A comparison of the diagnostic performance of ^{18}F-PSMA-1007 and ^{68}GA-PSMA-11 in the same patients presenting with early biochemical recurrence

Thabo Lengana[1] MD, Ismaheel O. Lawal[1] MD, Charl Janse Van Rensburg[2] PhD, Kgomotso M.G. Mokoala[1] MD, Evelyn Moshokoa[3] MD, Trevino Ridgard[3] MD, Mariza Vorster[1] MD, Mike M. Sathekge[1] MD, PhD

1. Department of Nuclear Medicine, University of Pretoria & Steve Biko Academic Hospital, Pretoria, South Africa
2. Biostatistics Unit, Pretoria MRC, South African Medical Research Council
3. Department of Urology, University of Pretoria & Steve Biko Academic Hospital, Pretoria, South Africa

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Corresponding author:
Mike M. Sathekge MD, PhD
Department of Nuclear Medicine, University of Pretoria and Steve Biko Academic Hospital, Private Bag X169, Pretoria 0001, South Africa
mike.sathekge@up.ac.za

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Abstract

Objective: Accurate early assessment of biochemical recurrence is essential in determining the correct treatment plan for patients with prostate cancer. Gallium-68-prostate-specific membrane antigen-11 (^{68}Ga-PSMA-11) targeting PSMA has been at the forefront of imaging in biochemical recurrence however the emergence of fluorine-18 (^{18}F)-PSMA-1007 may prove to be advantageous over the ^{68}Ga-PSMA-11 molecule due to its physical and physiological attributes. The aim of our study was to assess the diagnostic performance of ^{18}F-PSMA-1007 as compared to that of ^{68}Ga-PSMA-11 in the same patients who presented with biochemical recurrence. **Materials and Methods:** Twenty-one patients with biochemical recurrence prostate cancer were prospectively enrolled into the study. Fluorine-18-PSMA-1007 positron emission tomography/computed tomography (PET/CT) was performed on the same patient after ^{68}Ga-PSMA-11 PET/CT had been performed. Recurrence diagnosed on each of these studies was compared against a final diagnosis based on clinical follow-up and histological correlation where available. **Results:** Gallium-68-PSMA-11 identified fifteen (71,4%) patients as being negative for recurrence whilst five (23.8%) were identified as positive and one (4.8%) as uncertain. In comparison ^{18}F-PSMA-1007 identified eight (38.1%) as being positive with thirteen (61.9%) patients' scans identified as negative for recurrence. No scans were classified as uncertain for the ^{18}F-PSMA-1007 group. Fluorine-18-PSMA-1007 identified 8 lesions as positive for disease recurrence whilst only 6 lesions were identified on ^{68}Ga-PSMA-11. Of the 8 patients identified as having recurrence on ^{18}F-PSMA-1007 4 of those demonstrated local prostatic recurrence. The rest demonstrated local nodal recurrence and skeletal metastases. Fluorine-18-PSMA-1007 demonstrated a sensitivity, specificity, positive and negative predictive value of 88.9%, 100%, 100%, and 92.3% respectively whilst ^{68}Ga-PSMA-11 demonstrated a sensitivity, specificity, positive and negative predictive value of 44.4%, 83.3%, 80%, and 66.6%, respectively. **Conclusion:** In our pilot study ^{18}F-PSMA-1007 was able to detect more sites of recurrence as compared to ^{68}Ga-PSMA-11 which were mainly within the prostate and surrounding pelvic structures.

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Introduction

Prostate cancer remains among the leading causes of cancer in men worldwide coming second to lung cancer [1]. Patients with prostate cancer who present with localized disease generally respond well to intent to cure therapy however up to 30% of these patients may represent with recurrent prostate cancer evidenced by a detectable rise in serum prostate specific antigen (PSA) value after definitive therapy [2].

Early recurrence detection and accurate restaging of prostate cancer patients is crucial for implementation of the appropriate therapeutic modalities and survival especially at low PSA values [3-5].

Gallium-68-prostate-specific membrane antigen-11 (^{68}Ga-PSMA-11) has emerged as the leading positron emission tomography (PET) imaging agent of choice in biochemical recurrence demonstrating good sensitivity and specificity in the setting of low serum PSA values [6, 7]. Gallium-68-PSMA has been demonstrated to have a high interobserver reliability and was demonstrated to be superior to conventional imaging in the detection of nodal metastases in the initial staging of prostate cancer [8, 9]. In a metanalyses ^{68}Ga-PSMA for restaging has demonstrated to have high sensitivity and specificity in the detection of prostate cancer recurrence [10]. An additional advantage of ^{68}Ga-PSMA is its theragnostic application and detection of patients who may benefit from therapy with lutetium-177 (^{177}Lu)-PSMA [11]. Studies on the impact of ^{68}Ga-PSMA PET/computed tomography (CT) imaging on treatment intent have consistently demonstrated significant management changes as a result of positive findings on PSMA PET/CT scans [12, 13].

Gallium-68-PSMA-11 though does have significant challenges. Gallium-68 is obtained from a ^{68}Germinium/^{68}Gallium generator which can only be eluted for a limited number of times in a day limiting the number of patients which could be imaged in a day [14]. Gallium-68 also has a half-life of only 68 minutes not making it easily possible for ^{68}Ga-PSMA-11 to be shipped from a central source to a peripheral location for imaging.

The normal physiological biodistribution of ^{68}Ga-PSMA-11 involves uptake in the salivary glands, liver, spleen with significant tracer accumulation being noted in the ureters and bladder due to renal excretion of this tracer [15]. On the other hand fluorine-18 (^{18}F)-PSMA-1007 under goes hepatobiliary clearance resulting in minimal tracer accumulation in the ureters and bladder [16]. Fluorine-18-PSMA-1007 also has the advantage of being cyclotron produced resulting in greater availability of the tracer for imaging as compared to ^{68}Ga-PSMA-11. In addition ^{18}F has a lower positron energy as compared to ^{68}Ga thus exhibits a higher spatial resolution and due to its long half-life of 110 minutes delayed imaging may be acquired to improve target to background clearance [17].

The aim of our study was to assess prospectively the diagnostic performance of ^{18}F-PSMA-1007 as compared to ^{68}Ga-PSMA-11 in the same patients who presented with biochemical recurrence.

Materials and Methods

The study was approved by the University of Pretoria, Faculty of Health Research Ethics Committee, approval number 217/2018.

Patients with biochemical recurrence prostate cancer were prospectively enrolled into the study after signing informed consent (Table 1). The study was conducted according to the ethical principles defined on the Declaration of Helsinki and according to the principles of Good Clinical Practice. To be eligible for the study the patients had to have had histological confirmed prostate cancer, history of previous definitive prostate cancer therapy (prostatectomy/radiotherapy or both), biochemical recurrence with PSA <10ng/mL and signed informed consent. Biochemical recurrence was defined as a PSA value >0.2ng/mL after radical prostatectomy or a PSA value >2ng/mL from nadir after radiotherapy [18].

Gallium-68-PSMA-11 was prepared in-house as we have previously described by adding $^{68}GaCl_3$ obtained from a ^{68}Ge/^{68}Ga generator (iThemba LABS, Somerset West, South Africa) to a PSMA kit (ABX advanced biomedical compounds, GmbH, Radeberg, Germany). [19].

Fluorine-18-PSMA-1007 was supplied by NTP Radioisotopes South Africa and was synthesized as described by Giesel et al. (2018) [20].

Radiochemical purity of all injected radiopharmaceuticals was above 95%.

No particular special preparation was required of the patients prior to imaging. Whole body PET/CT images from crane vertex to mid-thigh were acquired on a Siemens Biograph 40 PET/CT scanner 60 minutes and 120 minutes after injection of ^{68}Ga-PSMA-11 and ^{18}F-PSMA-1007, respectively. Gallium-68-PSMA and ^{18}F-PSMA-1007 were acquired within 4 weeks of each other.

Table 1. *Age distribution, Gleason scores, PSA and primary therapy of study participants.*

Variable	Frequency	Percentage
Age (years)		
Mean ± SD	68.57±7.74	
Range	48-78	
Gleason Grade		
1	8	38.1
2	8	38.1
3	1	4
4	2	9.5
5	2	9.5
PSA		
Mean±SD	2.55±3.1	
Range	0.05-8.93	
<0.5	9	42.9
0.5-1.0	-	-
1.0-2.0	5	23.8
>2.0	7	33.3
Primarytherapy		
Prostatectomy	15	71.4
Prostatectomy + EBRT	2	9.5
Radiotherapy	4	19.1

SD: Standard deviation; EBRT: External Beam Radiotherapy

The median injected activity was 3.7mCi (range 1.24-8.25mCi) and 3.6mCi for (range 2.01-6.3) ^{18}F-PSMA-1007 and ^{68}Ga-PSMA-11, respectively.

Non-contrasted low dose CT scans were acquired for all studies for attenuation correction and anatomical localization. The CT parameters were adjusted for the patients' weight (120Kev, 40-150mAs) with a section width of 5mm and pitch of 0.8. Positron emission tomography imaging followed CT imaging and was acquired in 3-D mode at 4 minutes per bed position. Image reconstruction was done with ordered subset expectation maximization iterative reconstruction algorithm (four iterations, eight subsets) [21].

Image analysis

Acquired ^{18}F-PSMA-1007 PET/CT and ^{68}Ga-PSMA-11 images were interpreted independently by two board-approved

nuclear medicine physicians, blinded to the clinical and standard imaging results. Disagreement in image interpretation was resolved by consensus. Positron emission tomography/CT images were visually analyzed for the presence of sites of abnormal focal ^{18}F-PSMA-1007 and ^{68}Ga-PSMA-11 uptake. Uptake higher than background activity in lymph nodes and tissues either than stellate, coeliac and sacral ganglia, not corresponding to physiologic tracer accumulation, was considered pathologic and compatible with malignancy. The number of ^{18}F-PSMA-1007 and ^{68}Ga-PSMA-11 avid lesions and their location were recorded for all PET/CT patient studies as per mi-TNM classification [22]. The detection rate of recurrence by ^{18}F-PSMA-1007 PET/CT and ^{68}Ga-PSMA-11 was defined in the entire group of patients and for different levels of PSA, respectively <0.5ng/mL, between 0.5 ng/mL and 1ng/mL, between 1ng/mL and 2ng/mL, and above 2ng/mL.

Metastasis diagnosed on each of these studies was compared to the final diagnosis based on histological correlation and clinical follow-up.

Statistical analyses

Descriptive statistics of the demographic and clinical characteristics of the study population were done. A two-by-two contingency table was used to obtain the sensitivity, specificity, positive predictive value, negative predictive value as well as the accuracy of ^{18}F-PSMA-1007 PET/CT and ^{68}Ga-PSMA-11 PET/CT for the detection of recurrence. The diagnostic performances of the two imaging modalities at different Gleason grades were determined. Similar evaluation was done for the diagnostic performances of the two imaging modalities at different PSA levels (PSA <.5, 0.5-1.0, 1.0-2.0, >2.0). The diagnostic performances for the entire cohorts of ^{18}F-PSMA-1007 and ^{68}Ga-PSMA-11 PET CT for the detection of recurrence were compared using McNemar's test. The statistical significant level was set at a P value of <0.05. Statistical analysis was done using STATA 14.

Results

Twenty-one patients (mean age, 68.57 years, range, 48 – 78 years) with biochemical recurrence prostate cancer were prospectively enrolled into the study (Table 1).

Gallium-68-PSMA-11 identified fifteen (71,4%) patients as being negative for recurrence whilst five (23.8%) were identified as positive and one (4.8%) as uncertainand was considered a false negative. In comparison, ^{18}F-PSMA-1007 identified eight (38.1%) as being positive with thirteen (61.9%) patients' scans identified as negative for recurrence. No scans were classified as uncertain for the ^{18}F-PSMA-1007 group. Fluorine-18-PSMA-1007 identified 8 lesions as positive for disease recurrence whilst only 6 lesions were identified on ^{68}Ga-PSMA-11. Eight patients were identified as having recurrence on ^{18}F-PSMA-1007, 4 of those demonstrated local prostatic recurrence. The rest demonstrated oligometastatic local nodal recurrence and skeletal metastases (Table 3).

Five patients were identified as having recurrence on ^{68}Ga-PSMA-11, whilst a single patient demonstrated equivocal findings. Only a single nodal metastasis was identified on ^{68}Ga-PSMA-11. No skeletal lesions were identified on ^{68}Ga-PSMA-11 (Table 2).

Table 2. *Study participant PET CT study image findings of ^{18}F-PSMA-1007 and ^{68}Ga-11.*

Variable	^{18}F-PSMA-1007 PET/CT N (%)	^{68}Ga-PSMA PET/CT N (%)
Positive	8 (38.1)	5 (23.8)
Negative	13 (61.9)	15 (71.4)
Uncertain	--	1 (4.8)
Total Lesions Detected	8	6
Prostatic Bed Disease Only	4	5
Local Soft Tissue Disease	3	1
Skeletal Metastatic Disease	1	--

Seventeen patients had had previous prostatectomy. Fluorine-18-PSMA-1007 identified a site of recurrence in 7 of these of these patients whilst ^{68}Ga-PSMA-11 identified a site of recurrence in 4 patients (Table 3).

Four of the patients had primary radiotherapy. Fluorine-18-PSMA-1007 identified a site of recurrence in a single patient whilst ^{68}Ga-PSMA-11 did not identify a site of recurrence in any of the patients (Table 1).

Fluorine-PSMA-1007 demonstrated a sensitivity, specificity, positive and negative predictive value of 88.9%, 100%, 100%, and 92.3%, respectively whilst ^{68}Ga-PSMA-11 demonstrated a sensitivity, specificity, positive and negative predictive value of 44.4%, 83.3%, 66.7%, and 66.7%, respectively. The accuracy for ^{18}F-PSMA-1007 and ^{68}Ga-PSMA was 95.5% and 80.8%, respectively (Table 3).

Discussion

Early recurrence detection and accurate restaging of prostate cancer patients is crucial for implementation of the appropriate therapeutic modalities and survival, especially at low PSA values.

The early detection of recurrence and accurate restaging of prostate cancer patients is essential in aiding in the decision making for the most appropriate treatment modality and contributes to improved survival [5]. Gallium-68-PSMA -11has emerged as a leading PET imaging agent in bioche-

Table 3. *Patients based study findings of ^{18}F-PSMA-1007 and ^{68}Ga-PSMA-11.*

Patient	Gleason Grade	PSA ng/ml	RP	RT	HT	mi-TNM ^{18}F-PSMA-1007	mi-TNM ^{68}Ga-PSMA-11
1	2	0.34	Yes	No	No	T0 N0 M0	T0 N0 M0
2	1	1.73	Yes	EBRT	No	T0 N1a (II) M0	T0 N1a (II) M0
3	1	1.51	Yes	No	No	Tr N0 M0	T0 N0 M0
4	5	8.12	Yes	No	No	T0 N0 M1b (Oligo) L5, Left glenoid	Tr N0 M0
5	2	0.13	Yes	No	No	T0 N0 M0	T0 M0 N0
6	1	0.43	Yes	EBRT	Yes	Tr N0 M0	Tr N0 M0
7	1	8.53	Yes	No	Yes	Tr N0 M0	T0 N0 M0
8	2	0.33	Yes	No	No	T0 N0 M0	T0 N0 M0
9	2	2.04	Yes	No	No	T0 N1a (OP) para-rectal M0	T0 N0 M0
10	5	8.67	No	Brachy	Yes	T0 N0 M0	T0 N0 M0
11	1	3.18	Yes	No	No	T0 N0 M0	T0 N0 M0
12	2	0.22	Yes	No	Yes	T0 N0 M0	T0 N0 M0
13	2	1.73	Yes	No	No	T0 N0 M0	T0 N0 M0
14	2	1.24	Yes	No	Yes	T0 N0 M0	T0 N0 M0
15	1	8.93	No	Brachy	No	T3b N0 M0	T3b N0 M0
16	2	3.95	Yes	No	Yes	T0 N0 M0	T0 N0 M0
17	2	0.42	Yes	No	No	T0 N0 M0	T0 N0 M0
18	4	0.05	No	Brachy	Yes	T0 N0 M0	T0 N0 M0
19	1	0.16	Yes	No	Yes	T0 N1a (CI) M0	T0 N0 M0
20	1	0.06	No	Brachy	Yes	T0 N0 M0	Equivocal
21	3	1.67	Yes	Yes	No	T0 N0 M0	Tr N0 M0

RP: Radical prostatectomy, RT: radiotherapy, HT: hormonal therapy

Table 4. *Comparing the diagnostic performance of ^{18}F-PSMA-1007 and ^{68}Ga-PSMA PET/CT.*

Variables	Positive n=9 (%)	Negative n=12 (%)	Total N=21 (%)
^{18}F-PSMA-1007			
Positive	8 (100)	0 (0)	8
Negative	1 (7.69)	12 (92.31)	13
^{68}Ga-PSMA			
Positive	4 (80)	1 (20)	5
Negative	5 (33.33)	10 (66.66)	15
Suspicious[1]	0	1 (100)	1

Evaluation	^{18}F-PSMA-1007	^{68}Ga-PSMA PETCT
Sensitivity	88.9%	44.4%
Specificity	100%	83.3%
Positive predictive value	100%	66.7%
Negative predictive value	92.3%	66.7%
Accuracy	95.5$	80.8%

P=0.3750; 1-The suspicious case was considered as false negative

mical recurrence.

In a meta analyses ^{68}Ga-PSMA-11 PET/CT demonstrated an overall 86% detection rate in biochemical recurrence. The detection rate for recurrence reduced significantly as PSA levels dropped and was found to be 50% for PSA of 0.2-0.49 ng/mL and 53% for PSA levels of 0.50-0.99ng/mL. Prostate bed recurrence was only identified in 10% of the cases whilst the majority of the sites of recurrence included the lymph nodes [23].

Though demonstrating very good detection rates in biochemical recurrence ^{68}Ga-PSMA is not without limitations. Physiologic urinary excretion of ^{68}Ga-PSMA has been cited as a possible cause for both false negative and false positive findings on imaging. This is due to the fact that urinary activity may be mistakenly identified as a site of prostate cancer recurrence or alternatively sites of recurrence may be missed in the prostate bed or in close association to the ureters due to the adjacent urinary activity [24]. To mitigate this, forced diuresis and subsequent delayed imaging has been proposed in an attempt to increase detection rates [25].

The introduction of ^{18}F-PSMA-1007 PET/CT imaging was anticipated to yield increased sensitivity for locoregional staging/restaging adjacent to bladder and ureters [26]. Rauscher et al. (2020) demonstrated that ^{18}F-PSMA-1007 in comparison to ^{68}Ga-PSMA-11 was able to detect more sites of recurrence adjacent to the urinary bladder due to its higher tumor to background ratio [27]. Geisel et al. (2019) in a large cohort study demonstrated a detection rate of 81.3% in biochemical recurrence, which was 62% for patients with PSA levels between 0.5-0.2ng/mL [28]. Similar detection rates in the setting of low PSA were also seen by other researchers [29].

In our study we demonstrated a slightly lower detection rate of 38% for ^{18}F-PSMA-1007. This may be due to our small sample size and majority of our patients (42.9%) presenting with a PSA of less than 0.5ng/mL. Though ^{18}F-PSMA-1007 had a low detection rate when compared to other published data, this was still higher than that of ^{68}Ga-PSMA (23.8%) in the same patients.

Fluorine-18-PSMA-1007 did demonstrate an advantage over ^{68}Ga-PSMA-11 which was in line with the expected advantage from its unique physiological biodistribution. The majority of the sites of recurrence that were missed by ^{68}Ga-PSMA-11 were in the prostate bed or adjacent pelvic structures. Our findings suggested increased interpreter confidence with no study demonstrating equivocal findings non ^{18}F-PSMA-1007 PET/CT imaging.

McCarthy et al. (2019) found that the majority of patients with biochemical recurrence would present with oligometastatic disease which is confined to the pelvis in the majority of patients [30]. In our study we similarly identified mainly oligometastatic disease which was mainly limited the pelvis. This again highlights the advantage that ^{18}F-PSMA-1007 may have on renally excreted PSMA PET molecules due to

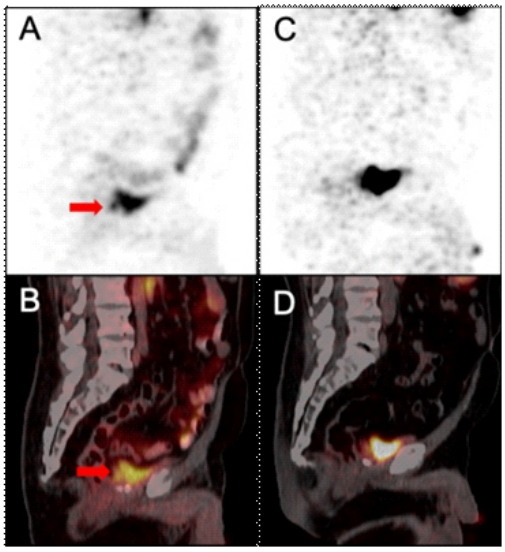

Figure 1. 75 year old male, Gleason grade 1, with PSA of 1.51ng/ml. Sagittal ^{18}F-1007-PSMA PET (A) and fused (B) images demonstrating prostatic recurrence (arrow). ^{68}Ga-PSMA-11 sagittal PET (C) and fused (D) images demonstrating negative uptake.

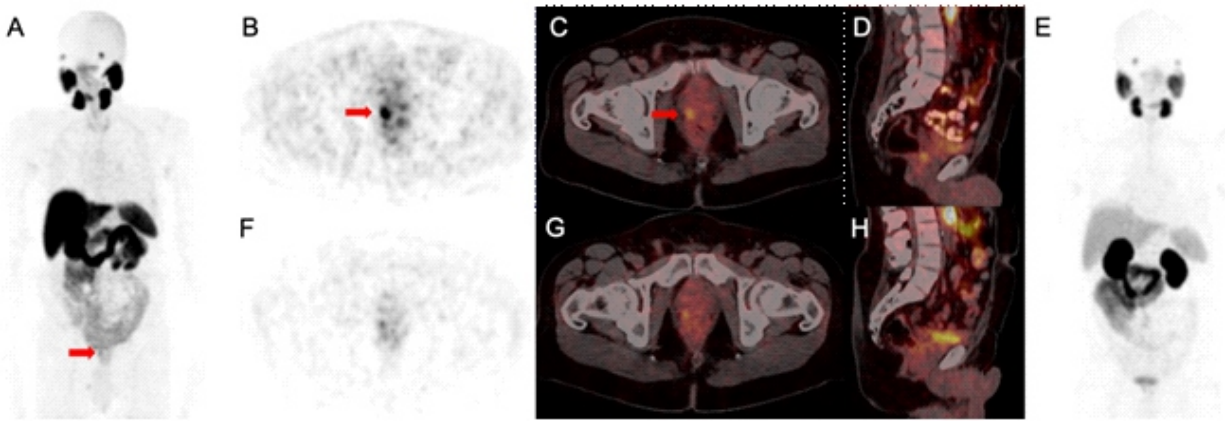

Figure 2. 68 year old male, Gleason grade 2, with PSA 2.04ng/ml. ^{18}F-1007-PSMA PET mip (A), axial PET (B) and fused axial(B) and fused sagittal (D) images demonstrating para-rectal recurrence (arrow). ^{68}Ga-PSMA-11 PET mip (E), axial PET (F), fused axial (G) and fused sagittal (H) images demonstrating negative uptake.

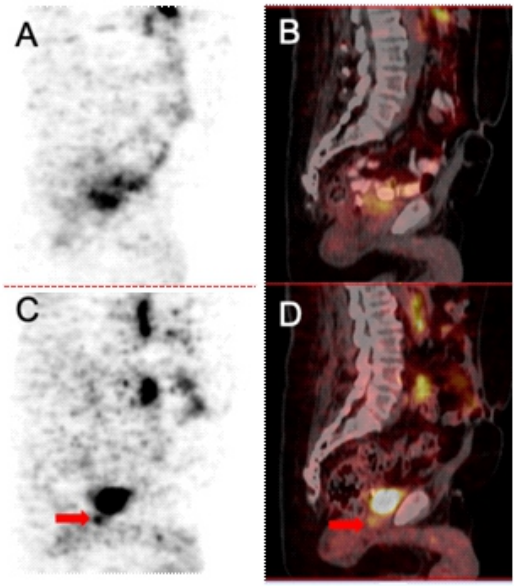

Figure 3. 69 year old male, Gleason grade 5, with PSA of 8.12ng/ml. Sagittal ^{18}F-1007-PSMA PET (A) and fused (B) images demonstrating negative local recurrence. ^{68}Ga-PSMA-11 sagittal PET (C) and fused (D) images demonstrating uptake which was deemed positive for prostate uptake (arrow).

its better visualization of the pelvis.

There have been reports of increased focal marrow uptake noted with ^{18}F-PSMA-1007 as compared to ^{68}Ga-PSMA-11 and that these areas of uptake should be interpreted with caution especially in the setting of no abnormal underlying morphological changes [27, 31].

Limitations

Histopathological correlation of all detected metastatic lesions was not possible.

Positive uptake of ^{68}Ga-PSMA-11 and or ^{18}F-PSMA-1007 were assumed metastatic based on clinical follow-up, follow-up imaging, correlation with other imaging modalities and histology were possible, it is possible however that some of the uptakes could be false positives [27, 32, 33]. The study was a small pilot study and findings would need to be corroborated in a larger cohort study.

In conclusion, though limited by a small study population ^{18}F-PSMA-1007 was able to detect more sites of recurrence as compared to ^{68}Ga-PSMA-11 which were mainly within the prostate and surrounding pelvic structures.

The authors declare that they have no conflicts of interest.

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