Asian Journal of Andrology (2021) 23, 1–2
www.asiaandro.com; www.ajandrology.com

Open Access

INVITED RESEARCH HIGHLIGHT

Erectile Dysfunction

# The emerging role of prostate-specific membrane antigen (PSMA) PET-CT in patients with high-risk prostate cancer: moving the bar in high-risk prostate cancer

**Jeanny B Aragon-Ching**

*Asian Journal of Andrology* (2021) **23**, 1–2; doi:10.4103/aja.aja_35_20; published online: 24 July 2020

**The proPSMA trial is a Phase III multicentric trial that examined the role of gallium-68-prostate-specific membrane antigen (PSMA)-positron emission tomography/computed tomography (PET/CT) scan versus conventional CT and bone scan to determine the presence of distant disease prior to curative-intent treatment with surgery or radiation for men with high-risk prostate cancer. The findings showed the superiority of PSMA PET/CT scan with 27% better accuracy and sensitivity at 92% versus conventional CT and bone scans, which yielded 65% ($P < 0.0001$). Further subgroup analyses showed that PSMA PET-CT was better in detecting pelvic nodal metastases at 91% versus 59% (32% absolute difference; 28%–35%), and in detecting distant metastases at 95% versus 74% (22% absolute difference; 18%–26%). In addition, the use of gallium-68-PET/CT scan also led to changes in the management of patients for curative intent surgery or radiation. In summary, the role of gallium-68-PET/CT scan has evolved and is very promising in the primary staging of high-risk prostate cancer.**

Prostate cancer is the most common noncutaneous cancer among American men. While early-stage prostate cancer is typically treated with curative-intent surgery or radiation, it is also well established that early treatment affords cure in most patients. However, men with high-risk prostate cancer while making up only 15% of men diagnosed with prostate cancer,[1] also are at a high risk of failure and potential for biochemical recurrence or distant disease. Prostate-specific membrane antigen (PSMA) is an integral transmembrane protein expressed in all types of prostatic tissue including prostate carcinoma,[2] and is emerging as a useful diagnostic and possibly therapeutic target. There are varying PSMA tracers which are frequently small molecules that bind to the PSMA receptor. The one that is commonly used is 68 gallium (68Ga)-PSMA-11, which is composed of a radioactive carrier gallium-68 and the small-molecule component of PSMA-11 that binds to the receptor. Targeted radiation therapy using radiolabeled small molecule that selectively binds to PSMA receptor has recently shown very promising results in men with metastatic castration-resistant prostate cancer, even heavily pretreated with chemotherapy and androgen-signaling agents.[3] Moreover, PSMA theranostics as the next wave of promising treatment for metastatic castrate-resistant prostate cancer has gained ground and likely will lead to the next viable treatment option.[4]

Similarly, the use of PSMA as a diagnostic tool has also garnered equal, if not more, attention given the potential to change therapy especially in the biochemical recurrence setting. In a single-arm, prospective trial that looked at 635 biochemically recurrent patients,[5] the positive predictive value was 0.84 and 68Ga-PSMA-11 PET detected localized recurrent prostate cancer in 475 of 635 (75%) patients.

The proPSMA trial was a Phase III multicentric randomized study conducted in Australia on 300 patients with untreated high-risk prostate cancer defined by Gleason grade Group 3–5, prostate-specific antigen (PSA) ≥20 ng $ml^{-1}$ , or clinical stage ≥T3.[6] Patients were randomized 1:1 to gallium-68-PSMA11 positron emission tomography/computed tomography (PET/CT) and conventional imaging, consisting of computed tomography of the abdomen/pelvis and bone scintigraphy with single photon emission computed tomography (SPECT)/CT. Patients with negative scan results, equivocal or oligometastatic disease, crossed over to receive the other imaging arm. A scan is considered positive if biopsy showed confirmation of prostate adenocarcinoma, change of a bone lesion to sclerotic or blastic lesion on follow-up scans, or other soft-tissue criteria were met.

The primary outcome of the trial was to determine the accuracy of first-line imaging for identifying either pelvic nodal or distant metastatic disease. The reference standard regarding the presence of pelvic nodal or distant metastases was determined by each site's investigator at 6 months, with accuracy being predefined using a scoring system incorporating histopathologic, imaging, and clinical follow-up at 6 months postrandomization. The secondary objectives include comparing management impact, the number of equivocal studies, the incremental value of second-line imaging in patients who cross over, health economics, radiation exposure, interobserver agreement, and safety of PSMA-PET/CT. While the trial did not specify the type of treatment, change in treatment as a result of the scan was recorded using a referrer-reported questionnaire. The trial included patients with a median age of 69

GU Medical Oncology, Department of Oncology, Inova Schar Cancer Institute, Fairfax, VA, USA.
Correspondence: Dr. JB Aragon-Ching (jeanny.aragon-ching@inova.org)
Received: 12 April 2020; Accepted: 20 April 2020

years, with a median PSA of 10 ng ml$^{-1}$, with 21.7% of PSA over 20 ng ml$^{-1}$ and 27% with T3 disease or more. The results showed that the accuracy of gallium-68-PSMA11 PET/CT was 27% greater (95% confidence interval [CI]: 23%–31%, $P < 0.0001$) than the conventional imaging (92% [95% CI: 88%–95%] *vs* 65% [95% CI: 60%–69%]), which translated to a lower sensitivity of the conventional CT and bone scan (38% [95% CI: 24%–52%] *vs* 85% [95% CI: 74%–96%]) for gallium-68-PSMA11 PET/CT scan with a specificity of 91% (95% CI: 85%–97%) for conventional imaging compared to 98% (95% CI: 95%–100%) for PSMA PET-CT. Further subgroup analyses showed that first-line PSMA PET-CT detected the following diseases including pelvic nodal disease in 30 of 148 men (20%), abdominal nodal metastases in 13 (9%), bone metastases in 15 (10%), and visceral metastases in one patient (1%). Changes in management were also seen. Among patients who underwent first-line PSMA PET-CT, 20 (14%) of 148 patients had a change from curative-intent treatment to palliative-intent treatment, a change in radiation technique was seen in 11 patients (7%), and the surgical technique was changed in 11 (7%) patients. Radiation exposure is also deemed higher in those who undergo conventional CT and bone scan. Radiation exposure from first-line diagnostic imaging was higher with that of conventional imaging (19.2 [95% CI: 18.2–20.3] mSv compared with PSMA PET-CT at 8.4 [95% CI: 8.1–8.7] mSv; $P < 0.001$).

This study provides the compelling use and value of PSMA scan as a diagnostic tool, which helps further delineate the presence of metastatic disease for patients who have high-risk or very high-risk prostate cancer for whom more aggressive multimodality therapy is more appropriate.[7] In addition, finding oligometastatic disease drives alternative management strategies such that whom primary local therapy may not be appropriate for the patient with widely metastatic disease.

However, questions remain as to the availability of these tracers and their applicability in different settings because guidelines formulated by the European Association of Nuclear Medicine and the Society of Nuclear Medicine and Molecular Imaging were based mainly on the experience and availability of the 68Ga-PSMA ligand as well as the wide variability of applicability in different institutions.[8] In addition, all the studies including those on treatment with chemotherapy or androgen-signaling agents in first-line metastatic prostate cancer were all based on conventional imaging rather than the more sensitive PSMA-based testing. There are other tracers such as 18F-DCFPyL which can be produced in larger quantities and 18F-PSMA-1007[9] which has a longer half-life than 68Ga-PSMA-11, which could be more technically accessible. In addition, further heightened sensitivity may be added by doing additional multiparametric magnetic resonance imaging (MRI) as shown in a biochemical recurrence study after radical prostatectomy.[10] Ultimately, the role of 68Ga-PSMA-11 in the diagnosis of high-risk prostate cancer would help change management decisions as it relates to proceeding with primary local therapy or need for additional intensified therapy.

## COMPETING INTERESTS

JBAC has previously served in the Speakers' Bureau of Astellas/Medivation and has served in the Advisory Board for Janssen and Bayer.

## REFERENCES

1 Chang AJ, Autio KA, Roach M 3rd, Scher HI. High-risk prostate cancer-classification and therapy. *Nat Rev Clin Oncol* 2014; 11: 308–23.
2 Chang SS. Overview of prostate-specific membrane antigen. *Rev Urol* 2004; 6 Suppl 10: S13–8.
3 Violet J, Sandhu S, Iravani A, Ferdinandus J, Thang SP, *et al*. Long term follow-up and outcomes of re-treatment in an expanded 50 patient single-center phase II prospective trial of Lutetium-177 ($^{177}$Lu) PSMA-617 theranostics in metastatic castrate-resistant prostate cancer. *J Nucl Med* 2020; 61: 857–65.
4 Iravani A, Violet J, Azad A, Hofman MS. Lutetium-177 prostate-specific membrane antigen (PSMA) theranostics: practical nuances and intricacies. *Prostate Cancer Prostatic Dis* 2020; 23: 38–52.
5 Fendler WP, Calais J, Eiber M, Flavell RR, Mishoe A, *et al*. Assessment of 68Ga-PSMA-11 PET accuracy in localizing recurrent prostate cancer: a prospective single-arm clinical trial. *JAMA Oncol* 2019; 5: 856–63.
6 Hofman MS, Lawrentschuk N, Francis RJ, Tang C, Vela I, *et al*. Prostate-specific membrane antigen PET-CT in patients with high-risk prostate cancer before curative-intent surgery or radiotherapy (proPSMA): a prospective, randomised, multi-centre study. *Lancet* 2020; 395: 1208–16.
7 Mano R, Eastham J, Yossepowitch O. The very-high-risk prostate cancer: a contemporary update. *Prostate Cancer Prostatic Dis* 2016; 19: 340–8.
8 Fendler WP, Eiber M, Beheshti M, Bomanji J, Ceci F, *et al*. $^{68}$Ga-PSMA PET/CT: joint EANM and SNMMI procedure guideline for prostate cancer imaging: version 1.0. *Eur J Nucl Med Mol Imaging* 2017; 44: 1014–24.
9 Giesel FL, Hadaschik B, Cardinale J, Radtke J, Vinsensia M, *et al*. F-18 labelled PSMA-1007: biodistribution, radiation dosimetry and histopathological validation of tumor lesions in prostate cancer patients. *Eur J Nucl Med Mol Imaging* 2017; 44: 678–88.
10 Freitag MT, Kesch C, Cardinale J, Flechsig P, Floca R, *et al*. Simultaneous whole-body $^{18}$F-PSMA-1007-PET/MRI with integrated high-resolution multiparametric imaging of the prostatic fossa for comprehensive oncological staging of patients with prostate cancer: a pilot study. *Eur J Nucl Med Mol Imaging* 2018; 45: 340–7.