11 is the small molecule that binds to the receptor. Two other similar molecules are also gaining in popularity, ^{18}F -DCFpYL and ^{18}F -PSMA-1007. ^{18}F -DCFpYL, which was developed at Johns Hopkins and is being commercialized by Progenics, is easier to make in large quantities than ^{68}Ga -PSMA-11

because fluorine-18 has a slightly longer half-life than gallium-68. ^{18}F -PSMA-1007, which was developed in Heidelberg, Germany, is another small molecule that binds to fluorine rather than gallium.

Those are the main tracers that are currently used in positron emission tomography (PET)/computed tomography (CT) scans in prostate cancer, and they all perform extremely well. The quality of the images is very similar, so the decision to use one over another is largely dependent upon local availability.

H&O What is the role of PSMA PET/CT in initial staging of prostate cancer?

MH PSMA PET/CT has a high sensitivity and high specificity compared with conventional imaging techniques such as computed tomography, bone scanning, and magnetic resonance imaging (MRI; Figure).

As the radiotracer is taken up by the prostate cancer, it lights up on the scan and allows us to identify the disease not only in the prostate gland, but also in the lymph nodes and distant metastases. The resolution is exquisite. For example, a PSMA PET/CT scan can detect disease as small as 3 mm across in the lymph nodes, which is not possible with conventional imaging.

In addition to its sensitivity, PSMA PET/CT provides high specificity. For example, a bone scan might detect a sclerotic lesion that appeared to be a metastasis but could be caused by a bone island or degenerative disease. With PSMA PET/CT, in contrast, benign lesions that otherwise might look like prostate cancer do not light up.

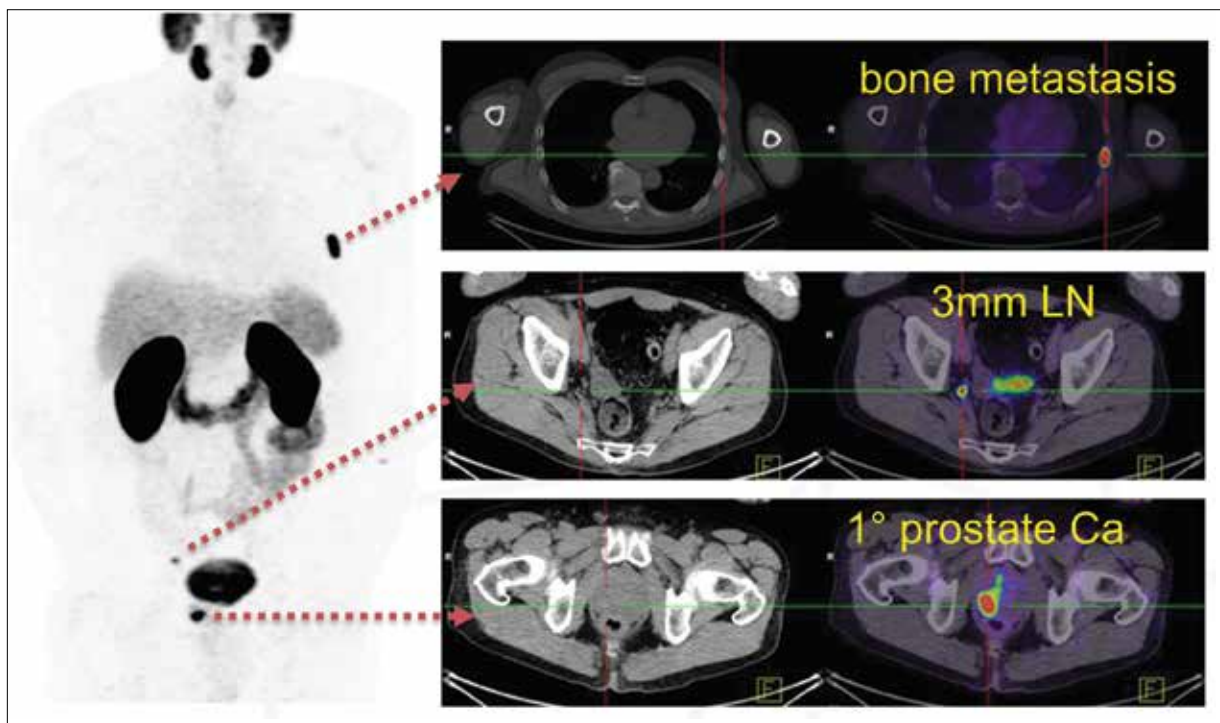


Figure. Patient with Gleason 9 (5 + 4) prostate cancer and normal computed tomography, bone scan, and pelvic magnetic resonance imaging. The patient was scheduled for a curative-intent prostatectomy. ^{68}Ga -PSMA-11 positron emission tomography/computed tomography demonstrated intense uptake in the primary site, a subcentimeter right pelvic lymph node, and a rib metastasis, changing the stage from N0 M0 to N1 M1b.

LN, lymph node; PSMA, prostate-specific membrane antigen.

H&O What is the role of PSMA PET/CT for staging of recurrent disease and metastatic disease?

MH Conventional imaging is poor at picking up early biochemical recurrence in men with low prostate-specific antigen (PSA) levels, such as those between 0.2 and 2.0 ng/mL. With PSMA PET/CT, it is possible to visualize abnormalities located in the prostate bed and locoregional lymph nodes, as well as those that have spread distantly—particularly throughout bones—even when PSA levels are very low.

H&O Has PSMA PET/CT been used to determine response to focal or systemic therapy?

MH Although PSMA PET/CT has not been used much to determine response to focal therapy, it has begun to play a role in determining the response to systemic therapy, including hormone therapy and chemotherapy. Preliminary data suggest that PSMA PET/CT is better than conventional imaging because it allows us to look

directly at changes in the tumor rather than changes in structure that are surrogates of response. Using a bone scan to differentiate between a healing response and progressive disease can be difficult because bone may become more sclerotic as it responds to treatment.

H&O What is the heterogeneity of PSMA expression in prostate cancer across disease states, and could this limit PSMA PET/CT detection?

MH More than 95% of early high-risk prostate cancers have high PSMA expression, and PSMA PET/CT is a very useful test in these patients. But changes in PSMA expression can occur as the disease progresses, particularly after multiple lines of therapy. In very aggressive disease, which transforms to a small cell, neuroendocrine, or poorly differentiated phenotype, PSMA expression can be lost and some sites of disease will no longer light up on PSMA PET/CT.

This is a potential limitation of PSMA PET/CT after several lines of therapy, so we need to interpret the scans

in the clinical context and in conjunction with other imaging findings.

H&O How is PSMA PET/CT being used to direct focal and systemic therapies for metastatic prostate cancer?

MH PSMA PET/CT can be used to identify sites of disease in the setting of biochemical recurrence, in which patients frequently have small-volume disease sites or oligometastases. These sites can then be targeted with stereotactic radiotherapy, salvage surgery, or other forms of targeted ablation therapy. This targeted treatment usually leads to a decrease in the PSA level and can allow the clinician to delay the use of androgen deprivation therapy, which produces side effects that many patients find objectionable.

The role of PSMA PET/CT in guiding therapy is less clear in the setting of metastatic disease, with the exception of therapies that specifically target PSMA. If metastatic prostate cancer has a high expression of PSMA, it will be more likely to respond to a PSMA-directed therapy. These PSMA-directed therapies, which include ^{177}Lu -PSMA-617, are evolving. The ^{177}Lu -PSMA-617 molecule is similar to what is used for the PET/CT scan, but the type of radiation is changed from gallium-68 or fluorine-18, which are positron emitters, to lutetium-177, which is a beta emitter. This is taken up into the tumors, with the beta energy traveling approximately 1 mm and depositing high-energy particles, much like external-beam radiotherapy, but in an “internal” targeted form.

^{177}Lu -PSMA-617 is an evolving therapy that appears to be highly effective for treating metastatic disease, as we described in a study published in *Lancet Oncology* in 2018. For this single-center trial, we administered up to 4 cycles of ^{177}Lu -PSMA-617 to 30 patients whose disease progressed after docetaxel chemotherapy and novel anti-androgen therapy. The trial was subsequently expanded to 50 patients. A PSA response of greater than 50% was observed in 64% of patients. Rapid symptomatic improvement often occurred in patients with bone pain. Disease eventually progressed in all patients, with the dominant pattern being marrow progression.

Two multicenter randomized trials are currently comparing ^{177}Lu -PSMA-617 with conventional or standard therapies. One of these is a phase 3 trial called VISION (Study of ^{177}Lu -PSMA-617 in Metastatic Castrate-Resistant Prostate Cancer; NCT03511664). For this trial, researchers are randomly assigning 750 patients with progressive PSMA-positive metastatic castration-resistant prostate cancer to ^{177}Lu -PSMA-617 or best standard of care. All participants must have cancer that has progressed after treatment with a taxane plus either abiraterone

acetate or enzalutamide (Xtandi, Astellas). I hope to see this trial lead to approval of this product and widespread availability.

Another pivotal trial, which began before VISION, is the Australian phase 2 TheraP trial (A Trial of ^{177}Lu -PSMA617 Theranostic Versus Cabazitaxel in Progressive Metastatic Castration Resistant Prostate Cancer; NCT03392428) that I have been chairing. This 200-patient, multicenter trial is comparing ^{177}Lu -PSMA-617 with cabazitaxel (Jevtana, Sanofi-Aventis) chemotherapy. So far we have recruited more than three-quarters of the patients, and we hope to see our first results in 2020.

A few other forms of PSMA-targeted therapies are in earlier development than the radioactive approach with lutetium. One of these is using a bispecific antibody that targets PSMA; some early phase 1 clinical trials are under way in that domain. We are also seeing early phase 1 studies related to the use of chimeric antigen receptor (CAR) T cells against PSMA.

H&O What are the side effects of targeting PSMA with ^{177}Lu -PSMA-617?

MH The treatment is very well tolerated, and in general, quality of life improves if there is a response to therapy. The most common side effect is dry mouth, which is usually grade 1 and is not treatment limiting. Grade 3 thrombocytopenia, which is attributable to the radiotracer, occurs in approximately 10% to 15% of patients. Blood platelet counts can be slow to recover in these patients, delaying the next cycle of therapy. Radiation can result in delayed toxicities. Renal toxicity also may occur, especially if the treatment is used earlier, because the radiotracer is renally excreted—although clinically significant renal toxicity is rarely seen. A possible uncommon but significant side effect is secondary myelodysplasia or leukemia, which is now documented with ^{177}Lu -dotatate (Lutathera, Advanced Accelerator Applications) for treating neuroendocrine tumors; this, however, has not been observed to date with ^{177}Lu -PSMA-617.

H&O What is the evidence to support the clinical utility of PSMA PET/CT beyond standard imaging for recurrent prostate cancer after local therapy?

MH PSMA PET/CT has largely evolved as a diagnostic imaging test performed as a standard of care after conventional imaging. Although this test has become widely available in countries including Australia and Germany, where clinicians are finding it significantly superior to conventional imaging, it has not gone through prospective randomized trials. There is an ongoing debate on

the rationale or need for randomized trials for imaging agents—they are not treatments, and the results can be directly compared with conventional imaging. PSMA PET/CT imaging is not readily available in the United States because the radiotracers are not approved by the US Food and Drug Administration (FDA). This approach has the advantage of encouraging high-quality research toward the goal of FDA approval. In some other countries, radiotracers made within a hospital radiopharmacy are less regulated and can be used without specific approvals. PSMA radiotracers are given in microgram quantities, so no physiologic or adverse effects are expected. PSMA radiotracers have been given to hundreds of thousands of patients globally, and no side effects have been reported.

In the setting of biochemical recurrence, an extensive body of research has shown that the sensitivity of PSMA PET/CT is substantially better than that of conventional imaging. A large meta-analysis published in *European Urology* earlier this year confirmed this based on data from several thousand patients.

The trickier question is whether this improved accuracy changes patient management and outcomes. We do have evolving evidence that PSMA PET/CT results change management. For example, the field for external beam radiation therapy may be altered after the test is performed. Whether this improves patient outcomes is yet to be determined, although logic suggests that targeting disease more accurately will improve outcomes.

Regarding the use of PSMA PET/CT for staging of high-risk prostate cancer, a number of trials are under way around the world. We are running a 10-center trial called ProPSMA (A Prospective Randomised Multi-Centre Study of the Impact of Ga-68 PSMA-PET/CT Imaging for Staging High Risk Prostate Cancer Prior to Curative-Intent Surgery or Radiotherapy; ACTRN12617000005358) in which we have randomly assigned 300 patients with high-risk prostate cancer and a Gleason grade group of 3 or higher to PSMA PET/CT or conventional imaging prior to curative-intent surgery or radiotherapy. We hope to present the results in early 2020 in order to determine how PSMA PET/CT affects accuracy and management. We are also looking at health economics, variability among the scans, and how the radiation dose from the scan differs from that of the conventional approach.

In the United States, Progenics is running several late-phase trials looking at ^{18}F -DCFPyL for staging and detection of biochemical occurrence, including CONDOR (Study of ^{18}F -DCFPyL PET/CT Imaging in Patients With Suspected Recurrence of Prostate Cancer; NCT03739684).

H&O How does ^{18}F -fluciclovine PET/CT compare with PSMA PET/CT?

MH ^{18}F -fluciclovine (Axumin, Blue Earth Diagnostics) is a PET radiotracer that has become quite popular in the United States since its FDA approval in 2016. It can be used for staging and also in the setting of biochemical recurrence. Although ^{18}F -fluciclovine sometimes gets confused with PSMA PET/CT, it is quite different. Fluciclovine is a radiotracer that images amino acid metabolism; it does not target PSMA. The uptake intensity of fluciclovine is not as intense as PSMA, and is more similar to choline PET. I anticipate that ^{18}F -fluciclovine PET will fall out of favor as soon as a PSMA PET/CT radiotracer is approved by the FDA.

Disclosure

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Suggested Readings

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