Commentary

Making the Case for Prostate-Specific Membrane Antigen-Targeted Positron Emission Tomography/Computed Tomography in Suspected Prostate Cancer

Abstract

Prostate specific membrane antigen (PSMA) over-expression is a hallmark of prostate adenocarcinoma and many PSMA targeting positron emission tomography (PET) radiopharmaceuticals have been developed over the last decade. The role of 68Ga-PSMA-11 PET-computed tomography (CT) is well established in staging and biochemical recurrence of PCa, with growing interest and evidence regarding its utility in suspected prostate cancer.

Keywords: *Diagnosis, prostate cancer, positron emission tomography, prostate specific membrane antigen*

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Prostate-specific membrane antigen (PSMA) has emerged as an important target for prostate cancer (PC) theranostics over the last decade. PSMA overexpression is a hallmark of prostate adenocarcinoma, and many PSMA-targeting positron emission tomography (PET) radiopharmaceuticals have been developed. The role of 68Ga-PSMA-11 PET-computed tomography (CT) is well established in staging and biochemical recurrence of PC, with the recently published proPSMA trial reporting better performance of 68Ga-PSMA PET-CT compared to conventional imaging in staging of high-risk PC.[1]

There is interest among treating oncologists regarding the utility of 68Ga-PSMA PET-CT in suspected PC due to limitations of existing modalities, viz., serum prostate-specific antigen (PSA) levels, digital rectal examination (DRE), transrectal ultrasonography (TRUS), TRUS-guided biopsy, and multiparametric magnetic resonance imaging (mpMRI). Development and introduction of newer modalities with high diagnostic performance in detecting PC are vital.

PSMA-targeted PET-CT has proven its potential to fit into the diagnostic algorithm of suspected PC. A recent meta-analysis by Satapathy *et al*.[2] evaluated the diagnostic performance of 68Ga-PSMA PET/CT in the initial detection of PC in patients with clinical or biochemical suspicion. Seven articles comprising 389 patients were included, and the pooled sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio using 68Ga-PSMA PET/CT were 0.97 (95% confidence interval [CI]: 0.90–0.99), 0.66 (95% CI: 0.52–0.78), 2.86 (95% CI: 1.95–4.20), and 0.05 (95% CI: 0.01–0.15), respectively. 68Ga-PSMA PET-CT showed high accuracy with the area under the Summary receiver operating characteristic (SROC) curve being 0.91 (95% CI: 0.88–0.93). Thereby, 68Ga-PSMA PET/CT showed excellent sensitivity and negative likelihood ratio to detect suspected PC and has potential utility as a "rule-out" test in this setting.

Despite high sensitivity, 68Ga-PSMA PET-CT showed moderate specificity. Improvement in reported specificity can be done by standardization and evolution of reporting criteria. Reporting of PSMA PET aims to quantify the PSMA expression. Prior studies have used visual interpretation of images with focal tracer uptake more than background and SUVmax cutoff estimation criteria to detect malignancy. With the aim of standardization, PSMA reporting and data system (RADS) version 1.0 and molecular imaging PSMA (miPSMA) scoring have been proposed.[3,4] PSMA RADS uses a Likert scale ranging from 1 (benign) to 5 (lesion typical of PC).

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For 68Ga-PSMA PET-CT, miPSMA score quantifies PSMA expression on a score from 0 to 3 on the basis of visual comparison of lesion uptake, with mean uptake in blood pool, liver, and parotid gland, with 0 score indicating no PSMA expression (uptake < blood pool), 1 indicating low PSMA expression (uptake ≥ blood pool but < liver), 2 indicating intermediate PSMA expression (uptake ≥ liver but < parotid gland), and 3 indicating high PSMA expression (uptake ≥ parotid) in the prostate. The scoring system is modified for different PSMA-targeting PET tracers. Uptake more than liver, i.e., miPSMA scores 2 and 3, is empirically considered typical for PC lesions. This is different from earlier studies, which reported uptake more than prostatic background as positive. This change in interpretation criteria has potential to improve specificity of 68Ga-PSMA PET-CT in suspected PC.

In the current study by Chandra *et al*.,[5] the authors retrospectively evaluated the accuracy of prebiopsy 68Ga-PSMA PET/CT for the detection of PCa in 64 patients with serum PSA <50 ng/ml. Using miPSMA scoring system, the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were 74%, 92%, 85%, 86%, and 86%, respectively. On receiver operating characteristic (ROC) curve analysis, SUVmax cutoff value of 5.6 on PSMA PET/CT showed a sensitivity of 95% and a specificity of 90.9%. They concluded that 68Ga-PSMA PET/CT can differentiate benign and malignant lesions of the prostate with very high accuracy. miPSMA score ≥2 yielded a higher specificity (92%), but with reduction in sensitivity to 74%. SUVmax cutoff performed better than miPSMA scoring in this study. In contrast to using visual comparison or SUVmean for miPSMA scoring, authors have used SUVmax and reported high variation in liver uptake. Two out of three false-positive lesions and three out of six false-negative lesions had SUVmax comparable to liver. In such cases, visual comparison and using SUVmean can show better results for miPSMA scoring system. Repeat biopsy or follow-up data were not available for validation of false result findings.

In a real-world setting, 68Ga-PSMA PET-CT can play an important role in diagnosis of PC in selected scenarios such as suspicion of PC with normal DRE, negative initial biopsy, equivocal MR results, and contraindication to mpMRI such as metallic implants and use of nephrotoxic intravenous contrast media, to offset radiation/cost concerns.[6] In addition, its utility needs to be evaluated in patients with lower PSA range of 4–10 ng/ml. The information obtained from PSMA PET can be used for targeting biopsy from suspected lesion using image fusion, cognitive targeting, or real-time PET-guided biopsy.

Along with the detection of primary tumor, reporting should also focus on tumor location and molecular imaging Tumor Node Metastasis (miTNM) staging in a single setting. Assessing reproducibility of PET findings is necessary as it is an important limitation of Prostate Imaging–Reporting and Data System (PIRADS) scoring on mpMRI. Demirci *et al*. measured interobserver and intraobserver agreement in 68Ga-PSMA PET/CT in 133 cases, which were reported independently by four different readers at different times according to the miTNM and PSMA RADS templates.[7] They found that PSMA PET has a lower interobserver variability and higher reproducibility than other imaging methods used for imaging of PC, including CT, MRI, and bone scintigraphy.

68Ga-PSMA PET-CT has shown high diagnostic accuracy in suspected PC cases, but the level of evidence remains weak. Prospective, multicenter randomized controlled studies comparing PSMA PET with mpMRI are needed to generate high level of evidence. Adoption of standardized and reproducible reporting scoring systems such as miPSMA or PSMA RADS can allow incorporation of 68Ga-PSMA PET-CT into prospective clinical trials and evidence-based guidelines.

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Conflicts of interest

There are no conflicts of interest.

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