

## MINI REVIEW

# Diagnostic Challenges in Prostate Cancer and <sup>68</sup>Ga-PSMA PET Imaging: A Game Changer?

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### Abstract

Prostate cancer (PC) is the most frequent solid tumor in men and the third most common cause of cancer mortality among men in developed countries. Current imaging modalities like ultrasound (US), computerized tomography (CT), magnetic resonance imaging (MRI) and choline based positron emission (PET) tracing have disappointing sensitivity for detection of nodal metastasis and small tumor recurrence. This poses a diagnostic challenge in staging of intermediate to high risk PC and restaging of patients with biochemical recurrence (PSA >0.2 ng/ml). Gallium-<sup>68</sup> labeled prostate specific membrane antigen (<sup>68</sup>Ga-PSMA) PET imaging has now emerged with a higher diagnostic yield. <sup>68</sup>Ga-PSMA PET/CT or PET/MRI can be expected to offer a one-stop-shop for staging and restaging of PC. PSMA ligands labeled with alpha and beta emitters have also shown promising therapeutic efficacy for nodal, bone and visceral metastasis. Therefore a PSMA based theranostics approach for detection, staging, treatment, and follow-up of PC would appear to be highly valuable to achieve personalized PC treatment.

**Keywords:** Prostate cancer- biochemical recurrence- CT and MRI- PET Choline- <sup>68</sup>Ga-PSMA PET-Theranostics

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### Introduction

Prostate cancer (PC) is the most common solid tumor in men and the third common cause of mortality among men of developed countries (Torre, 2015). Like other malignancies, accurate staging of PC is the fundamental step in the selection of the most appropriate therapeutic strategy. Radical prostatectomy and radiation therapy are considered as primary therapy with curative intent for localized PC and systemic therapy for patients with metastases. Currently morphological imaging like ultrasound (US), computerized tomography (CT), magnetic resonance imaging (MRI), functional imaging like bone scanning (BS) and hybrid imaging like choline based positron emission tomography and CT (PET/CT) are commonly used in diagnosis, staging and restaging of PC. But as a matter of fact these modalities have disappointing sensitivities (Heck et al., 2014) and no reliable imaging tool is available for diagnosis of site of disease recurrence in patients with biochemical recurrence (Ceci et al., 2014). However, in recent years, Gallium-<sup>68</sup> labeled Prostate Specific Membrane Antigen (<sup>68</sup>Ga-PSMA) has emerged with high diagnostic accuracy based on initial results (Eisenhut and Zechmann, 2012). In this mini-review we will discuss the limitations of existing imaging modalities and possible benefits of <sup>68</sup>Ga-PSMA in various clinical

settings among patients with PC.

### Diagnosis of Prostate Cancer

As per current clinical practice based on recent guidelines, US guided biopsy is the most commonly used way with considerably high diagnostic yield for diagnosis of PC. However, in suspected PC patients with negative US guided biopsies; MRI is used as a standard imaging procedure to guide the targeted re-biopsies of suspected lesions. But some lesions might also be missed on MRI-guided biopsies and these are the patients who pose a diagnostic challenge. In such diagnostic dilemma, new PET based tracer like <sup>68</sup>Ga-PSMA PET/CT is found to play an important role due to its high target to background ratio resulting in better delineation of tumor. In some preliminary studies using <sup>68</sup>Ga-PSMA PET/CT, a high diagnostic yield was found for targeted fusion biopsies (Storz et al., 2015; Zettinig et al., 2015).

### TNM Staging of Prostate Cancer

**Tumor (T) Staging:** In last decade MRI has emerged as a standard of care in local staging of PC like capsular breach and invasion of seminal vesicle. In current days multi-parametric MRI (mpMRI) which includes T2 weighted images (T2WI – hypointense PC focus), dynamic contrast enhanced (DCE – high influx and

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washout of contrast in PC), diffusion weighted imaging (DWI – restricted diffusion with low ADC in PC) and spectroscopy (MRS – shifted choline and citrate metabolism in PC) is assumed more accurate than MRI alone in local staging of PC (Futterer et al., 2006; Tan et al., 2012). mpMRI is considered to have high sensitivity and specificity for detection of aggressive PC as well. However, in some patients local changes after biopsy sampling like local bleed and inflammation might pose interpretation challenges to mpMRI. Introduction of simultaneous whole body PET/MRI has a promising role in staging of PC. Preliminary comparative studies using PET/MRI have shown better delineation of prostate lesions with <sup>68</sup>Ga-PSMA than choline derivatives (Eiber et al., 2014). Furthermore, <sup>68</sup>Ga-PSMA interpretation does not seem to be influenced by previous biopsies (Eiber et al., 2014).

#### *Nodal and Metastasis (N and M) Staging*

The fundamental goal of staging is to find nodal, bone or visceral metastasis as it assists the physicians in selecting the most appropriate therapeutic option. As probability of metastasis is very low in low risk PC, recent guidelines recommends staging examination in intermediate and high risk PC (<http://uroweb.org/guideline/prostate-cancer/>; <http://www.nccn.org/patients/guidelines/prostate>). Currently contrast enhanced CT (CECT) or MRI is used for detection of nodal and visceral metastasis and bone scan for osseous metastasis. The diagnostic criterion for nodal metastasis on CT and MRI is primarily based on node size (>8 mm). However, about 80% of metastatic nodes in PC are < 8 mm which poses a diagnostic challenge to CT and MRI. Published data shows a pooled sensitivity of 42% and 39% and specificity of 82% and 82% for CT and MRI respectively (Hovelset al., 2008). PET/CT based probes like 11C-Choline, 18F-Choline and 18FDG also have disappointing sensitivities and confounding the diagnostic challenge for nodal metastasis. Published meta-analyses about various cholines revealed pooled sensitivities ranging 33-49% and specificity of over 95% (Kjohledet al., 2014) and due to limited sensitivity, choline based PET/CT tracers are not included in recent guidelines for nodal staging in PC (<http://uroweb.org/guideline/prostate-cancer/>). However, recently introduced <sup>68</sup>Ga-PSMA ligands using PET/CT have shown promising role in preliminary studies. <sup>68</sup>Ga-PSMA based studies have shown a sensitivity of about 66% and specificity of 99% for nodal metastasis (Maurer et al., 2015) and detection of bony and visceral metastases in intermediate to high risk PC (Chakraborty et al., 2015). These early facts suggest <sup>68</sup>Ga-PSMA PET/CT or PET/MRI as a one-stop-shop for complete staging of intermediate to high risk PC patients but further research and evidence is required prior to drawing a robust conclusion.

#### *Staging of Biochemical Recurrence*

Despite of definitive therapy like radical prostatectomy and radiation therapy (RT), 15-40% patients develop rising PSA level heralding the tumor recurrence. According to European Association of Urology guidelines, an increase in serum PSA level >0.2 ng/ml and over 2 ng/ml above the

nadir value after RT is defined as biochemical recurrence. In such scenario a precise localization of site of tumor recurrence is paramount for selection of most appropriate therapy. But precise localization of site of recurrence is a major challenge for existing morphological and functional imaging modalities. In patients with biochemical recurrence having PSA <10 ng/ml after curative treatment, CT and bone scanning has limited diagnostic accuracy. For these reasons, in most guidelines imaging is recommended for symptomatic patients or for those having PSA level >10 ng/ml (<http://uroweb.org/guideline/prostate-cancer/>; Beresford et al., 2010). Choline based PET tracers (11C-Choline and 18F-Choline) have better detection rate in patients with recurrence but for patients with low PSA velocity or serum PSA level <2 ng/ml, even these tracer face challenges of low diagnostic yield [sensitivity ranges between 19-36%] (Krause et al., 2008 Krause et al., 2008). For same reason choline based PET imaging is also not recommended in early tumor recurrence. Therefore there was a dire need for new imaging techniques having a higher lesion detectability rate at a serum PSA >0.2 ng/ml (early stage of biochemical recurrence). <sup>68</sup>Ga-PSMA PET/CT preliminary studies have shown better detection rate in patients with biochemical recurrence. Recently published two studies using <sup>68</sup>Ga-PSMA have shown detection rates of 50% and 57.9% for serum PSA <0.5 ng/ml (Afshar et al., 2013; Eiber et al., 2015).

#### *Prostate Specific Membrane Antigen and PSMA-Ligands or Inhibitors*

PSMA is a type-II transmembrane glycoprotein having an intracellular, transmembrane and extracellular portions. PSM<sup>7</sup> is a truncated cytoplasmic PSMA and its function is unknown. PSM<sup>7</sup>/PSMA ratio increases with rise of Gleason score. PSMA is over-expressed in about 90% of PC to a degree of 100-1000 fold as compared to expression on normal epithelial cells of prostate, salivary gland, small bowel and renal tubules (Silver et al., 1997). This over-expression of PSMA which further increases with tumor aggressiveness, availability of a large extracellular domain as target for antibodies / inhibitors and a cytoplasmic domain having an internalization motif which increases intracellular concentration of conjugated radiometal ensure better imaging and therapeutic efficacy (Rajasekaran et al., 2003). PSMA expression has also been found in some tumors of small bowel, bladder, brain, breast and kidneys (Silver et al., 1997). The recognition of active binding domain on extracellular component of PSMA, has promoted the development of PSMA ligands or inhibitors which are smaller than monoclonal antibodies (like ProstaScint® and J 591) having limitations of poor tumor penetrability and sluggish blood clearance (Tagawa et al., 2010). There are 3 types of PSMA ligands or inhibitors including phosphorous, thiol or urea based inhibitors. Urea based inhibitors have the highest affinity and specificity for PSMA and very efficient internalization which makes them focus of current research. <sup>68</sup>Ga-PSMA-HBED-CC (PSMA -11) is the most widely used ligand which can be easily labeled with <sup>68</sup>Ga at room temperature with good stability, quick background clearance and high concentration even in small metastatic deposits. It has physiological intense

uptake over salivary gland, liver, spleen, small bowel and urinary tract.  $^{68}\text{Ga}$ -PSMA-Imaging and Therapy (I and T, having DOTAGA chelator) and PSMA-617 (having DOTA chelator) are new theranostics ligands which can also be labeled with Indium-111 ( $^{111}\text{In}$  for radioguided surgery) and Lutetium-177 ( $^{177}\text{Lu}$  for PSMA targeted therapy). Researchers have also introduced  $^{18}\text{F}$  labeled PSMA inhibitors due to its better imaging characteristic than  $^{68}\text{Ga}$  and easy availability of  $^{18}\text{F}$  because of its longer half-life (110 minute vs.  $^{68}$  minute) and higher yield of cyclotron.

#### PSMA Based Therapy

Unique over-expression of PSMA in PC which is further enhanced in high-grade, metastatic and castration-resistant PC (CRPC) and its labeling with beta and alpha particle emitters has opened new vista for PSMA based theranostics. Patients with CRPC have poor prognosis with 5 years survival of 29% (Siegel et al., 2012). First line treatment for asymptomatic patients includes abiraterone acetate plus prednisolone and enzalutamide. Second line treatment (for symptomatic patients) includes taxane-based therapies (docetaxel, cabazitaxel). Unfortunately, these therapies are only temporarily effective and development of treatment resistance is quite common. Radium-223 (Xofigo<sup>TM</sup>) is a bone seeking alpha emitting agent, having efficacy limited to bony metastasis. PSMA I and T and PSMA 617 labeled with beta emitters like Lutetium-177 or Yttrium-90 ( $^{177}\text{Lu}$  and  $^{90}\text{Yt}$ ) or alpha emitter like Bismuth-213 ( $^{213}\text{Bi}$ ) can be used in patients with mCRPC and biochemical recurrence. This single approach is considered effective for both visceral and bony metastases. Initial reports are quite encouraging with decline of PSA level (about  $\geq 50\%$ ) in 45% of patients (Rahbar et al., 2017) and further data are being gathered from many centres around the world. Kidneys and parotid glands are the target organs and dosimetry studies have shown that  $^{177}\text{Lu}$ -PSMA therapy is safe and a cumulative dose of 30 GBq (810 mCi) can be administered safely (Kabasakal et al., 2015).

PC is the most common solid tumor in men and imaging plays a vital role in diagnosis, primary staging and restaging in patients with intermediate to high risk PC and with biochemical recurrence. However, the current imaging modalities like US, CT, MRI and Choline based PET/CT have limited diagnostic accuracy especially for detection of subcentimeter nodal metastasis and localization of site of tumor in biochemical recurrence. Recently  $^{68}\text{Ga}$ -PSMA inhibitors based PET/CT and PET/MR have been used in staging and restaging of PC with very promising diagnostic accuracies. On the basis of these preliminary results, it is considered that  $^{68}\text{Ga}$ -PSMA PET/CT or PET/MRI could be used as one-stop-shop for complete staging or restaging and rendering further cross sectional imaging and bone scanning unnecessary. However, cost and availability are the current limitations. On therapeutic frontiers, in patients with oligometastasis,  $^{111}\text{In}$ -PSMA based radioguided surgery can be used for accurate localization and resection of tumor. Similarly, in patients with metastatic CRPC, PSMA ligands labeled with beta emitters ( $^{177}\text{Lu}$ -PSMA,  $^{90}\text{Yt}$ -PSMA) or alpha

emitter ( $^{213}\text{Bi}$ -PSMA) have been used with significant decline in PSA level. Therefore PSMA based theranostics approach for detection, staging, treatment, and follow-up of PC would be highly valuable to achieve personalized PC treatment.

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