Original Article

Incremental value of 68-gallium-prostate-specific membrane antigen positron emission tomography/computed tomography in patients with abnormal prostate-specific antigen and benign transrectal ultrasound biopsy

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Abstract

Introduction: Bladder outlet obstruction due to prostate enlargement is a common health problem in male and frequently investigated with prostate-specific antigen (PSA) and transrectal ultrasound (TRUS). TRUS-guided biopsy is critical to differentiate benign prostatic hyperplasia (BPH) or prostate cancer (PCa) even though it has been associated with false negative with reported 3%–16% incidence of PCa in BPH specimens. Prostate-specific membrane antigen positron emission tomography/computed tomography (PSMA PET/CT), a targeted molecular imaging for PCa, has showed promising results in recurrence and staging. We analyzed its role in patients with abnormal PSA and benign TRUS biopsy.

Material and Methods: Of 558 ^{68}Ga-PSMA PET/CT performed from July 2014 to February 2017, we found six patients with abnormal PSA (range 8.2–24.2 ng/ml, median: 13.3 ng/ml) with benign 12 cores TRUS biopsy as indication. These cases were reanalyzed in detail. Spearman's rank test was used entire correlation using SPSS version 21.

Results: ^{68}Ga-PSMA PET/CT showed mild diffuse tracer uptake in prostate in all patients with no focality and maximum standard uptake value normalized to body weight (SUV_{max}) range was 3.2-5.8 (median: 3.9). Two patients with PSA <10 ng/ml had normal ^{68}Ga-PSMA PET/CT and underwent medical management. In other four patients with PSA >10 ng/ml, two showed metastatic disease in pelvic lymph node in both and in lung in one; hence, ^{68}Ga-PSMA PET/CT changed these patients' management. Spearman's rank test showed no correlation with baseline PSA and SUV_{max} of prostate (r_s −0.0287, $P = 0.9571$) while strong positive correlation was seen with baseline PSA and ^{68}Ga-PSMA PET/CT scan positivity for extraprostatic disease ($r_s = 0.828$, $P = 0.042$).

Conclusions: ^{68}Ga-PSMA whole-body PET/CT can provide useful incremental information in patient with high PSA and negative TRUS biopsy and has a potential to guide management in this subgroup of PCa patients.

Keywords: 68-gallium-prostate-specific membrane antigen positron emission tomography/computed tomography, abnormal prostate-specific antigen, benign prostatic hyperplasia, lung metastasis, negative 12 cores transrectal ultrasound biopsy

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INTRODUCTION

Bladder outlet obstruction (BOO) due to prostate enlargement is a common health problem in male and frequently investigated with prostate-specific antigen (PSA) and transrectal ultrasound (TRUS). TRUS-guided biopsy has been critical to differentiate benign prostatic hyperplasia (BPH) or prostate cancer (PCa) even though it has been associated with false negatives with reported 3-16% incidence of PCa in BPH specimens.[1-5] 68-gallium-prostate-specific membrane antigen positron emission tomography/computed tomography (^{68}Ga-PSMA PET/CT) is a targeted molecular imaging technique for PCa. Recent literature has proved its impact in PCa recurrence in comparison to current standard and other molecules in research.[6,7] PSMA PET/CT has guided patient's management by detecting subcentimeter lymph node in staging patient as well.[8,9] However, its role in patients with abnormal PSA and benign TRUS biopsy has not been reported in the literature to the best of our knowledge.

MATERIAL AND METHODS

In our ^{68}Ga-PSMA PET/CT database of 558 patients referred for staging, restaging, response evaluation, suspected recurrence, and surveillance indications from July 2014 to February 2017, we identified that six patients with abnormal PSA and negative 12 cores TRUS-guided biopsy were referred to look for disease site. These patients were reanalyzed and reported by two independent nuclear medicine physicians for abnormalities in the prostate gland primarily and any other abnormal sites of PSMA avidity which could suggest disease. ^{68}Ga-PSMA was synthesized in-house by a standard synthesis protocol.[10] Two MBq/kg body weight of labeled PSMA was injected intravenously and a full body scan (vertex to mid-thigh) was acquired with a dedicated full ring hybrid PET/CT system (Biograph TruePoint40 with LSO crystal from Siemens Healthcare at Rajiv Gandhi Cancer Institute and Research Centre, Delhi, India) with 4 min per bed position in three-dimensional mode. A low-dose CT scan (40 mAs and 120 kVp) was used for attenuation correction and localization. Single voxel maximum standard uptake value normalized to body weight (SUV_{max}) was recorded for prostate gland and for all other abnormal PSMA positive lesions. Baseline PSA was correlated with prostate SUV_{max} and PSMA PET/CT scan positivity using Spearman's rank test. SPSS version 21 was used for statistical analysis.

RESULTS

Patient's details and the findings are summarized in Table 1. All patients showed mild diffuse tracer uptake in the prostate with SUV_{max} ranging from 3.2 to 5.8 (median: 3.9). No focal abnormality was seen in the prostate. Patients 1, 2, 3, and 6 did not show any PSMA avid lesion in rest of the body. Patient 4 and 5 showed abnormal PSMA avid pelvic lymph nodes in both and lung nodule only in patient 5 [Figures 1 and 2]. Subsequent histopathology with immunohistochemistry (NKX 3.1 and PSAP) from pelvic lymph node and lung nodule in case 4 and 5, respectively, showed metastatic adenocarcinoma from prostate. On Spearman's rank correlation [Table 2], we found no correlation of baseline PSA with SUV_{max} of prostate (r_s − 0.029, P = 0.957). However, a strong positive correlation was seen of baseline PSA with ^{68}Ga-PSMA PET/CT scan positivity for extra-prostate disease (r_s = 0.828, P = 0.042). Patient 1 underwent TURP for symptomatic relief with benign histology while patient 2 and 6 were treated medically. Patient 3 underwent radical prostatectomy (RP) with histopathology showing 5% tumor volume and 3 + 4 gleason score. Due to bilateral pelvic lymph node metastasis (one on each side) on ^{68}Ga-PSMA PET/CT scan in patient 4, RP with pelvic lymph node dissection was done. Histopathology showed acinar

Table 1: Patients demography with prostate-specific antigen, 68-gallium-prostate-specific membrane antigen positron emission tomography/computed tomography, prostate maximum standard uptake value normalized to body weight, treatment, histopathology, and follow-up findings

Age (years)	PSA (ng/ml)	^{68}Ga-PSMA PET/CT	Prostate SUV_{max}	Impact of PET (treatment)	Histopathology (tumor %, Gleason score)	Status at 6 months PSA (ng/ml)
73	12.1	Normal	3.7	TURP	BPH	0.12
43	8.2	Normal	3.8	Medical		1.20
50	14.6	Normal	4.4	RP	AA (5%, 3+4)	0.11
68	24.2	Bilateral pelvic LAP	3.2	RP + PLND	AA (1%, 4+4)	0.04
63	18.2	Right pelvic LAP with bilateral lung nodules	5.8	Lung biopsy	Metastatic AA	0.34
47	8.5	Normal	4.0	Medical		0.67

LAP: Lymphadenopathy, TURP: Transuretheral resection of prostate, RP: Radical prostatectomy, PLND: Pelvic lymph node dissection, BPH: Benign prostatic hyperplasia, AA: Acinar adenocarcinoma, SUV_{max}: Maximum standard uptake value normalized to body weight, PSA: Prostate-specific antigen, PET: Positron emission tomography, with ^{68}Ga-PSMA PET/CT: 68-gallium-prostate-specific membrane antigen positron emission tomography/computed tomography

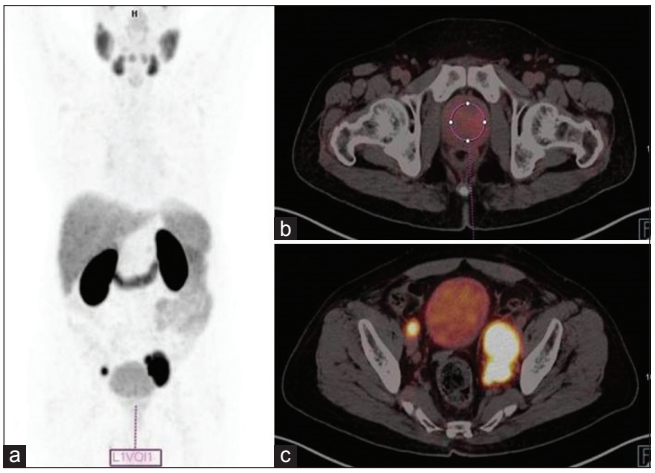

Figure 1: 68-gallium-prostate-specific membrane antigen positron a emission tomography/computed tomography maximum intensity projection (a) and axial-fused images (b and c) showing mildly avid prostate and intensely avid bilateral pelvic lymphadenopathy

Table 2: Spearman's rank correlation of baseline prostate-specific antigen, maximum standard uptake value normalized to body weight of prostate, and 68-gallium-prostate-specific membrane antigen positron emission tomography/computed tomography positivity for extra-prostatic disease

	Sample size	Spearman's coefficient of rank correlation (r_s)	*P*
Correlation of baseline PSA with SUV_{max} of prostate	6	−0.029	0.957
Correlation of baseline PSA with ^{68}Ga-PSMA PET/CT positivity for extra-prostate disease	6	0.828	0.042

PSA: Prostate-specific antigen, SUV_{max}: Maximum standard uptake value normalized to body weight, with ^{68}Ga-PSMA PET/CT: 68-gallium-prostate-specific membrane antigen positron emission tomography/computed tomography

adenocarcinoma (1% tumor volume, Gleason 4+4) with bilateral pelvic lymph node metastasis (one on each side). Patient 5 was treated with androgen deprivation therapy.

DISCUSSION

Enlarged prostate is a most common cause of BOO in male which may be due to BPH or PCa.[11] PSA screening is used to differentiate these two pathologies with a 25% risk of PCa in range 4–10 ng/ml and 42%–64% for PSA >10 ng/ml.[12] Twelve cores TRUS-guided biopsy is used for further characterization as standard but has a low sensitivity and considerable false negative rate and a repeat biopsy may be required in highly suspected cases. We propose ^{68}Ga-PSMA PET/CT as a one stop shop to evaluate such cases.

^{68}Ga-PSMA PET-CT is a promising molecular imaging modality currently investigated in high-risk PCa

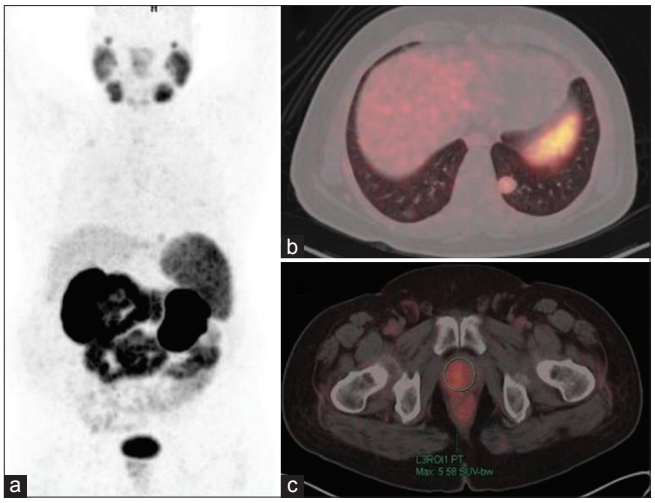

Figure 2: 68-gallium-prostate-specific membrane antigen positron emission tomography/computed tomography maximum intensity projection (a) and axial fused images (b and c) showing mildly avid prostate and left lung lower lobe nodule

primary staging and for restaging/metastatic workup in biochemical recurrence (BCR).[6-9,13] PSMA is a type II transmembrane glycoprotein exhibits folate hydrolase/glutamate carboxypeptidase II enzymatic activity and associated with prostatic carcinogenesis.[14,15] Its expression is directly proportional to gleason score, metastasis, and hormone resistance in PCa.[16] In the last several years, a number of small molecules with PSMA enzyme inhibitor property have been developed. Small molecule inhibitor developed by the Heidelberg group ^{68}Ga-HBED-CC-PSMA-11 (^{68}Ga-PSMA) has been shown to be a novel radiotracer with high cell uptake and prolonged retention after internalization for PCa.[17,18]

A recent systematic review and meta-analysis of ^{68}Ga-PSMA PET-CT showed that overall percentage of positive ^{68}Ga-PSMA PET was 40% for primary staging and 76% for BCR. For the PSA categories 0–0.2, 0.2–1, 1–2, and >2 ng/ml, 42%, 58%, 76%, and 95% scans, respectively, were positive for BCR.[19] Maurer *et al*.[9] in a retrospective review of 130 consecutive patients undergoing ^{68}Ga-PSMA PET before primary lymphadenectomy in high-risk PCa showed sensitivity of 65.9% and specificity of 98.9%. In our experience for lymph node staging in high-risk PCa, ^{68}Ga-PSMA PET-CT and MRI showed sensitivity and specificity of 66.67%, 98.61% and 25.93%, 98.61%, respectively.[13] However, no literature is available citing its role in benign TRUS biopsy cases with abnormal PSA. It has been a common practice to put these patients on follow-up due to no evidence of disease in routine imaging. We have identified a subset of patients who would need active treatment in this group.

Due to technical limitation, ^{68}Ga-PSMA PET/CT is expected to be negative in BPH cases harboring early stage (≤T1b) cancer.[20] Mild diffuse ^{68}Ga-PSMA uptake has been reported with SUV_{max} range from 2.4 to 5.5 and the highest median value of 8.3 after 60 min of tracer injection even in normal cases.[21,22] In our case series, SUV_{max} ranged from 3.2 to 5.8 (median: 3.9) and two patient (case 3 and 4) who underwent radical surgery had early stage PCa not detected by ^{68}Ga-PSMA PET/CT. However, ^{68}Ga-PSMA PET/CT had incremental value in picking up extra-prostatic and extra-pelvic disease. In case 5, lung was the only site of extra-pelvic metastasis which is atypical in PCa.[23]

Our study was associated with limitations as well. Main limitations were the small number of patients, retrospective study, and no control group. Due to very specific cohort selection and PSMA PET/CT is still in developmental stage, not many patients were investigated with this indication. However, these initial results in this subset were encouraging, and hence, we believe future studies will make PSMA PET/CT a strong contender in this indication as well.

CONCLUSION

^{68}Ga-PSMA whole-body PET/CT can provide useful incremental information in patient with high PSA and negative TRUS biopsy and has a potential to guide management in this subgroup of PCa patients.

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Conflicts of interest
There are no conflicts of interest.

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