# EDITORIAL

## The Agony and Ecstasy of Prostate Cancer PSMA PET

In December 2020, the FDA approved Gallium-68 PSMA-11 (Ga-68 PSMA-11) PET in the management of prostate cancer. The approval is based on multiple studies that indicate Ga-68 PSMA-11 PET is sensitive and highly specific in the detection of prostatic metastases even with very low serum PSA levels.

Prostate specific membrane antigen (PSMA) is a transmembrane glycoprotein overexpressed on most prostate cancer cells. Many news sources, including the FDA, declared that this was the "First PSMA-Targeted PET Imaging Drug for Men with Prostate Cancer". While true for PET scans, this is not the first PSMA targeted nuclear imaging agent. ProstaSinct (Indium-111 capromab pendetide) was previously approved based on a PSMA target to detect metastatic disease.[1] Technically, this was a SPECT (Single Photon Emission Computed Tomography) nuclear imaging technique, relying on gamma emitting isotope detection merged with CT. However, the ProstaSinct target was an intracellular epitope of PSMA (7E11), only exposed in dead or dying cells. There were concerns of false positive intra-abdominal adenopathy that also contributed to the decline in ProstaSinct use. This new family of small molecule urea based PSMA ligands, such as PSMA-11, target the extracellular PSMA domain and are linked to a radiolabeled moiety such as Gallium-68. This approach relies upon PET (positron emission tomography) detection fused with CT for both functional and anatomic localization.

There are many reasons to celebrate the FDA approval of Ga-68 PSMA-11 PET. Standard "everyday" PET scans using F-18 FDG (Fludeoxyglucose) have not been useful for prostate cancer except in some cases of castrate resistant disease due to the relatively low prostate cancer metabolism. Several other prostate cancer specific PET scans, often referred to as "next generation imaging" are currently available including C-11 (Carbon-11) choline, and F-18 (Fluorine-18) fluciclovine. These both target different metabolic abnormalities present in prostate cancer cells. However, these agents have limitations. First, they are only approved for use in the setting of recurrence following local therapy. Ga-68 PSMA-11 PET is now approved for use before definitive local therapy to rule out metastasis as well as in the evaluation of prostate cancer recurrence. In addition, C-11 Choline PET has limited availability due to the fact the isotope has a very short half-life (20 minutes) and a cyclotron-based C-11 isotope production site must be near the imaging facility. A benefit of this new approval is that Gallium-68 does not require a cyclotron, has a relatively longer half-life (68 minutes) and can be synthesized by a local generator. For completeness, 18-F-NaF (sodium fluoride) PET should also be noted as a prostate cancer related PET, but it is used primarily for skeletal imaging of metastases.

An exciting approach to treat prostate cancer is using theragnostics, an approach that combines imaging with treatment. This is novel therapy is dependent on PSMA PET localization.[2] Using PSMA targeting, it is possible to deliver toxic radioactive therapies using beta emitters such as Lu-177 (lutetium) PSMA-617. This is showing promise as a treatment for metastatic castration resistant prostate cancer. Two theragnostic trials using this radioligand approach (TheraP and VISION) have fully accrued and preliminary data from these and other early studies suggest both safety and efficacy.

What are the challenges with Ga-68 PSMA-11 PET? The most obvious is the limited availability at only two California sites. The FDA approval was only for institutional use at the University of California, Los Angeles (UCLA) and the University of California, San Francisco (UCSF) under an academic new drug application (NDA). It is hoped that other US sites will begin the application process to offer this PSMA PET imaging elsewhere outside of any currently available clinical trials. While many experts have called Ga-68 PSMA-11 a "game changer", this limited access can curb enthusiasm for this breakthrough test. PSMA PET has been widely available in Australia and many European countries for several years.

Interpretation of a PSMA based PET scan is not as simple as it may first appear. Although PSMA is commonly associated with prostate cancer, other tumor types such as gastric, colon, thyroid and kidney cancer can express high PSMA levels as can some normal tissues such as salivary glands.[3] Not all prostate cancers have elevated PSMA with subtypes such as high grade disease, neuroendocrine and ductal prostate cancer may not show significant uptake owing to variation in PSMA expression.

Another issue is that there is not just one generic PSMA PET scan. Ga-68 PSMA-11 (note the designation of this agent as "PSMA-11") is the first one approved in the US for use at UCLA and UCSF. Sometimes it feels like you need a score card to keep up with the current PSMA PET literature. PSMA-11 is also referred to in the literature as HBED-CC PSMA, and was originally developed in Germany. Also in the investigational phase are other PSMA related agents: DCFPyl, PSMA-617, and J591, to name just a few. Just when you thought PSMA was the ultimate PET agent for prostate cancer, one recent paper indicated that there are at least 60 registered studies pertaining to the use of PET tracers in prostate cancer with dozens completely unrelated to PSMA targeting.[4] Another evolving prostate cancer PET imaging agent to be aware of is Ga-68 DOTATATE which is useful to detect well-differentiated neuroendocrine tumors. Studies suggest this tracer uptake is higher in mCRPC patients with neuroendocrine or BRCA mutations, potentially filling a role for non-PSMA expressing prostate cancers.[5]

Can the ability of PSMA PET to detect the earliest stages of metastasis have unintended consequences on current standards of care? Will this new technologic advance be disruptive to current clinical trials designs that use standard CT, MRI and bone scan as entry criteria? Almost all recent clinical trials for prostate cancer have relied on this standard imaging approach. Introducing PSMA PET into routine clinical practice may suddenly reclassify a patient's disease state for a trial or otherwise alter standard clinical care pathways based on trials that used standard imaging. As a specific example, multiple androgen receptor pathway blockers have been approved for M0 prostate cancer using CT and bone scan. Using PSMA PET might cause the M0 space to suddenly "shrink" as metastasis are detected earlier with patients re-classified to stage M1. The utility of these medications and the clinical trials that supported their approval might suddenly be problematic if PSMA PET use becomes routinely used for M0 disease.

As always, when new technology is approved, which insurance carriers will pay for this PET imaging will be determined as more patients with different coverages are tested. Another unknown is will the new PSMA PET improve patient outcomes?

PSMA PET technologies are a major step forward in the management of prostate cancer. However, while we celebrate this advance and new applications such as PSMA based theragnostics become available, we also need to be aware of its limitations. Beyond the current US access issues, it is not clear if the newly approved Ga-68 PSMA-11 will prove to be the best or will other PSMA targeting agents be superior. PSMA uptake is not exclusively prostate cancer specific and can be taken up physiologically and pathologically in non-prostatic tissue. Interpretation of PSMA PET scans may require expertise similar to what is now being recognized for the optimum interpretation of studies such as prostate multi-parametric MRI. The real benefit of this next generation PSMA imaging should become obvious once it is available to more prostate cancer patients across the US.

*Leonard G. Gomella, MD*
*Editor-in-Chief*
*Philadelphia, PA, USA*

References

1. Mohammed AA, Shergill IS, Vandal MT, Gujral SS. ProstaSinct and its role in the diagnosis of prostate cancer. *Expert Rev Mol Diagn* 2007;7(4):345-349.
2. Abou D, Benabdallah N, Jiang W et al. Prostate cancer theranostics - an overview. *Front Oncol* 2020;10:884.
3. Shetty D, Pate D, Le K et al. Pitfalls in Gallium-68 PSMA PET/CT interpretation—a pictorial review. *Tomography* 2018;4(4):182-193.
4. Fraum TJ, Ludwig DR, Kim EH et al. Prostate cancer PET tracers: essentials for the urologist. *Can J Urol* 2018;25(4):9371-9383.
5. Bilen MA, Akintayo AA, Abiodun-Ojo et al. The role of 68Ga-DOTATATE for evaluation of patients with metastatic castration-resistant prostate cancer (mCRPC). *J Clin Oncol* 2020;38(Suppl 6):217.