

^{68}Ga PSMA PET-CT: New Hope in Prostate Cancer Imaging and Therapy

Shankar Kumar Dey

Director, Institute of Nuclear Medicine and Allied Sciences, Faridpur

Correspondence Address: Professor and Chief Medical Officer, INMAS, Faridpur. Bangladesh Atomic Energy Commission. E-mail: drskdey707@gmail.com

ABSTRACT

Prostate cancer is the second most common cancer in men. Its diagnosis and management are still challenging as both PSA levels and imaging have had their limitations. Prostate specific membrane antigen (PSMA) is a prostate specific cell surface protein and has been emerging as a novel target for PET imaging of prostate cancer. ^{68}Ga PSMA PET-CT imaging have been shown as a better imaging technology in primary prostate cancer and at the same time detecting lymph node and bone metastases even in low PSA levels. Moreover, its counterpart ^{177}Lu PSMA has a great prospect to be used for the treatment of castration resistant prostate cancer.

Key words: Prostate cancer, ^{68}Ga PSMA PET-CT imaging.

Bangladesh J. Nucl. Med. Vol. 22 No. 1 January 2019

Doi : <https://doi.org/10.3329/bjnm.v22i1.40507>

INTRODUCTION

Prostate cancer (PCa) is the second most common cancer and sixth leading cause of cancer death in man worldwide (1). Proper diagnosis and treatment of prostate cancer is still a major challenge faced by oncologists and radiologists all over the world; as both PSA levels and imaging have had their limitations with respect to diagnosis, staging, and prognosis. Both conventional radiological imaging and PSA levels show high false positives during screening due to confounding effects of benign prostatic hyperplasia and prostatitis (2).

Radical prostatectomy and radiation therapy are performed as primary therapy with a curative intent in patients with localized prostate cancer (3,4). While pelvic lymph node dissection is considered as gold standard in patients with nodal metastases (5). However, 20–40% of patients undergoing radical prostatectomy (6,7) and 30–50% of patients undergoing radiation therapy (RT) will experience increasing PSA levels known as biochemical recurrence within 10 years (8). So an

accurate diagnosis of the site of prostate cancer recurrence is a key factor for treatment planning and patient management (4).

Management of recurrent prostate cancer is mainly influenced by the presence or absence of metastases, since salvage radiation therapy (SRT) is indicated in localized recurrent disease while systemic therapy is indicated in metastatic disease. Studies with morphological imaging with CT and MRI or functional imaging with ^{18}F -FDG PET-CT and ^{18}F Choline PET-CT have shown disappointing sensitivity rates (9) and not reliable in detecting site of disease in patients with biochemical recurrence (10,11,12). These problems have led to identification of better diagnostic agent and tool for more precise localization of recurrence in patients with rising PSA after definitive therapy.

One such molecule is prostate specific surface antigen (PSMA). Prostate-specific membrane antigen (PSMA) is a cell surface protein expressed abundantly in prostate cancer cells (13). Its expression is 100–1000 times more in PCa cells (14) and level of expression is directly proportional to gleason score, androgen independence, metastases and progression (15).

The unique expression profile of PSMA provides an excellent target for prostate cancer imaging and therapy (16,17). This review revealed emerging role of ^{68}Ga -PS-MA PET-CT in diagnosis of prostate cancer and its metastases and also linking of PSMA with beta emitters for prostate cancer therapy.

Prostate Specific Membrane Antigen (PSMA)

Glutamate carboxypeptidase II, also known as prostate specific membrane antigen (PSMA) is highly expressed

by all prostate cancers and its expression increase with tumor aggressiveness, metastatic disease and disease recurrence (18-20). It is also expressed in small intestine, renal tubules, salivary glands and tumor neovasculature (14). The transmembrane location of PSMA with large extracellular domain allows for its internalization after binding, providing an accurate target for prostate carcinoma specific imaging and therapy (21, 22). Now a days, procedures have been developed to label PSMA with a number of radionuclides like ^{68}Ga , $^{99\text{m}}\text{Tc}$ and ^{123}I . ^{68}Ga -PSMA is increasingly being recognized as a novel radiopharmaceutical for PET imaging of prostate cancer.

Role in prostate cancer diagnosis, staging and recurrence

Over the years, imaging in prostate cancer had been limited to transrectal ultrasound (TRUS) for guidance of prostate biopsies and computed tomography (CT) and $^{99\text{m}}\text{Tc}$ bone scans for staging of the disease. But the advances in magnetic resonance imaging (MRI) technology (23,24) and the development of novel nuclear medicine radiotracers (25) have revolutionized PCa management.

While ^{18}F -FDG-PET-CT has been used in a wide range of malignancies (26), the use of ^{18}F -FDG-PET for prostate cancer has been limited by poor radiotracer uptake (27,28), lack of discrimination between neoplastic and benign conditions (29,30) and high concentrations of radiotracer in the urine (28). Radiotracers based on choline (^{11}C -choline, ^{18}F -choline) and acetate (^{11}C -acetate, ^{18}F -acetate) have been studied extensively in this setting but their performance for primary detection has been wanting (31).

Newer agents, specially PSMA ligands have shown greater cancer sensitivity and specificity allowing for improved in-gland detection (32). Initial human biodistribution studies of PSMA PET-CT imaging demonstrated intense radiotracer uptake in salivary glands, kidneys and urinary bladder due to excretion of radiotracer through these ways. High tracer uptake was observed at the sites of primary prostate cancer, lymph node and bone metastases with highest uptake at the sites of highest Gleason score (33,34).

In respect to staging, ^{68}Ga -PSMA has been reported to clearly improve detection of lymph node metastases compared with conventional morphologic imaging (MRI or CT) (35). Afshar-Oromich et al. studied 42 patients and compared the positive lymph nodes in PSMA PET-CT with biopsy or surgery results and found 100% specificity for pathological tracer uptake in lymph nodes (36). Earlier observations with ^{68}Ga -PSMA suggests that this novel tracer can detect prostate cancer relapses and metastases with high sensitivity (33,37,38). A recent meta-analysis has shown that PSMA has a greater likelihood of detecting extra-prostatic disease, along with lymph node and bone lesions compared to Choline or Acetate PET scans (39).

Another meta-analysis by von Eyben et al (40), which pooled 983 patients, ^{68}Ga -PSMA was found to have a sensitivity of 88% for recurrence detection at median PSA value of 2.3 ng/mL. Importantly, ^{68}Ga -PSMA was noted to have 50% sensitivity and 97% specificity in identifying recurrences in patients presenting with PSA values ranging from 0.2 to 0.5 ng/mL (41).

Relatively easy and efficient radiolabeling technique has made the compound a potential radiotracer that may detect prostate carcinoma relapse and metastases by targeting the PSMA (17). One thing to consider, ^{68}Ga has a shorter half life (68 min) and has to prepare in an on-site radiopharmacy.

Comparison with bone scintigraphy (BS)

Prostate cancer has a unique tendency to spread to bone (42). Hematogenous spread in red bone marrow of axial and appendicular skeleton leads to development of bone metastases (BMs). Bone metastases are the most frequent and main distant metastatic site in about 80% of prostate cancer patients and thus one of the most important determinants of treatment and outcome (43,44). Skeletal complications accounts for the most of the morbidity and mortality from prostate cancers (45). Bone scintigraphy (BS) with $^{99\text{m}}\text{Tc}$ -Methylene diphosphonate (MDP) is generally the most favored investigation for detecting bone metastases. Briganti has showed risk of bone

metastases in low, intermediate and high risk PCa of 1.8%, 8.5% and 16.4% respectively (46). Therefore, most guidelines suggest bone scintigraphy to be performed in patients with high risk prostate cancers or those presenting with bone symptoms (3,47,48).

Bone scintigraphy has number of limitations as well. It is a well known fact that bone metastases begins in bone marrow, hence bone scintigraphy will not be able to detect bone marrow lesions or early lesions with osteo-blastic activity. In addition, being a non-specific tracer many a times it is hard to differentiate between degenerative bone disease and bone metastases thus frequently requiring additional imaging modality for characterization (49). With the advent of modern hybrid imaging like SPECT-CT, MDP bone scintigraphy has largely addressed this issue of low specificity and the number of equivocal lesions dropped from 61% to 8% (50). Recently PSMA has been acclaimed as a distinct target in prostate cancer and for BMs, PSMA PET has unique distinction of being positive in bone marrow metastases and not in degenerative bone disease. In a direct comparison, PSMA PET outperformed planar bone scintigraphy for detection of affected bone regions as well as overall bone disease volume (51,52). Overall 17.6% of affected bone regions were exclusively recognized only by PSMA PET while only 1.2% of bony regions were exclusively detected by bone scintigraphy. PSMA PET showed significantly higher sensitivity and accuracy than bone scintigraphy (90.5% vs. 73.68% and 97.0% vs. 86%) for bone metastases (53).

Therapeutic prospect

A new and very exciting application of the PSMA ligands is their linking with beta emitters (^{90}Y and ^{177}Lu), for treatment of metastatic foci from prostate cancer. Cases who have got benefit from this type of therapy have already been reported (54). In a phase-1 trial (55) using ^{177}Lu -PSMA in 56 patients with castration resistant prostate cancer (CRPC), the targeted therapy had a low adverse effect profile, with 56% of the patients achieving a partial response. It has been shown that parotid glands and kidneys are the target organs for toxicity with ^{177}Lu -PSMA (56).

CONCLUSION

Newer PET agents like ^{68}Ga PSMA have shown great prospect in early diagnosis and staging, detection of metastases and recurrence in prostate cancer patients not previously possible with running imaging technologies. Though it is yet to be approved by FDA, it can be expected that ^{68}Ga -PSMA PET-CT will soon be included in treatment strategy in patients with prostate cancer and it will become one-stop shop for prostate cancer workup.

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