



Impact of the ^{68}Ga Prostate-Specific Membrane Antigen (^{68}Ga -PSMA) PET/CT on the Management of Prostate Cancer

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Abstract

This review discusses the efficiency and sensitivity of ^{68}Ga -labelled prostate-specific membrane antigen (PSMA) positron emission tomography (PET)/computed tomography (CT) imaging in comparison to other radiotracers and imaging techniques. It also conveys its impact on the treatment or management of prostate cancer patients. PSMA, observed in almost all prostate cancer cells, is used for staging and treatment, due to its high multiplication in this cancer when compared to normal tissues. PSMA PET/magnetic resonance imaging (MRI) has applications in the management of prostate cancer. Though PSMA PET/MRI has yielded preliminary results, it is still studied as an imaging biomarker for tumor responses. PSMA-PET/CT is known for its highly sensitive resolution, as it lights up only the parts harboring prostate cancer or tumor cells and not any other kind of lesion. Therefore, ^{68}Ga -PSMA-PET imaging is chosen over other variants of ^{68}Ga -PSMA-11, such as ^{177}Lu -PSMA or ^{225}Ac -PSMA, and it is used for its greater ability to detect metastatic sites in patients with biochemical recurrence and low serum prostate-specific antigens values. The efficacy of ^{68}Ga -PSMA PET/CT also allows for estimation of oligometastases, as it supports the design of therapeutic trials in measuring long-term effects in patients. Finally, ^{68}Ga -PSMA PET/CT is effective in identifying recurrence localization and, hence, permits the ability to choose the best therapeutic strategy as early as possible.

Introduction

Prostate cancer (PCa) holds the second position for most commonly occurring cancer and is a remarkable cause for the majority of death in men. According to research conducted in the UK, the incidence of PCa has increased by 44% since 1990.¹ Every year in Australia and the UK, death of men due to PCa (3,306 deaths in Australia; 12,032 deaths in the UK) is more than the death of women due to breast cancer (3,058 deaths in Australia; 11,371 deaths in the UK).^{1,2} Twenty-sixty percent of patients treated for PCa fail primary therapy, and less than thirty percent of the patients having high-volume metastatic disease achieve 5-year survival.³

Keywords: Oligometastases; Metastatic sites; Nodal metastasis; Baseline staging.

Abbreviations: BCR, biochemical recurrence; CRPC, castration-resistant prostate cancer; CT, computed tomography; FCH, fluorocholine; FDG, fluorodeoxyglucose; MRI, magnetic resonance imaging; mp-MRI, multi-parametric magnetic resonance imaging; PCa, prostate cancer; PET, positron emission tomography; PSA, prostate-specific antigens; PSMA, prostate-specific membrane antigen; RLT, radioligand therapy; RP, radical prostatectomy; RT, radiotherapy.

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Imaging techniques like computed tomography (CT) or magnetic resonance imaging (MRI) are used for staging of cancer.⁴ In non-metastatic cancer patients, about 30–35% patients treated by radical prostatectomy (RP) or radiotherapy (RT) have a rise in the prostate-specific antigens (PSA) levels and biochemical recurrence (BCR) in the years following treatment.⁵ Increasing levels of PSA after RT or surgery indicate a higher risk of death in men. These high levels of PSA and the early PSA failure in patients indicates a greater need for ^{68}Ga -prostate-specific membrane antigen (PSMA) positron emission tomography (PET)/CT scanning.⁶ Treatment or management strategies differ for each patient depending on their risk, which usually increases after therapies like hormonal therapy, RT, chemotherapy or sometimes a combination of all these therapies.⁷

PSMA is a glycoprotein present on the outer surface of prostate cells, hyper-regulated during metastatic conditions and castrate-resistant PCa (CRPC).⁸ Though the exact functions of PSMA are yet to be defined, it is still used for staging and treatment due to its high multiplication in PCa.^{8,9} Many other malignancies, namely breast cancer, colorectal carcinoma, follicular lymphoma, etc., also express PSMA with ^{68}Ga -PSMA avidness. Highly expressed PSMA (type-II-transmembrane glycoprotein) is also observed in almost all PCa cells, except the 5–10% of PCa cells without PSMA expression.⁹ In 2016, a study in Brazil estimated 61,200 new cases of PCa, which made it the second most prevailing neoplasia in men throughout the country and the third most common reason of death by cancer in men of Western countries.¹⁰ This review discusses the

efficiency and sensitivity of ^{68}Ga -PSMA PET/CT imaging in comparison to other radiotracers and imaging techniques. It also conveys its impact on the treatment or management of PCa patients.

PSMA-PET and PSMA-PET/CT Technique

PSMA-PET increases its positivity with an increase in the grade and stage of the tumor, level of PSA, and time. PSMA expression is linked directly to the status of disease (PCa) and therapeutic effects, indicating a parallel relationship with PSA values in treatment techniques like RT, chemotherapy and radionuclide therapies (with $^{177}\text{Lu}/^{225}\text{Ac}$ -PSMA or ^{223}Ra).¹¹ PSMA-PET has a specific molecular imaging target for tumors expressing PSMA. Each imaging modality has a specific capability of identifying the sites of the tumor that would otherwise be neglected or considered negative by the other techniques. Hence, PSMA-PET is emerging as the most favorable imaging tool and a potential prognostic biomarker. PET scanning by using various tracers poorly detects early BCR with low levels of PSA. Only ^{68}Ga -PSMA-PET imaging is used due to its precise detection of metastatic sites in patients having BCR with low serum PSA values.^{10,12,13}

PSMA-PET/CT has a highly sensitive resolution to detect tumors as small as 3 mm, across the lymph nodes.⁸ It is highly specific, as it lights up only the parts having PCa or any tumor tissue and not any kind of lesion which may look like PCa. Also, PSMA-based imaging shows improved detection in those patients having primary PCa (intermediate to high risk) when compared to CT or multi-parametric (mp-)MRI, making bone scintigraphy or additional cross-sectional imaging unnecessary.¹⁴

^{68}Ga -PSMA PET/CT-11

^{68}Ga -PSMA PET/CT-11 is a PSMA tracer, wherein Ga-68 is a radioactive carrier and PSMA-11 is a small molecule that binds to the receptor. An automated synthesis system usually synthesizes Ga-68 of high efficiency and purity. PSMA radiotracers are given in micrograms so that no side-effects or adverse effects are perceived. These tracers are now widely used in PET and CT, due to their higher efficacy and precision in PCa scans when compared to bone scanning or MRI. PSMA radiotracers, given to hundreds of thousands of patients globally, have no reported side effects.⁸ Presently, using ^{68}Ga , the physiological biodistribution of radiolabeled PSMA includes various glands, like salivary and lacrimal, other organs, like liver and spleen, and low-level uptake in the prostate tissue.^{15,16} The specificity and sensitivity of ^{68}Ga -PSMA PET/CT estimates the detection of PCa as it supports the design of therapeutic trials in measuring long-term effects in patients. Hence, ^{68}Ga -PSMA PET/CT is a novel imaging technique that detects BCR with greater sensitivity and is effective in identifying recurrence localization and permitting the choice for the best therapeutic strategy as early as possible.

Variants of ^{68}Ga -PSMA-11

^{177}Lu -PSMA, a variant of ^{68}Ga -PSMA-11, is also used for PET/CT imaging. Lutetium-177 is a short-path length beta emitter, having a crossfire effect of targeting all cells in 1 mm radius by supplying effective radiation only to the tumor, reducing the damage to other normal cells/tissues around it. The single-center, single-arm phase-2 trial, is the only trial showing that ^{177}Lu -PSMA radioli-

gand therapy (RLT) has a favorable anti-tumor activity and toxicity profile, depicting a significant improvement in the mCRPC patients with disease progression though treated with standard options/procedures.¹⁷ ^{177}Lu -PSMA RLT is administered after considering all traditional therapies, though its exact sequence remains uncertain in the treatment procedure.

In mCRPC patients who previously failed in treatments like chemotherapy, ^{177}Lu -PSMA RLT has been shown to increase the progression-free survival in 40–70% of patients by decreasing the levels of PSA, tumor volume, and activity.^{18–24} This treatment is well-tolerated due to its minimal or moderate side-effects. In smaller studies, targeted alpha therapy using ^{225}Ac -PSMA showed decreased levels of PSA, tumor volumes and activity in patients who failed the ^{177}Lu -PSMA therapy. ^{225}Ac -PSMA therapy also showed a noticeable effect on the function of the salivary gland. Though, the long-term toxicities of these therapies, if any, are yet to be studied.²⁵

^{18}F -Labeled PSMA Tracers

^{18}F -labeled compounds are also being preferred over ^{68}Ga radionuclide due to various factors, such as low positron energy resulting in short positron range in tissues, the long half-life, and potential to be shipped through existing distribution networks (decreasing the cost).²⁶ Due to low positron energy, ^{18}F has more greatly improved resolution than ^{68}Ga . ^{18}F can be produced in larger quantities, as it is obtained from the cyclotron, unlike ^{68}Ga . Therefore, all these factors have increased the need to develop ^{18}F -labelled PSMA compounds.²⁷ One such compound is ^{18}F -PSMA-1007, which quickly clears from blood but has a decreased clearance through the urinary tract.²⁸ A study reported that ^{18}F -PSMA-1007 PET/CT is better than other PSMA PET agents as its detection ability is efficient and highly sensitive, even in patients with low PSA level (0.2–0.5 ng/mL), in comparison to ^{68}Ga -PSMA-11.^{29,30} The management was improved in these patients due to the precise identification of recurrence sites by ^{18}F -PSMA-1007 PET/CT.

^{18}F -Fluorodeoxyglucose (FDG) PET/CT is a tracer used in many tumors, but its results in PCa are not promising, due to the decreased metabolic activity of PCa cells and increased excretion of ^{18}F in the urine.^{31,32} Its effectiveness, however, is observed in hormone-resistant weakly differentiated cell types found in PCa patients.^{33–35} As the use of ^{18}F -FDG is limited, other radiotracers for PCa have been developed. One such class of PET tracer encompasses the choline derivatives, which have been examined abundantly over the past few years. Membranes of the prostate cell consist of choline, which is imaged with choline radiotracers such as ^{18}F -fluorocholine (FCH). Soyka *et al.*³⁶ reported that 48% (75/156) of patients showed management changes (RT or salvage therapy, or both) based on the results of ^{18}F -FCH PET/CT. Therefore, concluding that ^{18}F -FCH PET/CT has a huge impact on the therapeutic strategies of PCa patients. Though ^{18}F -FCH PET/CT had a high detection rate, there are no studies yet to prove its usefulness in diagnosing and evaluating the extent of localized tumors in PCa patients.

Impact of the ^{68}Ga -PSMA PET/CT on Management Changes

^{68}Ga -PSMA PET/CT has been reported to be of greater clinical importance to stage primary PCa. Roach *et al.*³⁷ reported that management changes after PCa detection using ^{68}Ga -PSMA PET/CT accounted for one-fifth of all the patients imaged. The management changes were suggested as a change from hormonal and

Table 1. Change of intended treatment options after ⁶⁸Ga-PSMA PET/CT imaging

Category	Treatment options ⁴¹
Primary treatment	Salvage surgery Salvage radiotherapy Metastasis-directed ablative radiation therapy (stereotactic body radiation therapy) Androgen deprivation therapy Chemotherapy PSMA radionuclide therapy Other systemic treatment (vaccine therapy, immunotherapy) Active surveillance
Management changes chosen post- ⁶⁸ Ga PSMA PET/CT imaging	Conversion to focal treatment Conversion to new focal treatment Conversion to systemic treatment Changed systemic treatment (addition or removal of systemic treatment) Conversion to active surveillance

CT, computed tomography; PET, positron emission tomography; PSMA, prostate-specific membrane antigen.

radical therapy to surgery (namely prostatectomy, regional lymph node detection), radiation treatment, systemic therapy, additional biopsies, and imaging. Replanning the treatment due to the prognostic implication in these patients is substantial. Bluemel *et al.*³⁸ showed management changes in about 40% of the patients due to ⁶⁸Ga-PSMA PET/CT. Salvage RT in the presence of BCR or PSA was suggested as a management change after prior radical therapy.

Müller *et al.*³⁹ reported that the overall management changes of ⁶⁸Ga-PSMA PET/CT were 60% (122/203). The use of metastasis-targeted treatment increased with a decrease in systemic treatment due to management changes, like targeted RT with and without hormonal therapy, based on the ⁶⁸Ga-PSMA PET/CT scan. A meta-analysis reported management changes in 54% (628/1,163) of its patients.⁴⁰ An increase was seen in RT, surgery and multimodal treatment, with a decrease in systemic treatment referred as management changed due to the ⁶⁸Ga-PSMA PET/CT scan findings. Calais *et al.*⁴¹ showed that, when changes based only on scans with positive findings were considered, 114 of 152 patients (75%) had management changes. The changes in management due to the impact of ⁶⁸Ga-PSMA PET/CT findings were measured as the fraction of patients who had a change in treatment plan after the scan. However, the intended management changes early after ⁶⁸Ga-PSMA PET/CT is usually different from implemented management changes. Post ⁶⁸Ga-PSMA PET, the number of systemic treatments decreased with increased local treatments.

High detection rate (74%) of ⁶⁸Ga-PSMA-11 PET, which was nearly 50% even in the patients with low PSA values, formed the basis for the changes in patient management. These detection rates were observed to be consistent, even in larger retrospective studies.³⁰ Androgen deprivation treatment alters both PSMA status and PSMA PET. In a study by Müller *et al.*,³⁹ 15.6% (33/223) of patients received androgen deprivation treatment at some point prior to the scan, with rise in PSA levels. Higher detection rate was observed in this subgroup compared to other groups (88% vs. 74%), with a positive scan in 31/35 patients. The high detection rate of recurrent PCa with ⁶⁸Ga-PSMA PET changed management in 60% of the patients. The patients were suggested to undergo salvage surgery, chemotherapy, radical therapy, or secondary hormonal therapy as management changes after the ⁶⁸Ga-PSMA-PET/CT scan.⁴² Moreover, this cohort (60%) showed a slightly high impact on management when compared to the management changes found by Afaq *et al.*⁴³ (39% of patients) and Sterzing *et al.*⁴⁴ (51% of patients).

The accuracy of ⁶⁸Ga-PSMA PET/CT scan has paved its way for future personalized treatment of PCa, as it has already replaced

the conventional scans, like CT. This precise scanning may also aid in the development of various drugs to increase the precision or localization of the metastases.

Hypothesis

The changes in management due to ⁶⁸Ga-PSMA PET/CT (Table 1) not only showed a clinical benefit in PCa patients with very low PSA values and BCR but also a benefit to the PCa patients with a higher risk even after the planned curative treatment. The sensitivity and specificity of this imaging technique decreased the possibility of unsatisfactory post-operative outcomes, while increasing the survival rate with better outcomes compared to the conventional treatments planned before the scan. ⁶⁸Ga-PSMA PET/CT could be advised in the routine check-up of PCa patients due to its effectiveness in the identification of metastasis followed by increased PSA levels, which are usually seen after the primary treatment. Another advantage of this type of scanning is that it can stage and image only the tumors and not any lesions. This precise scanning may also aid in the development of various drugs to increase the precision or localization of the metastases.

Conclusions

⁶⁸Ga-PSMA PET/CT is effective in identifying recurrence localization and hence permits choosing the best therapeutic strategy as early as possible. ⁶⁸Ga-PSMA PET/CT shows a significant impact on the management changes in PCa patients.

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Conflict of interest

The authors declare no conflict of interests.

Author contributions

Design, analysis and critical revisions of the manuscript (SG); design, coordination and drafting of the manuscript (SS, SK). All authors read and approved the final manuscript.

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