Original Article

Role of Early Dynamic Positron Emission Tomography/Computed Tomography with 68Ga-prostate-specific Membrane Antigen-HBED-CC in Patients with Adenocarcinoma Prostate: Initial Results

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Abstract

Rationale: Prostate-specific membrane antigen positron emission tomography/computed tomography (PSMA PET/CT) is widely used for imaging of prostate cancer (PC) nowadays. However, appearance of bladder activity many a times hampers lesion detection vis-a-vis primary as well as regional nodes. We aimed to assess if early dynamic PET/CT can be a potential solution to this issue. **Methodology:** A total of 15 biopsy-proven PC patients who were referred to our department for ^{68}Ga-PSMA PET/CT for staging/restaging were prospectively studied. Dynamic PET/CT was done with on table intravenous injection of 2–3 mCi (74–111 MBq) of the radiotracer. Dynamic images were acquired over the pelvis with a frame time of 1 min for 10 min. Static images of 2 min per bed position were acquired between 45 and 60 min after injection. A 3D volume of interest was plotted on the primary lesion, involved nodes if any, pelvic bones at involved and uninvolved sites, gluteal muscles, and bladder. **Results:** Six patients were referred for staging and 9 for restaging. Mean age of 15 patients was 66.7 years, median prostate-specific antigen level was 17.25 ng/ml (Range 0.05–218), mean Gleason score was 8. All patients showed high target to nontarget ratio in the early dynamic images comparable to that seen on the delayed images in different sites (prostatic primary: n = 15 patients; lymph nodes: n = 10 patients; bone: n = 5 patients). All pathologic lesions showed tracer uptake within the first 3 min and reached maximum uptake during the dynamic study in last 3 min, indicating an increasing uptake pattern, whereas urinary bladder (UB) activity was insignificant within the first 3 min of dynamic imaging in all patients, reached maximum during last 3 min. SUV_{max} was significantly higher in primary lesions in the first 4 min compared to UB accumulation. Static images showed more tracer accumulation than dynamic images in primary, nodal, and bony lesions. However, all regional nodes seen on delayed static imaging also showed uptake on dynamic imaging. **Conclusion:** Early dynamic imaging ^{68}Ga-PSMA PET/CT can demarcate the primary tumor clearly due to nonaccumulation of bladder activity and appears to have comparable efficacy in detecting pelvic nodal sites as delayed imaging.

Keywords: *Adenocarcinoma prostate, early dynamic positron emission tomography/computed tomography, ^{68}Ga-prostate-specific membrane antigen-HBED-CC*

Introduction

Over the last decade, ^{68}Ga-labelled prostate-specific membrane antigen 68Ga-Prostate-specific membrane antigen positron emission tomography/computed tomography (PSMA-11 [HBEDD-CC] PET/CT) has proven its significance in the diagnostic evaluation of prostate cancer (PC) patients with biochemical recurrence. Recent literature highlights the role of 68Ga-PSMA PET/CT in diagnosis, staging as well as response assessment in PC patients. PSMA is a type II membrane glycoprotein that is highly expressed by all PCs, and the expression increases with tumor aggressiveness, metastatic disease, and disease recurrence.[1-3] The unique expression of PSMA provides an excellent target for PC imaging and therapy.[4,5] Conventional imaging modalities such as CT or magnetic resonance imaging (MRI) have played limited role in the staging of PC patients as these techniques focus on morphologic information and nodal involvement is mainly assessed by size. Because of the high recurrence rate (up to 50%), timely and accurate detection of recurrence is crucial as it impacts patient management.[6-8] MRI has proven to be a sensitive method in detecting recurrence.[9,10] However, as evaluation of the prostatic fossa with MRI

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using endorectal coils is limited to the pelvis, additional imaging modalities are necessary to assess the presence of nodal involvement and distant metastases. Whole-body PET/CT imaging with ^{68}Ga-PSMA has shown high diagnostic accuracy and is increasingly established as the primary staging tool in PC and in patients with suspicion of recurrent disease.[11-13] With respect to the overall detection rate, ^{68}Ga-PSMA-11 PET/CT seems to perform better than other PET tracers for PC imaging such as 18F-choline and 11C-choline.[14-16] Apart from prostate and PC lesions, 68Ga-PSMA-11 shows physiological uptake in salivary glands, lacrimal glands, kidneys, and urinary bladder (UB) due to renal route of excretion. It is important for all the imaging modalities to detect local recurrence (LR) at an early stage (when disease is still confined to the prostatic fossa) since treatment modalities with higher efficacy such as salvage radiotherapy are available.[17] However, detection of primary prostatic lesion or the LR is hampered by increased physiological radiotracer uptake in the UB on whole-body scans, conventionally acquired at 60 min p.i.[15,18,19] To overcome this limitation, postdiuresis view is often acquired after the whole body PET/CT imaging. This view might improve the lesion detection and interpretation but is time-consuming and is not an option for patients with impaired renal function. Implications of early dynamic imaging in PSMA PET/CT has been documented by very few authors in literature.[20-22] We designed this study with the primary objective of assessing the role of early dynamic PET/CT with ^{68}Ga-PSMA-HBED-CC in biopsy-proven PC patients (primary and/or recurrent). The secondary objective was to evaluate PSMA uptake patterns and assess quantitative parameters including time activity curve (TAC) and time to peak activity (T-peak) from tumor and nontumor sites.

Methodology

This was a prospective cohort-based study conducted at the Department of Nuclear Medicine of a tertiary care hospital in India. The patients were recruited over a period of 1 year.

Fifteen patients with biopsy-proven adenocarcinoma prostate referred for ^{68}GA-PSMA-HBED-CC PET/CT for primary staging as well as those with rising prostate-specific antigen (PSA) levels after receiving primary treatment were included in the study. Written informed consent was obtained from all patients. Patients with dual malignancy, renal impairment (Serum creatinine >1.2 mg%), and/or hepatic impairment (Total Bilirubin >1.3 mg%, Elevated SGOT/SGPT/Alkaline phosphatase) were excluded. All patients underwent ^{68}Ga-PSMA-HBED-CC dynamic PET/CT followed by delayed whole-body PET/CT on Biograph mCT PET/CT with lutetium oxyorthosilicate crystal and 64 slice CT scanner (Siemens Inc., Germany).

Image acquisition

First a low dose noncontrast CT was acquired over pelvic region at 50–100 mAs followed by on-table tracer injection (2–3 mCi [74–111 MBq]). Dynamic images were acquired in one-bed position, at 1 min/frame for 10 min. At 45–60 min postinjection, whole body PET/CT images of 2–3 min per bed position from vertex to midthigh were acquired. No intravenous or oral contrast was used. Images were reconstructed with iterative reconstruction using OSEM algorithm with 3 iterations and 21 subsets.

Image analysis

Dynamic and static images were interpreted by two Nuclear Medicine physicians, independently. Volume of interests (VOIs) was drawn on the primary lesion (P), UB, normal bone (B), muscle (M), artery (A) and bony lesion (BI) and node (N), if present. The VOI drawn on one frame was replicated to the other frames. TACs were generated. Semi-quantitative and quantitative analysis was done and parameters such as SUV_{max}, $SUV_{mean,}$ Time to peak, and TAC were calculated.

Pathological diagnosis for the primary lesion was available in all patients. For nodal lesions, findings were correlated with available MRI, serum PSA levels. Lymph nodes with increased PSMA expression in the draining areas of the prostate and with loss of architecture on CT were considered metastatic. For bony lesions, CT features of dense sclerosis with increased PSMA expression on PET in the setting of commensurately increased PSA levels were considered metastatic. Bone scan was used for corroboration where available.

Statistical analysis

Descriptive statistics was applied to all parameters to estimate mean, median, range, and standard deviation. SUV_{max} values of *P* were compared with that of UB, B, M, A, BI, and N. To test the significance of difference of SUVs between *P* and other areas, Wilcoxon signed rank sum test was used.

Results

Mean age of the patients was 66.7 years (range: 60–76 years). Mean PSA level was 17.25 ng/ml (range 0.05–373) and mean Gleason score was 8. Of the 15 patients included, 6 patients were referred for staging while 9 for restaging. All the patients showed significant tracer uptake in the prostatic lesion on PSMA PET/CT whole body image, while nodal and bone involvement was seen in 9 and 5 patients, respectively [Table 1].

Tracer uptake was observed in prostatic lesion (P) as early as 1 min p.i. in all patients that followed a temporally increasing trend reaching its zenith during the dynamic study in the last 3 min (at 10 min p.i.). On the other hand, the radioactivity in UB was visually insignificant

until 4 min p.i. and reached maximum during last frame (10 min p.i.) [Figure 1]. SUV_{max} of the prostatic lesion was significantly higher than that of UB throughout the dynamic study at all time points (P = 0.0008 at 3 min and 0.017 at 10 min). However, the difference between SUV_{max} of the prostatic lesion and bladder on delayed image at 60 min p.i. was insignificant (P = 0.26).

Median SUV_{max} of all the studied regions (P, UB, B, M, A, BI, N) at all time points during the dynamic scan and at delayed scan time are given in Table 2. The activity in B and M remained low in all the patients throughout the dynamic scan. TAC of various regions during dynamic imaging is given in Figure 2.

The activity in involved node also remained less than that of primary lesion at all time points. Involved bone lesions showed variable activity depending on the nature and extent of metastasis [Figure 2]. All the nodes and bone lesions in the pelvic region detected on delayed images could also be seen on early dynamic images.

Median P-to-UB ratio at different time points during dynamic scan and delayed scan are given in Table 3. P/UB ratio was highest at 3 min p.i. followed by a gradual decrease and reached minimum at the delayed whole body scan time point that is at 60 min p. i [Figure 3].

Early dynamic images of a patient and a comparison with delayed scan are given in Figure 4. Early dynamic images display better delineation of prostatic lesion due to insignificant bladder activity. However, on delayed image, primary lesion to background contrast is poor due to radioactivity in bladder [Figure 4].

Table 1: Lesionwise comparison of early dynamic and delayed static image in pelvic region

Lesions	Early dynamic image	Static image
Primary (prostate)	15	15
Node	9	9
Bone	5	5

Table 2: Median maximum standardized uptake value of various regions over first 10 min of dynamic scan and at 60 min p.i., that is at delayed scan

Time (min)	P	B	BI	BU	A	M	N
1	2.25	0.58	2.69	0.95	3.67	1.23	1.97
2	4.37	0.83	2.91	1.59	4.55	1.64	3.13
3	5.34	0.95	3.94	1.72	4	1.41	3.4
4	5	1.05	4.54	1.4	3.51	1.58	3.35
5	6	1.08	5.92	1.39	3.64	1.59	3.41
6	5.7	1.85	6.49	1.52	2.74	1.96	4.26
7	6.27	2.23	4.3	1.16	2.61	1.74	3.39
8	6.71	2.46	5.92	1.33	2.61	2.08	2.72
9	7	2.51	4.065	1.15	2.62	2.96	4.22
10	7.7	3.31	5.835	0.83	2.2	1.76	3.02
60	16.7	24.35	3.35	1.74	1.09	9.35	0.91

P: Primary lesion, B: Normal bone, M: Muscle, A: Artery, BI: Bony lesion, N: Node, BU: Bone uninvolved

Table 3: Prostate to urinary bladder ratio at different time points

Time (min)	P/UB (median)
1	3.409090909
2	4.789473684
3	6.47133758
4	5.4
5	5.191011236
6	4.014084507
7	2.80418251
8	2.482587065
9	2.381877023
10	2.947019868
60	1.182622687

UB: Urinary bladder, P: Primary lesion

Discussion

In the present prospective study, we analyzed the role of early dynamic imaging using 68Ga-PSMA-11 PET/CT in detection of PC lesions (primary/recurrent). We observed that early dynamic images display better delineation of primary prostatic lesions due to insignificant bladder activity. Furthermore, on delayed images, primary lesion to background contrast is less due to radioactivity in bladder. Most of the studies in literature have investigated the role of ^{68}Ga-PSMA PET/CT for restaging of PC in the setting of biochemical recurrence and have demonstrated very promising results with high sensitivity and specificity.[7-9] However, the utility of ^{68}Ga-PSMA PET/CT in assessment of primary PC before prostatectomy is yet to be fully determined. Initial studies regarding the early dynamic imaging in PET/CT was done using 18F-choline. Early dynamic acquisition of the pelvic region within the first 8 min p.i. helped to distinguish LR from UB activity.[23] Simone *et al*. demonstrated a significant increase in diagnostic accuracy in 18F-choline PET with the help of early dynamic phase compared to standard whole-body imaging 10–20 min p.i. The majority of LR was only visible on early dynamic images, resulting in a detection rate for LR to be 67.1%.[24] With the same concept, studies using ^{68}Ga PSMA are emerging in recent times. Kabasakal *et al*. evaluated the diagnostic value of early imaging of the pelvis in ^{68}Ga-PSMA PET/CT in 28 patients having PC. They acquired images at 5 and 60 min after injection. Intense radiotracer uptake was seen in 23 patients (77%) at the site of primary tumor. Lymph node metastases were detected in 10 patients (36%), and bone metastases were detected in seven patients (25%). No difference in the number of lesions was found when early and late pelvic images were compared. The author concluded that early images help better distinguish between UB (before tracer accumulation occurs) and tumor lesions.[20] This study is in concordance with our study results. Our study showed tracer uptake in prostate

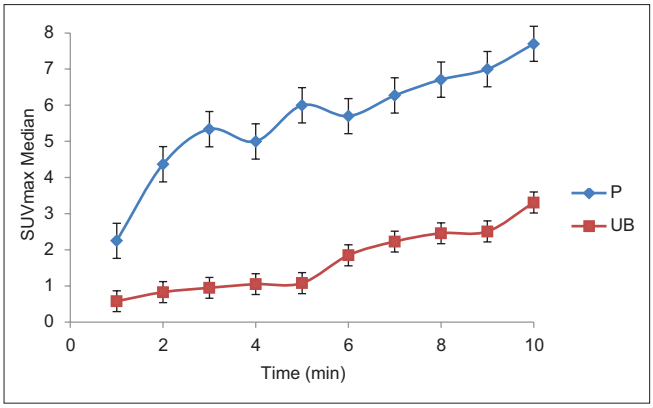

Figure 1: Time-activity curve of primary and urinary bladder during dynamic imaging for 15 patients

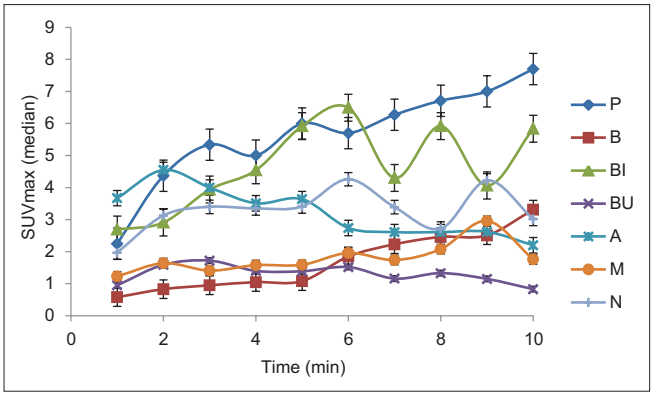

Figure 2: Time-activity curve of various regions during dynamic imaging

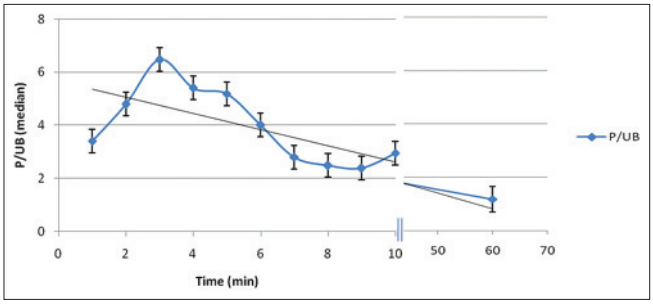

Figure 3: Prostate to urinary bladder ratio at different time points

lesion as early as 1 min p.i. Furthermore, prostate to bladder ratio is higher in early dynamic images than that in delayed images. The ratio was highest at 3 min and then decreased gradually [Figure 3]. Furthermore, we observed that the difference between tracer uptake in the prostatic lesion and bladder was significant (higher in prostate lesion) on dynamic images, but it was insignificant on delayed image indicating much higher contrast between primary lesion and bladder in early images. Uprimny *et al*. included 203 consecutive PC patients with biochemical failure with 68Ga-PSMA-11 PET/CT. They performed early static images of the pelvis at a median time of 283s p.i. (range: 243–491s) and whole-body PET/CT scan at 60 min p.i. 12.8% of the patients were reported positive for LR on PET scans 60 min p.i. (median SUV_{max}: 10.8; range: 4.7–40.9), whereas early PET imaging (median SUV_{max}: 5.9; range: 2.9–17.6) detected LR in 24.6% of patients, suggestive of a significant rise in detection rate ($P < 0.001$). Equivocal findings on PET scans 60 min p.i. decreased significantly with the help of early imaging (15.8% vs. 4.5% of patients; $P < 0.001$). They concluded that early imaging in 68Ga-PSMA-11 PET/CT along with whole-body scans 60 min p.i. increases the detection rate of LR in PC patients with biochemical recurrence.[21] However, a study by Schmuck *et al*. deferred in opinion. They concluded that primary PC is detected on early dynamic and static delayed ^{68}Ga-PSMA PET images and that the tumor-to-nontumor ratio in the prostate gland improves over time, highlighting the role of delayed imaging. They conducted ^{68}Ga-PSMA I and T PET/CT in 20 patients with PC before prostatectomy.[22] In our study, although the absolute SUV_{max} increased with time and was higher in delayed images, the contrast and P/UB ratio was higher in the early dynamic images.

Very few methods are available to reduce the bladder radioactivity, such as administration of diuretics or voiding the bladder before scan. However, these protocols do not sufficiently reduce the bladder activity.[25] Furthermore, these methods are often time-consuming making the patients noncompliant. In addition, the administration of diuretics cannot be applied to patients with renal impairment. The early dynamic imaging proposed in this study may not only enhance the contrast between the lesion and background but can also save time by potentially avoiding a postdiuresis view. This aspect needs to be explored further. In the conventional method, PET/CT images are acquired at 60 min p. i and then a separate postdiuresis view is taken after ~45–60 min. In a tertiary care hospital of a developing country, where the patient load is very high, this method can reduce patient waiting time considerably while simultaneously enhancing the lesion detection. The second objective of this study was to generate the TAC for tumor and nontumor tissues so as to evaluate PSMA uptake patterns. We also observed that all metastasized nodes and the bone lesions in pelvic bed that were detected on delayed image could also be visualized on early dynamic images, primarily because of the lower background radioactivity. Limitations of our study included a small sample size of 20 patients. Furthermore, a follow-up imaging would have helped us to accurately characterize the lesions. We relied upon a single time point interpretation for the purpose of this study. Further research with a larger sample size is required to validate the results.

Conclusion

Early dynamic imaging with 68Ga-PSMA-11 PET/CT facilitates better delineation of the prostatic primary lesions because of the considerably low radioactivity in UB resulting in enhancing target to background ratio. Furthermore, regional nodes and pelvic bony lesions are

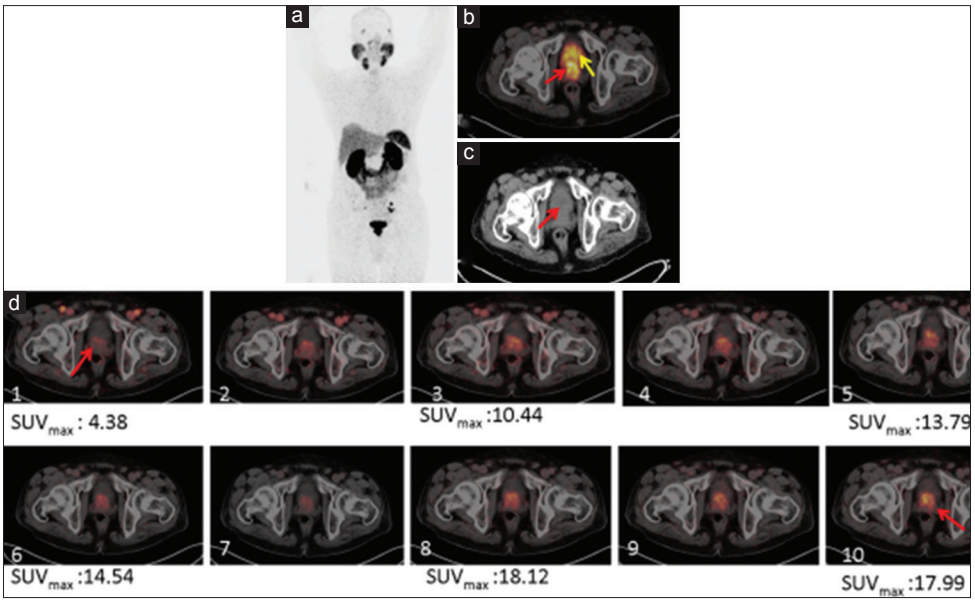

Figure 4: ^{68}Ga- Prostate-specific membrane antigen-11 positron emission tomography/computed tomography in a prostate cancer patient with biochemical recurrence (prostate-specific antigen: 34.5ng/mL). Maximum intensity projection (a) fused positron emission tomography/computed tomography (b) and computed tomography (c) of whole-body PET 60 min p.i. showing uptake in pathologic lesion (SUV_{max}: 35.2) as well as urinary bladder. (d) Dynamic images showing progressively increasing uptake in prostate lesions whereas urinary bladder activity remains insignificant

equally well seen in early dynamic as well as delayed static images. Early dynamic images may be conducted in combination with the routine 60 min whole body scan to avoid overlooking smaller lesions. Early dynamic imaging using 68Ga PSMA PET/CT is a promising additional protocol along with whole-body imaging in patients with primary/recurrent PC patients.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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