



## Review Article

# $^{68}\text{Ga}$ -prostate-specific membrane antigen-positron emission tomography/computed tomography in advanced prostate cancer: Current state and future trends



Cristian Udovicich <sup>a, b, c</sup>, Marlon Perera <sup>d</sup>, Michael S. Hofman <sup>e</sup>, Shankar Siva <sup>f</sup>,  
Andres Del Rio <sup>g</sup>, Declan G. Murphy <sup>h</sup>, Nathan Lawrentschuk <sup>d, h, i, \*</sup>

<sup>a</sup> Department of Surgery, Mildura Base Hospital, Melbourne, Australia

<sup>b</sup> Department of Surgery, Western Health, Melbourne, Australia

<sup>c</sup> Department of Surgery, Alfred Health, Melbourne, Australia

<sup>d</sup> Department of Surgery, Austin Health, The University of Melbourne, Victoria, Australia

<sup>e</sup> Centre for Molecular Imaging, Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia

<sup>f</sup> Department of Radiation Oncology, Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia

<sup>g</sup> Department of Radiology, Austin Health, Melbourne, Victoria, Australia

<sup>h</sup> Division of Cancer Surgery, Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia

<sup>i</sup> Olivia Newton-John Cancer Research Institute, Melbourne, Australia

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## ABSTRACT

The early and accurate detection of prostate cancer is important to ensure timely management and appropriate individualized treatment. Currently, conventional imaging has limitations particularly in the early detection of metastases and at prostate-specific antigen (PSA) levels < 2.0 ng/mL. Furthermore, disease management such as salvage radiotherapy is best at low PSA levels. Thus, it is critical to capture the disease in the oligometastatic stage as disease progression and commencement of systemic therapies can be delayed by metastasis-directed therapy. Prostate-specific membrane antigen (PSMA) is overexpressed in prostatic cancer cells. Novel imaging modalities using radiolabeled tracers with PSMA such as  $^{68}\text{Ga}$ -PSMA-positron emission tomography (PET)/computed tomography (CT) have shown promising results. We review the literature regarding  $^{68}\text{Ga}$ -PSMA-PET/CT in the setting of primary prostate cancer and biochemical recurrence. At present, the best utilization of  $^{68}\text{Ga}$ -PSMA-PET/CT appears to be in biochemical recurrence.  $^{68}\text{Ga}$ -PSMA-PET/CT has high diagnostic accuracy for lymph node metastases and has been shown to have superior detection rates to conventional imaging, especially at low PSA levels.

The exact role of  $^{68}\text{Ga}$ -PSMA-PET/CT in primary prostate cancer is not yet entirely clear. It has an improved detection rate for smaller lesions and may be able to identify nodal or distant metastatic disease at an earlier stage. While still experimental, there may also be value in combining  $^{68}\text{Ga}$ -PSMA-PET to multiparametric magnetic resonance imaging for staging of intraprostatic disease. To date,  $^{68}\text{Ga}$ -PSMA-PET/CT has been shown to have considerable clinical value and to impact treatment selection for patients with prostate cancer. Still in its infancy, the results of future clinical trials will be excitedly awaited.

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## 1. Introduction

Radiological diagnostics are critical in the evaluation of patients with suspected metastatic or biochemically recurrent prostate cancer (PCa).<sup>1,2</sup> The identification and localization of metastatic

disease may significantly alter treatment options available to the patient. Moreover, the importance of expeditious identification of metastatic spread is increasing being recognized, specifically, at the oligometastatic setting.<sup>3</sup> Multiple groups have now demonstrated oncological benefit of salvage lymph node dissection (LND) or

\* Corresponding author. Department of Surgery, Austin Health, The University of Melbourne, 145 Studley Road, Heidelberg, Victoria, Australia.  
E-mail address: [lawrentschuk@gmail.com](mailto:lawrentschuk@gmail.com) (N Lawrentschuk).

radiotherapy in the setting of low-burden metastatic disease.<sup>4,5</sup> Furthermore, in the setting of isolated metastatic deposits, stereotactic radiotherapy or metastasectomy to distant metastases may provide benefit. These findings are corroborated by a recent systematic review and meta-analysis.<sup>4</sup> Specifically, Ost et al<sup>6</sup> have demonstrated an improved progression-free survival for oligometastatic PCa recurrence for patients treated with high-dose stereotactic body radiotherapy (3-year progression-free survival 99% vs. 79% with low dose).

Traditionally, serial Prostate-specific membrane antigen (PSMA), computed tomography (CT), and bone scan have represented the mainstay of disease staging in advanced PCa.<sup>1,2,7,8</sup> Diagnostic limitations to CT and bone scan imaging approaches have prompted the use of positron emission tomography (PET) in staging for advanced PCa. Early PET/CT scans utilized either choline- or flourodeoxyglucose-based tracers. While the early results were promising, these probes have a limited capability—particularly during the early stages of metastatic spread or biochemical recurrence (BCR).<sup>9</sup> Thus, there is a need for an imaging modality that can detect metastatic disease progression at an earlier stage.

PSMA is a transmembrane protein that is expressed at the cell surface of prostatic cells.<sup>10</sup> PSMA is an ideal target in PCa, because its expression increases with increasing cellular dysplasia. Numerous antibodies to PSMA have been developed; some of which have been radiolabeled to facilitate nuclear imaging. More recently, small molecules that bind with high affinity to PSMA have been developed. Initially reported in 2012, the most widely studied type of PSMA based PET/CT is <sup>68</sup>Ga-labeled on the small molecular inhibitor PSMA-11 (also known as PSMA HBED-CC).<sup>11</sup> We aim to provide a comprehensive review of the current state of <sup>68</sup>Ga-PSMA-PET/CT in advanced PCa.

## 2. PSMA

PSMA is a 750-amino-acid, 100-kDa, type II transmembrane glycoprotein. It consists of an 18-amino-acid intracellular domain, a 25-amino-acid transmembrane region, and a 707-amino-acid extracellular portion.<sup>12</sup> The gene for PSMA (*FOLH1*) has been located on the short arm of chromosome 11 (11p11.2)<sup>13</sup> and other genes from this same portion have also been associated with PCa.<sup>14</sup> PSMA is highly specific for the prostatic tissue and has a limited extraprostatic expression. Nevertheless, PSMA may be expressed in some tissues including neural tissue, salivary glands, neuroendocrine tissue, small bowel, and kidney.<sup>15</sup> However, prostatic expression has shown to be 12 times greater than that of the next highest organ.<sup>16</sup>

Within the prostate, PSMA is expressed on the epithelium surrounding the prostatic ducts, on the apical region of the prostatic cells.<sup>17</sup> Dysplastic changes of the prostate results in the expression of PSMA on the surface of the prostatic ducts.<sup>18</sup> Indeed, PSMA expression is increased significantly in both prostatic adenocarcinoma tissue and lymph node metastases (LNMs) and is lowest in benign prostatic tissue.<sup>19</sup> Indeed, PSMA expression is 100–1000-fold higher in PCa cell membranes when compared to normal cells.<sup>15,20</sup> Furthermore, increasing stage and grade of PCa results in increased cell membrane PSMA expression.<sup>15,20</sup> The eventual progression to advanced PCa and castration resistance corresponds with further increases in expression of PSMA.<sup>21</sup> Sweat et al<sup>19</sup> demonstrated that only 2% of LNMs were negative for PSMA expression. Furthermore, Mannweiler et al<sup>22</sup> found ~5% of primary tumors and 15% of metastases (mostly skeletal) were PSMA negative. PSMA has also been found to be expressed in bladder cancer and renal cell carcinoma, however it has a specificity of 94.5% for PCa compared with any other type of malignancy.<sup>23,24</sup> As such, PSMA represents a promising target for imaging of PCa.

Small molecules similar in structure to peptides that bind with affinity to PSMA with subsequent cell internalization have been developed. PSMA-11 labeled to <sup>68</sup>Ga, a generator produced positron emitter, via the HBED chelator (<sup>68</sup>Ga-PSMA HBED-CC or <sup>68</sup>Ga-PSMA-11) has been the most extensively studied in radiological diagnostics in advanced PCa.<sup>11</sup>

## 3. <sup>68</sup>Ga-PSMA-PET/CT in BCR staging

A vast majority of evidence supporting the use of <sup>68</sup>Ga-PSMA-PET/CT is reported in the setting of BCR.<sup>25</sup> In a recent meta-analysis,<sup>25</sup> a positive finding was detected in 76% of patients with BCR undergoing <sup>68</sup>Ga-PSMA-PET/CT. Indeed, this meta-analysis highlights that pre-PET PSA predicts the positivity rate of <sup>68</sup>Ga-PSMA-PET/CT in the setting of BCR. Specifically, on pooled analysis, positivity rates for PSA 0–0.19 ng/mL, 0.2–1.0 ng/mL, 1.0–1.99 ng/mL, and > 2.0 ng/mL were 42%, 58%, 76%, and 95%, respectively. Indeed, current data suggest that one of the advantages of <sup>68</sup>Ga-PSMA-PET/CT is the detection rate at low PSA levels in the setting of BCR. A metaregression performed in the same meta-analysis demonstrated that a PSA of 1.0 ng/mL was associated with a 70% risk of positive <sup>68</sup>Ga-PSMA-PET/CT. Similar findings were observed in a recent study by Meredith et al.<sup>26</sup> In their large cohort of 425 patients with BCR after radical prostatectomy (RP), a detection rate of 53.3% was observed for PSA levels from 0.5 ng/mL to 1 ng/mL and 79.1% for 1 ng/mL to < 2 ng/mL. It should be noted that there may be variation when comparing the detection rates of different case series as test positivity is associated with the prevalence of disease in the underlying cohort. Nevertheless, high-volume comparable series have been published, assessing the positivity rates of traditional choline-based tracers in advanced PCa. Specifically, Graziani et al<sup>27</sup> demonstrated that at PSA < 1.16 ng/mL, the detection rate of choline-based tracers was 26.8%.<sup>27</sup>

Data pertaining to the direct comparison between <sup>68</sup>Ga-PSMA-PET/CT and choline-PET imaging on individual patients is available.<sup>28</sup> Afshar-Oromieh et al<sup>29</sup> demonstrated improved nodal detection rates in <sup>68</sup>Ga-PSMA-PET/CT compared with <sup>18</sup>F-choline-based PET/CT ( $P = 0.04$ ) in 37 patients with BCR. All lesions identified on choline PET/CT (26 patients) were detected on <sup>68</sup>Ga-PSMA-PET/CT and lesions in a further six patients were detected on <sup>68</sup>Ga-PSMA-PET/CT only. Another advantage of <sup>68</sup>Ga-PSMA-PET/CT was the significantly higher uptake intensity and tumor-to-background ratio. Similarly, Schwenck et al<sup>28</sup> reported an increased detection rate for <sup>68</sup>Ga-PSMA-PET/CT compared with choline-PET in a retrospective analysis of 103 patients with BCR after primary treatment. On a per-lesion based analysis for LNMs, 39% were detected only by <sup>68</sup>Ga-PSMA-PET/CT and 6% only by choline-PET. Furthermore, <sup>68</sup>Ga-PSMA-PET/CT was able to detect significantly smaller lymph nodes. As alluded to above, at PSA < 1 ng/mL the detection rate for <sup>68</sup>Ga-PSMA-PET/CT was 56% but only 22% for choline-PET. The addition of <sup>68</sup>Ga-PSMA-PET/CT affected tumor–node metastasis staging in 30/103 patients. Specifically, nodal stage migration occurred in 15 patients due to <sup>68</sup>Ga-PSMA-PET/CT and two patients due to choline-PET. Regarding the differentiation of poly- or oligometastatic disease, <sup>68</sup>Ga-PSMA-PET/CT and choline-PET were concordant in 80% of cases.

The sensitivity and specificity of <sup>68</sup>Ga-PSMA-PET/CT has received relatively limited attention in the current literature. This is, in part, because a comparative gold standard measure does not easily exist. Histopathology is not always feasible in the setting of BCR and can be subject to sampling error; particularly given the small volume of disease that is often detected on <sup>68</sup>Ga-PSMA-PET/CT. Rauscher et al<sup>30</sup> performed a comparison on <sup>68</sup>Ga-PSMA-PET/CT with traditional morphological imaging in detecting LNMs prior to salvage LND. From this, <sup>68</sup>Ga-PSMA-PET/CT had a resulting

sensitivity and specificity of 78% and 97%. In comparison, morphological imaging [CT and magnetic resonance imaging (MRI)] had a sensitivity of 27% and specificity of 99%. The aforementioned meta-analyses identified 11 studies that reported correlative histopathological data with  $^{68}\text{Ga}$ -PSMA-PET/CT. However, of these 11, only five were suitable for pooled analysis as several studies included series where patients underwent selective nodal dissection, which falsely inflates the specificity values.<sup>25,31</sup> From this meta-analysis, on a per-patient based analysis, the sensitivity, specificity, and positive and negative predictive value were 86%, 86%, 83%, and 89%, respectively. Similarly, on a per-lesion based analysis, the sensitivity, specificity, and positive and negative predictive values were 80%, 97%, 82%, and 97%, respectively (for nodal recurrences only). Comparative meta-analytical data from choline PET/CT was published by Evangelista et al,<sup>32</sup> including 19 individual series and representing 1,555 patients. For choline ( $^{11}\text{C}$  and  $^{18}\text{F}$ ), the sensitivity and specificity for LNM was 100% and 81.8%, respectively. While these values are consistent with those of  $^{68}\text{Ga}$ -PSMA-PET/CT, it must be noted that the inclusion criteria for the respective choline-based meta-analysis has not been clearly reported. Specifically, it is not clear whether biopsy and resulting histopathological correlation was clinical performed on clinical discretion. As discussed, the inclusion of such series unduly inflates sensitivity and specificity profiles.

#### 4. $^{68}\text{Ga}$ -PSMA-PET CT in primary staging of high-risk PCa

The use of  $^{68}\text{Ga}$ -PSMA-PET/CT in the primary staging of high-risk PCa is increasingly being reported.<sup>33</sup> Most of this has been performed in patients with intermediate- or high-risk disease.<sup>25</sup> In a retrospective analysis, Budaus et al<sup>34</sup> analyses 30 patients that underwent preoperative  $^{68}\text{Ga}$ -PSMA-PET/CT imaging prior to RP and extended pelvic LND. Twelve of these patients were histopathologically positive for LNM, and  $^{68}\text{Ga}$ -PSMA-PET/CT detected four of these with no false-positive findings. After analysis, the sensitivity and specificity was 33.3% and 100%, respectively. A study of similar methodology was performed by van Leeuwen et al.<sup>35</sup> After histopathological correlation, 11 of 30 patients had LNM. The sensitivity and specificity was 56% and 98%, respectively. It appears that only the smallest of LNMs were undetected with a mean size of 2.7mm for  $^{68}\text{Ga}$ -PSMA-PET/CT-negative lesions. The largest series performed in this cohort was reported by Maurer et al,<sup>36</sup> who compared  $^{68}\text{Ga}$ -PSM-PET/CT to conventional imaging (CT and MRI) for the detection of LNM for patients prior to RP and pelvic LND.  $^{68}\text{Ga}$ -PSMA-PET/CT resulted in a sensitivity and specificity of 65.9% and 98.9% on a per-patient level compared with 44.9% and 85.4% for conventional imaging. Schewneck et al<sup>28</sup> compared  $^{68}\text{Ga}$ -PSMA-PET/CT and choline-PET in the initial staging of PCa. In all 20 patients, uptake was detected in the prostate by both imaging modalities. While more lymph node and bone metastases were detected on a per-lesion level by  $^{68}\text{Ga}$ -PSMA-PET/CT, there was no significant difference on a per-patient level.

While there is improved clarity in the role of  $^{68}\text{Ga}$ -PSMA-PET/CT in BCR, the role in primary staging is yet to be definitively determined. The benefit of  $^{68}\text{Ga}$ -PSMA-PET/CT in primary staging in this setting appears to be identifying metastatic disease earlier and in uncommon locations, such as the mesorectum.<sup>37</sup> The identification of such disease may considerably alter the treatment algorithms for a given patient. No doubt, higher-volume prospective series with oncological outcomes are required. A phase III randomized controlled trial comparing  $^{68}\text{Ga}$ -PSMA-PET/CT to conventional imaging is currently being undertaken in Australia (ProPSMA study, Australian New Zealand Clinical Trials Registry 1261700005358).

#### 5. $^{68}\text{Ga}$ -PSMA-PET in staging of intraprostatic disease

Multiparametric MRI (mpMRI) represents a promising imaging modality in the diagnosis of primary PCa.<sup>38</sup>  $^{68}\text{Ga}$ -PSMA-PET/CT in combination with CT and mpMRI has increasingly been utilized in experimental protocols to diagnose and localize intraprostatic PCa.<sup>39–41</sup> Fendler et al<sup>39</sup> studied the value of  $^{68}\text{Ga}$ -PSMA-PET/CT in localization of primary tumor lesions.  $^{68}\text{Ga}$ -PSMA-PET/CT was performed shortly before RP was correlated with histopathological six-segment prostate specimens. On a per-segment analysis,  $^{68}\text{Ga}$ -PSMA-PET/CT had a sensitivity and specificity of 67% and 92%, respectively. However, of the 21 patients, two (10%) were  $^{68}\text{Ga}$ -PSMA-PET/CT negative. The sensitivity for detection of seminal vesicle invasion was 73%, with a specificity of 100%. Several groups have explored the utility of the novel integrated PET/MRI unit in combination with the  $^{68}\text{Ga}$ -PSMA ligand. Eiber et al<sup>41</sup> correlated findings from mpMRI, PET and combined  $^{68}\text{Ga}$ -PSMA PET/MRI with histopathological findings from prostate biopsy for a cohort of intermediate and high-risk patients. On a per-patient basis, the sensitivity of  $^{68}\text{Ga}$  PSMA PET/MRI was superior (98%) to that of PET alone (92%) and mpMRI (66%). On a per-sextant basis comparing  $^{68}\text{Ga}$  PSMA PET/MRI to a recent meta-analysis,<sup>42</sup> a similar sensitivity (76% vs. 78%) with a superior specificity was found (97% vs. 79%). Current data suggest that  $^{68}\text{Ga}$  PSMA-PET/MRI may improve diagnostic yield and localization of primary intraprostatic PCa. Despite the experimental status of such techniques, the improved localization may play a role with the growing evidence base for focal therapies for localized PCa.<sup>43</sup> Moreover,  $^{68}\text{Ga}$  PSMA-PET/MRI may aid the prompt detection of local intraprostatic recurrence after radiotherapy; particularly in light of the increased feasibility of salvage prostatectomy.<sup>44</sup>

#### 6. Current state of $^{68}\text{Ga}$ -PSMA PET/CT in contemporary clinical practice

In current guidelines, there is limited recognition of  $^{68}\text{Ga}$ -PSMA-PET/CT in either the setting of primary staging or BCR of PCa.<sup>45,46</sup> In the most recent updates, only the European Association of Urology guidelines make reference to  $^{68}\text{Ga}$ -PSMA-PET/CT.<sup>1</sup> The extent of this reference highlights that only preliminary results have been reported to date and also reflects regional variation of accessibility of  $^{68}\text{Ga}$ -PSMA-PET/CT due to varying regulation around administration of novel radiopharmaceuticals. The recent establishment of national registries for PCa will hopefully capture the imaging modality utilized.<sup>47</sup>

Despite this,  $^{68}\text{Ga}$ -PSMA-PET/CT imaging has been increasingly reported in routine clinical practice in countries where scanning is available. Moreover, several series have reported the considerable utility of  $^{68}\text{Ga}$ -PSMA-PET/CT, and it has been reported to alter management plans in 29–76% of patients.<sup>48–52</sup> Bluemel et al<sup>48</sup> reported on 45 patients with BCR after RP who were scheduled to receive salvage RT to the prostate bed. If  $\leq 5$  metastases were found, high-dose radiotherapy was given, and if  $> 5$  metastases were found, then androgen deprivation therapy was commenced. After  $^{68}\text{Ga}$ -PSMA-PET/CT imaging, the treatment recommendation changed in 42.2% of cases.<sup>48</sup> However, in these series no other imaging modality has been used as a comparator and follow-up data are limited. Henkenberens et al<sup>51</sup> analyzed patients with BCR who underwent  $^{68}\text{Ga}$ -PSMA-PET/CT-directed radiotherapy. Of the cohort, there was 100% local control after 12 months, which delayed the commencement of androgen deprivation therapy or other systemic therapies. In the context of patients under consideration of salvage radiotherapy to the prostate bed, early treatment before significant PSA rises (as low as  $< 0.20$  ng/mL) is associated with improved clinical outcomes.<sup>53</sup> Thus, due to low sensitivity at



these levels,  $^{68}\text{Ga}$ -PSMA-PET/CT needs further investigation and possibly combination with other imaging modalities before it can be routinely recommended to screen patients for adjuvant or salvage radiotherapy.

## 7. Conclusions

Current evidence points towards a role for  $^{68}\text{Ga}$ -PSMA-PET/CT in the setting of BCR. The superiority of  $^{68}\text{Ga}$ -PSMA-PET/CT compared to current imaging modalities seems to be most marked at low PSA levels. Detecting PCa recurrence expeditiously is critical as metastases are more likely to be locally confined or oligometastatic at this point. Metastasis-directed therapies, both lymphadenectomy and radiotherapy, are of use in this setting. Additionally, recent updated analysis from the CHAARTED trial have also shown the value of differentiating high- or low-volume disease.<sup>54</sup> With a minority of studies focusing on  $^{68}\text{Ga}$ -PSMA-PET/CT in primary PCa, there is less evidence for its use in this setting as the true sensitivity for the detection of LNM is not clear. Nevertheless, the majority of results so far were from retrospective case series. Studies validating imaging findings with histopathology are required as well as analysis of longer-term outcomes of  $^{68}\text{Ga}$ -PSMA-PET/CT-directed therapy.

## Conflicts of interest

All authors have nothing to disclose.

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