^{18}F-PSMA-1007 in Recurrent Prostate Cancer, A New Frontier in Prostate Cancer PET Imaging

by

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Declaration

I, Thabo Lengana, student number 14446325, hereby declare that this dissertation, "*^{18}F-PSMA-1007 in Recurrent Prostate Cancer, A New Frontier in Prostate Cancer PET Imaging*," submitted in accordance with the requirements for the Doctor of Philosophy degree at the University of Pretoria, is my own original work and has not previously been submitted to any other institution of higher learning. All sources cited or quoted in this research paper are indicated and acknowledged with a comprehensive list of references.

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Thabo Lengana

01 November 2020

Dedication

I dedicate this research to my parents, Khitsane and Sophie Lengana for their tireless support and encouragement and to my daughter, Lerato.

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Abstract

Prostate cancer remains a significant cause of cancer morbidity and mortality in men worldwide accounting for the second-highest incidence of all cancers in males. A disproportionate incidence, morbidity and mortality of prostate cancer have been reported in black males than their white counterparts however very little is known of their imaging differences when presenting with biochemical recurrence. The imaging modalities employed in cancer staging (computed tomography, magnetic resonance imaging, bone scan and positron emission tomography) have been under debate due to their varying sensitivities. The prostate bed is the most common site of early recurrence of prostate cancer. The currently used PSMA ligands (^{68}Ga-PSMA and ^{99m}Tc-PSMA) undergo early urinary clearance resulting in interfering physiological activity within and surrounding the prostate. This can result in sites of cancer recurrence being obscured. ^{18}F-PSMA-1007 has an advantage of delayed urinary clearance thus the prostate region is reviewed without any interfering physiological activity. There however is limited data on the diagnostic performance of ^{18}F-PSMA-1007 in early biochemical recurrence.

To our knowledge we were the first to describe the differences in ^{68}Ga-PSMA imaging findings between black and white prostate cancer patients with biochemical recurrence. We found a significant correlation between PSA values and the diagnostic performance of ^{68}Ga-PSMA imaging in both groups. However there was no significant difference in the detection rate, distribution pattern and the median number of lesions between the two racial groups suggesting that the tumour burden and growth rate of androgen dependent prostate cancer may be similar in both races.

We also found ^{68}Ga-PSMA to be superior to bone scan in the assessment of skeletal metastases in the initial staging of high-risk prostate cancer, demonstrating a higher detection rate and specificity, indentifying marrow and lytic skeletal metastases thath had been missed by bone scan.

To our knowledge we were also the first to conduct a head to head comparison of ^{68}Ga-PSMA and ^{18}F-PSMA-1007 in this thesis. Though limited by a small number of patients, ^{18}F-PSMA-

1007 detected more recurrence sites than ^{68}Ga-PSMA. ^{18}F-PSMA-1007 demonstrated a sensitivity, specificity, positive and negative predictive value of 88.9%, 100%, 100%, and 92.3% respectively while ^{68}Ga-PSMA-11 demonstrated sensitivity, specificity, positive and negative predictive value of 44.4%, 83.3%, 80%, and 66.6% respectively.

In our thesis, ^{18}F-PSMA-1007 performed equally to other reported PSMA PET agents when compared with a similar cohort of patients with biochemical recurrence and low PSA value. PSA doubling time proved significantly related to the detection rate of ^{18}F-PSMA-1007 whilst no significant relationship was seen with PSA velocity. We found the optimal PSA cut-off value of 1.26ng/ml to identify biochemical recurrence.

Key Terms:

Prostate cancer, early biochemical recurrence, ^{18}F-PSMA-1007, ^{68}Ga-PSMA, PET CT

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1 Introduction

Prostate cancer is biologically and clinically a heterogeneous disease that makes imaging evaluation challenging. The role of imaging in prostate cancer should include characterization (indolent vs. lethal) of the primary tumour, determination of extracapsular spread, guidance and evaluation of local therapy in organ-confined disease, staging of locoregional lymph nodes, detection of locally recurrent and metastatic disease in biochemical relapse, planning of radiation treatment, prediction and assessment of tumour response to salvage and systemic therapy, monitoring of active surveillance and definition of a trigger for definitive therapy.

The accurate detection of disease confined to the prostate gland versus extra-glandular spread to the lymph nodes or skeleton is crucial when defining the therapeutic approach. Imaging modalities play an important role in the staging of prostate cancer. However, the optimal use of imaging modalities in the staging of prostate cancer is still under debate, as the reported sensitivity and specificity of current imaging methods—such as bone scintigraphy, computed tomography (CT), magnetic resonance (MR) imaging, and ultrasonography (US) vary considerably.

Prostate-specific membrane antigen (PSMA) ligand imaging has excelled in prostate cancer imaging due to the fact that there is increased expression of the PSMA antigen in prostate cancer tissue[1]. Because of the PSMA ligands' high affinity to the PSMA antigen good tumour to background clearance is also noted. In Chapter 2, a review of the literature focused on the clinical and diagnostic modalities currently used in biochemical recurrence of prostate cancer.

Bone scan has historically been the nuclear medicine imaging agent of choice in biochemical recurrence of prostate cancer. Bone scan however suffers from a lack of specificity and cannot assess soft tissue recurrence[2]. The advent of PSMA targeted imaging has revolutionized prostate cancer imaging and ^{68}Ga-PSMA PET-CT has emerged as the leading imaging agent of choice to detect sites of biochemical recurrence[3]. There is however limited data on the

imaging modality of choice in the initial staging of prostate cancer. Initial staging with bone scan is reserved for high-risk prostate cancer patients. ^{68}Ga-PSMA PET-CT was found to have good sensitivity and specificity for the assessment of nodal disease in prostate cancer; there is improving data on the ability for ^{68}Ga-PSMA to detect bone metastases in the initial staging of prostate cancer patients[4,5]. A head-to-head comparison of bone scan and ^{68}Ga-PSMA PET-CT reported on the superiority of ^{68}Ga-PSMA, although the study was limited by its retrospective nature[6]. In Chapter 3, we prospectively compared the diagnostic performance of ^{68}Ga-PSMA PET-CT and bone scan to assess skeletal metastases in in patients with high risk prostate cancer.

Disproportionately higher incidence and death rates from prostate cancer have been reported in black males as compared to white male. Multiple biological and environmental factors have been explored and cited as possible reasons for these diferrences[7-9]. ^{68}Ga-PSMA imaging findings in black vs white patients in the initial staging of prostate cancer demonstrated disproportionately increased tumour ^{68}Ga-PSMA uptake in black patients which correlated significantly to the baseline PSA as compared to white patients[10]. Adding further evidence of more aggressive disease in black patients. There however is limited knowledge of the imaging differences between black and white patients who present with biochemical recurrence after primary therapy. In Chapter 4, we compared the diagnostic accuracy of ^{68}Ga-PSMA PET-CT in detecting prostate cancer recurrence in black versus white patients.

The rationale for evaluating ^{18}F-PSMA1007 as an oncologic tracer applicable to prostate cancer is because one of the most common sites of prostate cancer recurrence is within the prostate. The currently used PSMA ligands (^{68}Ga-PSMA and ^{99m}Tc-PSMA) undergo early urinary clearance resulting in interfering physiological activity within and surrounding the prostate. This can result in sites of cancer recurrence being obscured. Preliminary data had demonstrated that ^{18}F-PSMA-1007 has the advantage of delayed urinary clearance thus allowing evaluation of the prostate region without any interfering physiological bladder activity[11]. The fact that ^{18}F-PSMA-1007 is cyclotron-produced is an added advantage as it has increased availability as compared to the generator-capacity-limited ^{68}Ga-PSMA.

In Chapter 5, we prospectively compared ^{18}F-PSMA and ^{68}Ga-PSMA PET-CT findings in the same patients with early biochemical recurrence of prostate cancer. To our knowledge this is the first time that such an analysis was done, as previous investigations only compared ^{18}F-PSMA-1007 and ^{68}Ga-PSMA in two different study populations.

Other advantages of ^{18}F-PSMA-1007 are that higher activities can be administered to the patient, and the longer half-life (110 minutes)allows performing delayed images increasing target-to-background ratio thus increasing sensitivity. The increased sensitivity and lesion detection of prostate cancer recurrence with ^{18}F-PSMA-1007 may result in ^{18}F-PSMA-1007 replacing MRI, CT and bone scan as the imaging gold standard in patients with suspected recurrence. The early detection of prostate cancer recurrence will have a direct impact on patient care resulting in an increased likelihood of detecting localised recurrence thus earlier initiation of salvage therapy with a curative intent and improved patient outcomes. In Chapter 6 we evaluate the diagnostic performance of ^{18}F-PSMA-1007 PET-CT imaging for restaging and selection for therapy in patients with prostate cancer with early biochemical recurrence.

The reason for targeting the PSMA antigen in prostate cancer is due to the fact that PSMA is over expressed with increasing tumour grade, castration resistance and metastatic disease[12-14]. PSMA is overexpressed in neovascularization sites which may result in false-positive uptake of PSMA targeting imaging agents in non-prostate cancer malignancies and benign tissue[15-17]. In Chapter 7 we describe a case of false positive uptake of ^{18}F-PSMA-1007 in prostate cancer.

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2 Literature Review

2.1 Background

Prostate cancer remains the leading cancer diagnosed in men worldwide with its incidence varying from country to country [1,2]. According to GLOBOCAN over one million new cases of prostate cancer were diagnosed worldwide in 2012 with higher incidence rates in countries where prostate specific antigen (PSA) screening was prevalent resulting in increased biopsy rates [3]. Prostate cancer detected whilst still limited to the prostate gland yields an expected 5 year survival of nearly 100% whilst the 5 year survival of metastatic prostatic cancer is only 33% [4]. Curative treatment for prostate confined prostate cancer includes prostatectomy, external beam radiotherapy, brachytherapy, high-intensity focused ultrasound (HIFU) and cryosurgery [5].

Though the treatment with intent to cure of localized prostate cancer has been successful up to 30% of these patients will re-present with prostate cancer recurrence in the form of a detectable rising serum PSA value (biochemical failure) after initial treatment [6]. Biochemical recurrence may be defined as PSA value >0.2ng/ml after radical prostatectomy or a PSA value >2ng/ml from nadir after radiotherapy [7]. Salvage radiotherapy may be given in patients with biochemical recurrence however its success has been inversely related with the PSA value with patients with low PSA values <1.0 demonstrating the greatest benefit [8,9]. This underscores the importance of the accurate assessment and detection of early stage (low PSA) disease recurrence.

Nomograms have demonstrated an ability to predict with an 80% accuracy prostate bed local recurrence after radical prostatectomy where there is biochemical recurrence in more than 3 years after radical prostatectomy, a PSA doubling time (PSADT)> 11 months, Gleason Score (GS) <7 and a pT3apN0 and pTxN1. In contrast, nomograms demonstrated an ability to predict systemic recurrence with an accuracy of about 80% in patients in whom there is a biochemical recurrence distance of less than 1 year after radical prostatectomy, PSADT of about 4-6 months, GS> 7 and stage of pT3b and pTxpN1 [7,10]. Whilst nomograms have demonstrated good sensitivity in predicting local prostatic recurrence versus extra-prostatic recurrence the

nomograms are unable to distinguish the type of extra-prostatic i.e. skeletal versus nodal disease and the volume of disease recurrence.

As biochemical recurrence will not always be synonymous with intra-prostatic recurrence accurate imaging is essential in these patients so that the correct therapy (localized salvage or systemic) can be instituted.

2.2 Morphological Imaging in Suspected Biochemical Recurrence

CT plays a limited role in the setting of suspected prostate cancer recurrence due to its low sensitivity for local recurrence and has been suggested that it rather should be used for the exclusion of distant disease and determination of radiation ports when adjuvant radiotherapy is being planned [11].

MRI gives excellent soft tissue resolution and has become the leading imaging modality where prostate cancer is suspected and biopsy results come back negative. MRI is also indicated in the initial staging of intermediate to high-risk prostate cancer patients and in the setting of suspected biochemical recurrence [5,7]. Advances in MRI techniques such as multiparametric MRI (mp-MRI) which combine functional and anatomical imaging have resulted in MRI taking the lead in the evaluation of intra-prostatic recurrence in the setting of low volume biochemical recurrence, these techniques though are hampered by granulomatous scar tissue after surgery, fibrotic changes after radiotherapy and interfering artefacts from brachytherapy seeds [12]. MRI is limited by the fact that it is unable to assess lymph node metastases in normal sized lymph nodes [13].

2.3 Bone Scintigraphy

BS with ^{99m}Tc phosphonates or phosphates has been favoured in the assessment of skeletal metastases in prostate cancer due to the fact that the skeletal metastases in prostate cancer are mainly osteoblastic, its role in suspected early recurrence is limited by the low incidence of skeletal metastases when PSA is slowly rising or is < 20ng/ml [14]. Whilst bone scintigraphy has a high sensitivity its poor specificity may result in non-cancerous lesions being mistaken

for malignancy and there is a delay in demonstrating changes when therapy is successful limiting its role in treatment assessment [15].

2.4 Non-PSMA PET Tracers

2-deoxy-2-(^{18}F)fluoro-D-glucose (^{18}F-FDG) is the most commonly used positron emission tomography (PET) oncologic imaging tracer due to the fact that it mimics cellular glucose metabolism that is expected to be up regulated in the setting of malignancy. It however has demonstrated to be of limited use in prostate cancer due to the fact that prostate cancer cells have a low glucose metabolism that results in ^{18}F-FDG having a low sensitivity [16].

^{11}C-Choline and ^{18}F-Flourocholine gained interest in PET imaging of prostate cancer as malignant prostate cancer cells demonstrated an increased phosphatidylcholine metabolism which is an essential component of the cell membrane, this resulted in the increased metabolism and uptake of its pre-cursers choline and flourocholine as compared to normal tissue [17].

Indications for the choline derived PET tracers include initial staging prior to definitive therapy and suspected recurrence with the choline derived tracers demonstrating a far higher sensitivity for nodal metastases as compared to ^{18}F-FDG [18].

^{18}F-Choline, was noted to have a lower detection rate for prostate cancer recurrence sites in settings of biochemical failure and low PSA as compared to ^{68}Ga-PSMA [19,20].

2.5 PSMA

Prostate specific membrane antigen (PSMA) is a Type II membrane protein with a C-terminal extracellular component made up of 707 amino-acids and an intracellular N-terminal region that is made up of 19 amino-acids [21]. The intracellular N-terminal region of the PSMA molecules is responsible for PSMA internalization after ligand binding [22]. Internalization of PSMA is important as this results in increased tumour uptake and retention of the bound ligand which leads to better tumour to background clearance and thus improved image quality [23].

The PSMA gene is located on Chromosome 11 and in benign prostate tissue PSMA is limited to the cytoplasm and apical side of the epithelium [21,24,25]. Malignant transformation of prostate cells leads to the relocation of PSMA from the apical surface to the luminal surface of the prostate gland ducts [25].

PSMA has gained increasing interest in prostate cancer imaging and therapy as a possible molecular target due to some of its favourable characteristics in prostatic cancerous tissue:

- Malignancy – PSMA is expressed in benign and cancerous prostate tissue. In benign prostate tissue PSMA is expressed in low to insignificant levels whereas in malignancy there is a significant up-regulation and expression of PSMA [26,27].

- Tumour Grade – Gleason scores have demonstrated positive correlation with PSMA expression. It has been demonstrated that a rising tumour grade is associated with an increasing PSMA RNA transcription and PSMA expression [28,29].

- Castration resistance – It has been demonstrated that there is associated correlation between PSMA expression and castration resistance. Reviews of tissue samples of patients with prostate cancer who have undergone either physical castration or androgen deprivation therapy have demonstrated significantly increased PSMA expression [30,31].

- Metastatic disease – Metastatic prostate cancer cells have also demonstrated increased PSMA expression proving far more reliable than PSA assessment. [32,33]

PSMA over-expression has also been noted in neovascularization in other malignancies outside of prostate cancer including colon and breast cancer, this in future may offer new diagnostic and therapeutic options for these malignancies [34-36].

2.5.1 Gamma PSMA Imaging Agents

^{111}In-Capromab was amongst the initial clinical agents targeting PSMA for prostate cancer imaging [15]. It consisted of a murine antibody that has a high affinity for the intracellular component of PSMA [37]. It is indicated in the initial staging of high risk prostate cancer patients with negative conventional imaging and when there is suspected recurrence after definitive therapy, it demonstrated a sensitivity and specificity of 49% and 71% respectively in the detection of prostate fossa recurrence [38]. Its low sensitivity has resulted in reduced clinical usage of ^{111}In-Capromab, this has been mainly attributed to the fact that it binds to the intracellular domain of PMSA thus is only able to bind to cells which have lysed [37]. Another significant disadvantage of ^{111}In-Capromab is its equivalent dose of 50mSv per 5mCi activity [39].

Monoclonal Antibody J591 binds to the extracellular domain of PSMA thus overcoming some of the limitations of ^{111}In-Capromab [40]. J591 can be bound to ^{111}In, ^{90}Y or ^{177}Lu thus it is not only limited to imaging of patients but also can be used for therapeutic indications [41,42]. In a phase I and II trial to assess the utility of immune PET in prostate cancer imaging ^{89}Zr-J591 demonstrated 89% sensitivity for the detection of skeletal lesions whilst soft tissue lesion detection was only 50%. ^{89}Zr-J591 was significantly hampered by the slow clearance of the tracer due to its large size thus resulting in the need for delayed and prolonged imaging [43]. ^{89}Zr-J591 also had an unfavourably high radiation burden that averaged around 70mSv per 5mCi activity [44].

Because of the slow background clearance of the large antibody molecules smaller PSMA targeting tracers were developed which would result in far quicker background clearance which in turn would result in earlier imaging and better image quality and would have the added benefit of a reduced radiation burden as compared to the early antibody based PSMA targeting agents.

SPECT imaging tracer with these qualities include the ^{123}I radiolabeled MIP-1072 and MIP-1095 which are urea based inhibitor molecules which target PSMA [45].

These molecules had rapid background clearance and were able to detect nodal and skeletal prostate cancer metastases and were investigated in the assessment of disease response to

chemotherapy [46,47]. ^{123}I-MIP-1072 and ^{123}I-MIP-1095 as compared to the monoclonal antibodies demonstrated favorable effective doses of 0.022mSv/MBq and 0.032mSv/MBq respectively but were still however limited by the concerns of renal toxicity due to the high radiation burden to the kidneys [46].

^{99m}Tc remains the most widely available and used radionuclide in Nuclear Medicine due to its favorable gamma imaging properties and several ^{99m}Tc based agents targeting PSMA have been developed [48]. ^{99m}Tc-HYNIC-PSMA had the added benefit of being easier to label and demonstrated a good affinity for prostate cancer with faster blood clearance and rapid urinary excretion as compared to the ^{99m}Tc-MIP's resulting in favourable effective dose of 3.42mSv/740MBq [49]. In a comparator to ^{68}Ga-PSMA PET/CT, Lawal et al demonstrated a sensitivity of 78.3% for the detection of prostate cancer metastases but however found that the sensitivity reduced significantly in the setting of low volume disease such as in low PSA values making them of little value in early suspected recurrence [50].

2.5.2 ^{68}Ga-PSMA

^{68}Ga-PSMA has gained traction as the PET imaging agent of choice in prostate cancer with several urea based PSMA inhibitors being investigated [51-53]. Of these ^{68}Ga-HBED-CC (^{68}GA-PSMA-11) has been widely reported not only in recurrence of prostate cancer but also in the initial staging of prostate cancer [25,54].

^{68}Ga-PSMA PET/CT has demonstrated a sensitivity and specificity of 86% and 80-97% respectively [54]. ^{68}GaPSMA PET/CT has favorable effective dose of 3mSv/150Mbq [55].

Positive ^{68}Ga-PSMA imaging has been associated with management change in a high percentage of patients who referred for imaging especially those patients with suspected recurrence post radical radiotherapy [56].

Despite the reported success of ^{68}Ga-PSMA there remain significant challenges for this tracer:

- ^{68}Ga is obtained from a ^{68}Germinium/ ^{68}Gallium generator which can only be eluted for a limited number of times per day with each elution only being sufficient for

imaging up to two patients a day. This significantly limits the ability of ^{68}Ga-PSMA to meet the demand for imaging in prostate cancer.

- ^{68}Ga has a half-life of only 68 minutes and thus it is not always possible to synthesize and ship ^{68}Ga-PSMA from a central source to peripheral locations for imaging.

2.5.3 ^{18}F-PSMA

The radionuclide ^{18}F has additional benefits to ^{68}Ga that are over and above those previously mentioned and include:

- ^{18}F has a smaller positron energy as compared to ^{68}Ga thus yielding increased image resolution
- ^{18}F is cyclotron produced, thus a greater amount of radiopharmaceutical can be produced allowing for more patients to be imaged

Several ^{18}F based PSMA targeting ligands have been investigated to date however ^{18}F-DCFPyL) and (((3S,10S,14S)-1-(4-(((S)-4-carboxy-2-((S)-4-carboxy-2-(6-^{18}F fluoronicotinamido)butanamido)butanamido)methyl)phenyl)-3-(naphthalen-2-ylmethyl)-1,4,12- trioxo-2,5,11,13-tetraazahexadecane-10,14,16-tricarboxylic acid)) (^{18}F-PSMA-1007) were considered the most promising candidates [57,58] and have recently been introduced clinically [59,60].

Some of the favorable characteristics of ^{18}F-PSMA-1007 include:

- dosimetry of 4.4-5.5mSv for 200-250MBq which is comparable to other PET/CT tracers
- rapid background clearance allowing for better visualization of target lesions
- lipophilic nature which favors biliary clearance as compared to other PSMA tracers which mainly undergo urinary clearance [60]

In a comparison between ^{18}F-DFCPyl and ^{18}F-PSMA-1007 we found that ^{18}F-PSMA-1007 was superior in the detection of local recurrence and pelvic nodal involvement as compared to ^{18}F-DCFPyl mainly due to the fact that ^{18}F-PSMA-1007 does not undergo early urinary clearance [61]. The lack of early urinary clearance allows for review of the prostate and

surrounding pelvis without interference from tracer activity in the bladder and urinary system.

In a case report ^{18}F-PSMA-1007 demonstrated a superior prostate cancer detection rate as compared to conventional imaging including CT in detecting prostate cancer lymph node metastases which were on average 6mm in diameter [62]. In another case report Paddubny et al compared ^{18}F-PSMA-1007 with mpMRI in a patient who had presented with biochemical recurrence after prostatectomy with a PSA of 0.3ng/ml. ^{18}F-PSMA-1007 was able to detect the recurrence in the right prostatic bed which had been missed on mpMRI [63].

In a pilot study in patients with biochemical recurrence, Giesel et al imaged 12 patients with ^{18}F-PSMA-1007 to localize the site of recurrence[64]. In their preliminary findings they demonstrated that ^{18}F-PSMA-1007 PET/CT was able to detect the site of prostate cancer recurrence in 75% of the patients with PSA being as low as 0.08ng/ml in one of the patients and average lymph node short axis diameter of less than 8mm [65]. ^{18}F-PSMA was found to have a higher detection rate for recurrence as compared to ^{68}Ga-PSMA and proved to have good detection rate in patients with very low PSA[66,67].

Table 1 PSMA targeting agents

Radiopharmaceutical	Cellular Target	Indication	Effective Dose	Current Role
^{111}In-Capromab (15, 37-39)	Intracellular component of PSMA	Initial staging high risk patients and suspected recurrence after definitive therapy	50mSv/185MBq	49% sensitivity and 71% specificity in the detection of prostate fossa recurrence . Limited clinical use due to low sensitivity and specificity and high radiation burden
Human Monoclonal Antibody J591, bound to radionuclides ^{89}Zr, ^{111}In, ^{90}Y, ^{177}Lu (40-44)	Extracellular component of PSMA	Imaging and Therapeutic agent		89% sensitivity for skeletal lesions and 50% sensitivity for soft tissue lesions. Could be utilised for both imaging and therapeutically. Limited by the fact that tracer background clearance is slow resulting in delayed and prolonged imaging [43].
^{123}I-MIP-1072, ^{123}I-MIP-1095 (45,46)	Urea based small, small molecule inhibitor	Assessment of response to chemotherapy	0.022mSv/MBq and 0.032mSv/MBq for ^{123}I-MIP-1072 and ^{123}I-MIP-1095 respectively	Good background clearance with favourable radiation exposure. However risk of renal toxicity.
^{99m}Tc-HYNIC-PSMA (48-50)	Urea based, small molecule inhibitor		3.42mSv/740MBq	Favourable GAMMA imaging qualities and effective dose. 78.3% sensitivity in the detection of prostate cancer lesions however this reduces significantly in the setting of low volume disease.
^{68}Ga-PSMA-11 (51-56)	Urea based, small molecule inhibitor	Initial staging, suspected recurrence, assess suitability for and response to PRLT	3mSv/150MBq	Sensitivity and specificity of 86% and 80-97% respectively.
^{18}F-PSMA-1007 (58-66)	Urea based, small molecule inhibitor	Initial staging, Suspected recurrence	4.4-5.5mSv for 200-250MBq	Delayed urinary clearance allowing review of pelvis without interfering activity from bladder. Ability to detect recurrence in PSA as low as 0.08 ng/ml and lymph node metastases as small as 8mm in diameter.

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3 ^{68}Ga-PSMA PET/CT Replacing Bone Scan in the Initial Staging of Skeletal Metastasis in Prostate Cancer: A Fait Accompli?

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Micro Abstract

We compared the findings of ^{99m}Tc-MDP bone scintigraphy and ^{68}Ga-PSMA-PET/CT in 113 patients who referred for initial skeletal staging of prostate cancer. ^{68}GaPSMA PET/CT was found to be superior to ^{99m}Tc-MDP bone scintigraphy due its ability to additionally detect lytic

and bone marrow lesions. ^{68}Ga-PSMA-PET/CT should potentially replace bone scan in the initial staging of skeletal metastases.

ABSTRACT BODY

Objectives: ^{68}Ga-ligands targeting prostate-specific membrane antigen (PSMA) are rapidly emerging as a significant step forward in the management of prostate cancer, based on the fact that PSMA is a type II transmembrane protein with high expression in prostate carcinoma cells. We prospectively evaluated the use of ^{68}Ga-PSMA-PET/CT in patients with prostate cancer and compared the results with those for ^{99m}Tc-MDP bone scintigraphy.

Methods: A total 113 patients with biopsy-proven prostate cancer referred for standard-of-care bone scintigraphy were prospectively enrolled in this study. ^{68}Ga-PSMA-PET/CT was performed after bone scintigraphy. Metastasis diagnosed on each technique was compared against a final diagnosis based on CT, MRI, skeletal survey, clinical follow-up, and histological correlation.

Results: Ninety-one bone lesions were interpreted as bone metastases in 25 men on ^{68}Ga-PSMA-PET/CT, compared to only 61 lesions in 19 men on ^{99m}Tc-MDP bone scintigraphy. Of the 7 bone scans that missed skeletal metastases, 54% of these missed lesions were due to either marrow or lytic skeletal metastases. The median standardized uptake value (SUV) in all malignant bone lesions was 13.84. ^{68}Ga-PSMA-PET/CT showed significantly higher sensitivity and accuracy than bone scintigraphy (96.2% vs. 73.1%, and 99.1% vs. 84.1%) for the detection of skeletal lesions. For extra skeletal lesions, ^{68}Ga-PSMA-PET/CT showed an additional 96 unexpected lesions with a median standardized uptake values (SUV) of 17.6.

Conclusions: ^{68}Ga-PSMA PET/CT is superior to and can potentially replace bone scan in the evaluation for skeletal metastases in the clinical and trial setting due to its ability to detect lytic and bone marrow metastases.

Introduction

Prostate cancer is among the foremost cancers faced by men and is among the leading causes of cancer-related deaths worldwide[1,2]. Early detection through screening and resultant treatment at an organ-confined stage results in an improvement of the expected 5-year survival to 100% [3].

Accurate early staging of prostate cancer is crucial to patient risk stratification. The accurate detection of disease either confined to the prostate gland versus extra-glandular spread to the lymph nodes (LNs) or skeleton is essential in determining the most appropriate patient specific therapeutic strategy [4,5].

Imaging modalities including computed tomography (CT), magnetic resonance (MRI), and ultrasonography (US) play an important role in the initial staging of prostate cancer. However, the optimal imaging modality in the initial staging of prostate cancer is still under debate due to the variable sensitivity and specificity of these imaging modalities [6,7].
Bone scintigraphy in initial staging is reserved for patients with elevated PSA and an increased Gleason score. Whilst bone scan may have an increased sensitivity for the detection of osteoblastic skeletal metastases it however suffers from reduced specificity [8].

PET/CT offers increased image resolution and diagnostic confidence as compared with single photon imaging with a gamma camera. Some of the PET/CT tracers used in the staging of prostate cancer include ^{18}F-NaF and ^{18}F/^{11}C- Choline. ^{18}F-NaF demonstrates increased sensitivity for the detection of skeletal metastases but will not inform on soft tissue involvement. ^{18}F-Flouro-Choline has demonstrated low specificity and sensitivity in the setting of low PSA [9].

^{68}Ga-ligands targeting prostate-specific membrane antigen (PSMA) are rapidly emerging as a significant step forward in the management of prostate cancer, based on the fact that PSMA is a type II transmembrane protein with high expression in prostate carcinoma cells [10]. PSMA overexpression by prostate cancer cells is further enhanced in increasing tumour grade, metastases and by hormone refractoriness [11,12].

The clinical utility of ^{68}Ga-PSMA PET/CT has been reported on not only with regards to limited stage disease but also in suspected recurrence. Accurate exclusion of extra-prostatic disease is essential in treatment planning in prostate limited disease prior to localized therapy, ^{68}Ga-PSMA has been found to be superior to conventional imaging in the identification nodal disease in patients with moderate to high risk prostate cancer [13]. There however is limited literature on the clinical utility of ^{68}Ga-PSMA PET/CT in the assessment for skeletal metastases in the primary staging of prostate cancer.

We prospectively evaluated the diagnostic performance of ^{68}Ga-PSMA-11 PET/CT in patients with high-risk prostate cancer and compared the results with those for ^{99m}Tc-MDP bone scintigraphy (BS).

Materials and Methods

The study was approved by the local research ethics committee.

One hundred and thirteen patients (mean age, 66,65 years, range, 43 – 88 years) with biopsy-proven prostate cancer referred for standard-of-care BS were prospectively enrolled in this study. Exclusion criteria included no histology result and having started any prostate cancer related therapy.

BS was done as per standard protocol [14]. Patients underwent whole body, static and lumbar SPECT imaging 2-3 hours after injection of 30mCi ^{99m}Tc-MDP. Additional SPECT/CT images were acquired as indicated for localization of uncertain uptake.

^{68}Ga-PSMA-11 was prepared in-house as we have previously described [15]. Whole body PET/CT images from vertex to mid thigh were acquired on a Siemens Biograph 40 PET/CT scanner 60 minutes after injection of ^{68}Ga-PSMA-11, the median injected activity was 3.7mCi (range 1.24-8.25mCi). Non-contrasted low dose CT scans were simultaneously acquired for attenuation correction and anatomical localization.

Image analysis

On both studies, we counted a maximum of 5 skeletal lesions.

Additionally on the ^{68}Ga-PSMA-11 PET/CT scans, we also count a maximum of 5 soft tissue metastases.

Two experienced Nuclear Physicians blinded to the results of the studies independently reviewed either the bone scan or PET/CT studies. Focal uptake greater than background and not in keeping with physiological uptake was deemed to be positive for prostate cancer involvement on ^{68}Ga-PSMA-11 PET/CT. BS was interpreted as per standard guidelines [14]. Disagreement was resolved by consensus.

Metastasis diagnosed on each of these techniques was compared against a 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 ^{68}Ga-PSMA-11 PET/CT and BS for the detection of skeletal metastases. The diagnostic performances of the two imaging modalities at different Gleason scores of <7, 7 and Gleason score >7 were determined. Similar evaluation was done for the diagnostic performances of the two imaging modalities at different PSA levels (PSA <10, 10-20 and >20) as well as their performances in different age groups i.e. patients who were 65 years or younger at the time of diagnosis versus patients older than 65 years. The diagnostic performances for the entire cohorts of ^{68}Ga-PSMA-11 PET/CT and BS for the detection of bone metastases were compared using Chi square test. Chi square test was also used to test if any significant difference exists in the abilities of the tests to detect skeletal metastases at different Gleason scores, PSA levels and in different age groups of patients. The statistical significant level was set at a p value of <0.05. Statistical analysis was done using IBM SPSS Statistics version 21.0 (IBM Corp., Armonk, New York, USA).

Results

One-hundred-and-eleven (98.2%) patients demonstrated positive uptake for prostate cancer on ^{68}Ga-PSMA-11 PET/CT with only two patients not demonstrating any ^{68}Ga-PSM-11 uptake despite histology demonstrating prostate cancer involvement. 69 (61,1%) of the ^{68}Ga-PSMA-11 PET/CT scans demonstrated prostate-confined disease, whilst 42 (37,16%) demonstrated metastatic disease. A total of 91 bone lesions were interpreted as bone metastases in the 25 men on ^{68}Ga-PSMA-11 PET/CT, compared with only 61 lesions in 19 men on BS. The median maximum standardized uptake values (SUVmax) in all malignant bone lesions was 13,84 (Table 1).

^{68}Ga-PSMA-11 PET/CT was positive for skeletal metastases in 7 (8.4%) of the negative BS whilst 11 (36.7%) of the positive BS were negative on ^{68}Ga-PSMA-11 PET/CT (Table 3 and 6, Figure 1,2 and 3). ^{68}Ga-PSMA-11 PET/CT showed significantly higher sensitivity and accuracy than BS (96.2% vs. 73.1%, and 99.1% vs. 84.1%) for the detection of skeletal lesions (Table 2). For extra-skeletal lesions, ^{68}Ga-PSMA-11 PET/CT showed 96 unexpected metastatic lesions with a mean SUV of 17.6 (Table 1).

Ten (8.8%) of the patients had a Gleason score of less than 7 whilst 42 (37.2%) and 61 (54.0%) patients had Gleason scores of 7 or greater than 7 respectively. 13.3% of patients had a PSA less than 10ng/mL whilst 11.5% and 75.2% presented with PSA values of 10-20 ng/mL and greater than 20ng/mL respectively. A total of 30 (26.5%) bone scans that were acquired were positive for skeletal metastases on BS whilst 83 (73.5%) were negative (Table 4 and 5).

Table 1: Age distribution, Gleason scores, PSA and image findings of study participants

Variable	Frequency	Percentage
Age (years)		
Mean ± SD		66.65 ±7.98
Range		43 – 88
< 65	40	35.4
≥ 65	73	64.6
Gleason		
< 7	10	8.8
7	42	37.2
> 7	61	54.0
PSA		
< 10	15	13.3
10 – 20	13	11.5
> 20	85	75.2

	^{99m}Tc-MDP Bone Scan
Variable	**N (%)**
Positive	30 (26.5)
Negative	83 (73.5)
Total skeletal lesion	61

	^{68}Ga-PSMA PET/CT	
Variable	**N (%)**	**SUVmean (sd)**
Positive	111 (98.2)	
Negative	2 (1.8)	
Localised Disease Only	69 (61.1)	12.6 (±9.6)
Metastatic Disease	42 (37.2)	14.52 (±10.6)
Skeletal Metastatic Disease	25 (22.1)	12.75 (±9.4)
Total Skeletal Lesions	91	14.4 (±13.3)
Additional Soft Tissue Lesions	96	17.6 (±13.1)
Soft Tissue Disease only	14 (12.3)	16.8 (±11.9)

Table 2: Comparing the diagnostic performance of Bone scan and PSMA PET/CT in detecting skeletal metastasis

	Positive	Negative	Total	χ^2	*p* value
Variables	**n = 26 (%)**	**n = 87 (%)**	**N = 113 (%)**		
Bone scan					
Positive	19 (63.3)	11 (36.7)	30	37.491	**<0.001***
Negative	7 (8.4)	76 (91.6)	83		
PET CT					
Positive	25 (100.0)	0 (0.0)	25	107.419	**<0.001***
Negative	1 (1.1)	87 (98.9)	88		

Evaluation	**Bone Scan**	**PSMA/ PETCT**
Sensitivity	73.1%	96.2%
Specificity	87.4%	100.0%
Positive predictive value	63.3%	100.0%
Negative predictive value	91.6%	98.9%
False positive	12.6%	0.05%
False negative	26.9%	3.8%
Accuracy	84.1%	99.1%

χ^2: Chi square; *: *p* value <0.05

Discussion

PET/CT has demonstrated higher image resolution and diagnostic confidence as compared to gamma imaging, however this comes at a higher cost. In a resource constrained setting it may not be feasible to do a ^{68}Ga-PSMA PET/CT study in all patients with prostate cancer.

BS is recommended as part of initial workup in patients with intermediate to high-risk prostate cancer to exclude skeletal metastases [16,17].

We prospectively aimed to identify subsets of patients who may benefit from a ^{68}Ga-PSMA-11 PET/CT study as part of their routine baseline imaging.

In a retrospective series Pyka et al demonstrated a higher ^{68}Ga-PSMA sensitivity and specificity as compared to bone scan of 100% and 100% vs. 71.4% and 65.2% respectively for the detection of skeletal metastases in the initial staging of Prostate cancer, which was similar to our findings [18]. Similarly, Thomas et al in a study population comprising of patients being worked up for Radium Dichloride therapy demonstrated that ^{68}Ga-PSMA was superior to BS in the detection of skeletal metastases in Prostate cancer with a ^{68}Ga-PSMA detecting nearly

double the amount of skeletal lesions as compared to BS [19], our study confirmed similar results even when having limited lesions to 5.

Age is one of the risk factors in prostate cancer [20]. Patients with prostate cancer onset prior to the age of 65 have a higher risk of having genetic mutations that may confer a risk of more aggressive prostate cancer [21-24].

6 (15%) of the 40 patients below the age of 65 presented had skeletal metastatic disease whilst 20 (27.4%) of the patients above the age of 65 presented with metastatic disease. BS missed 2 patients with skeletal metastatic disease in the group below the age of 65 years compared to 5 patients in the group older than 65 years (Table 3). ^{68}Ga-PSMA-11 PET/CT out performed BS with a higher sensitivity and accuracy of 100% and 100% vs. 66.7% and 82.5% respectively in the group below the age of 65 years (Figure 1, Table 3).

Various risk classification systems have been developed in an attempt to risk stratify prostate cancer patients prior to therapy. Some of the risk factors used include PSA and Gleason score [25,26]. The majority of our patients presented with a Gleason score of ≥7. Of those patients with a Gleason of <7, none had a Gleason score below 6. Only a single patient within this cohort presented with skeletal metastases whilst BS did not miss any skeletal metastases. The low yield for skeletal metastases in this patient cohort is not surprising and is in keeping with what has been described in literature[27].

^{68}Ga-PSMA-11 PET/CT had a significant impact in the ≥7 group and was able to correctly reclassify 10 false positive and 7 false negative cases on BS (Table 4). ^{68}Ga-PSMA-11 PET/CT did however demonstrate a single false negative within this group. It was a patient with a Gleason of 10 on histology with pelvic bone metastases noted on bone scan that demonstrated low-grade tracer uptake on PET/CT which was deemed negative (Figure 2). Whilst cellular PSMA expression is increased with increasing prostate cancer aggressiveness, it is anticipated that with higher Gleason scores there may be a down regulation of PSMA cellular expression as cells become more poorly differentiated [11,28].

Skeletal metastases occur less frequently in patients with a PSA below 10ng/ml, an increasing detection rate of skeletal metastases is expected with rising PSA value [29-31]. 15 (13.2%) of the patients presented with a PSA of <10ng/mL, BS missed skeletal metastases in only a single

patient in this group whilst incorreclty assessing 4 patients as having skeletal metastases. ^{68}Ga-PSMA-11 PET/CT was able to detect 7 false positive and 6 false negative cases for skeletal metastases on BS in the patients with a PSA ≥10ng/mL (Table 5).

The development of skeletal metastases progress from red marrow seeding, followed by osteoclastic activation and then osteoblastic activation [32]. BS will not detect bone marrow metastases and has a low sensitivity for lytic skeletal lesions and early sclerotic lesions. ^{68}Ga-PSMA PET/CT's superiority over BS was further highlighted by the fact that of the 7 BS that missed skeletal metastases, 6 (54%) of these missed skeletal lesions were due to either marrow or lytic skeletal metastases on ^{68}Ga-PSMA PET/CT (Table 6). Figure 3 demonstrates a missed skeletal metastases on BS that was due to a marrow lesions identified on ^{68}Ga-PSMA PET/CT. Of the 11 BS that were incorrectly interpreted as bone metastases, 13 (72%) of these lesions were determined to be due to osteo-degenerative changes.

Though our study focused on reviewing the diagnostic performance between ^{68}Ga-PSMA-11 PET/CT and Bone Scan in detecting skeletal metastases, lymph nodes are among the common sites of prostate cancer metastases after the skeleton [33]. An additional value of imaging with ^{68}Ga-PSMA-11 is the detecting of lymph node and soft tissue disease. In our study ^{68}Ga-PSMA-11 PET/CT detected soft tissue metastases in 14 (12.3 %) patients who had negative bone scans. In total an additional 96 soft tissue lesions were detected in our study (Table 1). Interestingly no additional soft tissue lesions outside of the prostate were noted in the patients who were falsely assessed as having skeletal metastases on BS.

^{68}Ga-PSMA however has significant shortcomings which include its limmited half-life and the fact that ^{68}Ga is obtained from a ^{68}Germinium/ ^{68}Gallium generator which can only be eluted for a limited number of times per day, with each elution only being sufficient for imaging up to two patients at a time. This significantly limits the ability of ^{68}Ga-PSMA to meet the demand for imaging in prostate cancer. To this regard ^{18}F-PSMA ligands have gained traction as ideal PET tracers due to their favourable physical properties which allow for delayed imaging and higher activity to be administerd to the patient which results in improved sensitivity for the detection of prostate cancer deposits[34]. In resource limited settings ^{99m}Tc-PSMA agents have become an attractive alternative to the PET PSMA tracers due to the widespread availability

of ^{99}Mo/^{99m}Tc generators and gamma cameras. Amongts the available gamma imaging radionuclides ^{99m}Tc-HYNIC-PSMA has the added advantage of being easier to label and having a good sensitity in the detection of prostate cancer deposits[35].

Limitations

Histopathological evaluation of all detected metastatic lesions was not possible.

Positive uptake of 68Ga-PSMA-11 were assumed pathological (metastatic) based on 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 [36,37]. SPECT/CT improves BS sensitivity and lesion detection however it was not always possible to routinely conduct SPECT/CT imaging on all Bone Scans due to logistical constraints [14].

Conclusion

^{68}Ga-PSMA PET/CT is superior to and can potentially replace BS in the clinical and trial setting. ^{68}Ga-PSMA-11 PET/CT demonstrated a reduced false positive findings and a higher sensitivity and accuracy as compared to BS including the detection of lytic and bone marrow metastases. The extra skeletal lesions that were detected on 68Ga-PSMA-11 PET/CT could further impact patient management.

Table 3: Comparing and evaluation of diagnostic performance of Bone scan and PSMA/ PETCT in detecting skeletal metastasis based on age group

Variables	Positive n = 26 (%)	Negative n = 87 (%)	Total N = 113	χ^2	*p* value
Age group < 65 years					
Bone scan					
Positive	4 (44.4)	5 (55.6)	9	7.897	**0.005***
Negative	2 (6.5)	29 (93.5)	31		
Total	*6*	*34*	*40*		
PET CT					
Positive	6 (100.0)	0 (0.0)	6	40.000	**<0.001***
Negative	0 (0.0)	34 (100.0)	34		
Total	*6*	*34*	*40*		
Age group ≥ 65 years					
Bone scan					
Positive	15 (71.4)	6 (28.6)	21	28.734	**<0.001***
Negative	5 (9.6)	47 (90.4)	52		
Total	*20*	*53*	*73*		
PET CT					
Positive	19 (100.0)	0 (0.0)	19	68.066	**<0.001***
Negative	1 (1.9)	53 (98.1)	54		
Total	*20*	*53*	*73*		

Evaluation	Bone Scan		PETCT	
	< 65 years	≥ 65 years	< 65 years	≥ 65 years
Sensitivity	66.7%	75.0%	100.0%	95.0%
Specificity	85.3%	88.7%	100.0%	100.0%
Positive predictive value	44.4%	71.4%	100.0%	100.0%
Negative predictive value	93.5%	90.4%	100.0%	98.1%
False positive	14.7%	11.3%	0.0%	0.0%
False negative	33.3%	25.0%	0.0%	5.0%
Accuracy	82.5%	84.9%	100.0%	98.6%

χ^2: Chi square; Fisher's exact *p* value used; *: *p* value <0.05

Table 4: Comparing and evaluation of diagnostic performance of Bone scan and PSMA/ PETCT in detecting skeletal metastasis based on Gleason scores

Variables	Positive n = 26 (%)	Negative n = 87 (%)	Total N = 113	χ^2	p value
Gleason < 7					
Bone scan					
Positive	1 (50.0)	1 (50.0)	2	4.444	0.200[F]
Negative	0 (0.0)	8 (100.0)	8		
Total	*1*	*9*	*10*		
PET CT					
Positive	1 (100.0)	0 (0.0)	1	10.000	0.100[F]
Negative	0 (0.0)	9 (100.0)	9		
Total	*1*	*9*	*10*		
Gleason = 7					
Bone scan					
Positive	3 (33.3)	6 (66.7)	9	3.394	0.101[F]
Negative	3 (9.1)	30 (90.9)	33		
Total	*6*	*36*	*42*		
PET CT					
Positive	6 (100.0)	0 (0.0)	6	42.000	**<0.001***
Negative	0 (0.0)	36 (100.0)	36		
Total	*6*	*36*	*42*		
Gleason > 7					
Bone scan					
Positive	15 (78.9)	4 (21.1)	19	29.400	**<0.001***
Negative	4 (9.5)	38 (90.5)	42		
Total	*19*	*42*	*61*		
PET CT					
Positive	18 (100.0)	0 (0.0)	18	56.446	**<0.001***
Negative	1 (2.3)	42 (68.9)	43		
Total	*19*	*42*	*61*		

Evaluation	**Bone Scan**			**PETCT**		
	Gleason scores			**Gleason scores**		
	< 7	**7**	**> 7**	**< 7**	**7**	**> 7**
Sensitivity	100.0%	50.0%	78.9%	100.0%	100.0%	94.7%
Specificity	88.9%	83.3%	90.5%	100.0%	100.0%	100.0%
Positive predictive value	50.0%	33.3%	78.9%	100.0%	100.0%	100.0%
Negative predictive value	100.0%	90.9%	90.5%	100.0%	100.0%	97.7%
False positive	11.1%	16.7%	9.5%	0.0%	0.0%	0.0%
False negative	0.0%	50.0%	21.1%	0.0%	0.0%	5.3%
Accuracy	90.0%	78.6%	86.9%	100.0%	100.0%	98.4%

χ^2: Chi square; Fisher's exact *p* value used; *: *p* value <0.05

Table 5: Comparing diagnostic performance of Bone scan and PSMA/ PETCT in detecting skeletal metastasis based on PSA groups

Variables	Positive n = 26 (%)	Negative n = 87 (%)	Total N = 113	χ^2	p value
PSA < 10					
Bone scan					
Positive	2 (33.3)	4 (66.7)	6	1.111	0.525[F]
Negative	1 (11.1)	8 (88.9)	9		
Total	*3*	*12*	*15*		
PET CT					
Positive	3 (100.0)	0 (0.0)	3	15.000	0.002*[F]
Negative	0 (0.0)	12 (100.0)	12		
Total	*3*	*12*	*15*		
PSA 10 – 20					
Bone scan					
Positive	2 (33.3)	4 (66.7)	6	2.758	0.192[F]
Negative	0 (0.0)	7 (100.0)	7		
Total	*2*	*11*	*13*		
PET CT					
Positive	2 (100.0)	0 (0.0)	2	13.000	0.013*[F]
Negative	0 (0.0)	11 (100.0)	11		
Total	*2*	*11*	*13*		
PSA > 20					
Bone scan					
Positive	15 (83.3)	3 (16.7)	18	42.195	**<0.001***
Negative	6 (9.0)	61 (91.0)	67		
Total	*21*	*64*	*85*		
PET CT					
Positive	20 (100.0)	0 (0.0)	20	79.707	**<0.001*[F]**
Negative	1 (1.5)	64 (98.5)	65		
Total	*21*	*64*	*85*		

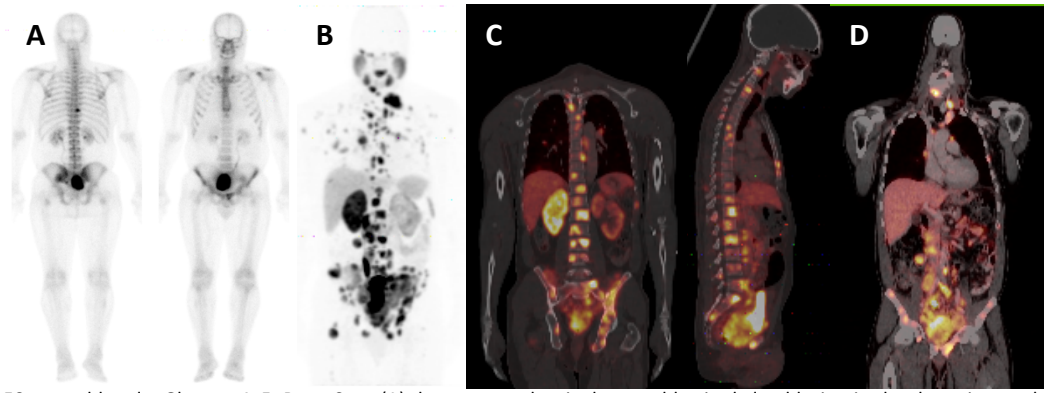
Evaluation	**Bone Scan**			**PETCT**		
	PSA			**PSA**		
	< 10	**10 – 20**	**> 20**	**< 10**	**10 – 20**	**> 20**
Sensitivity	66.7%	100.0%	71.4%	100.0%	100.0%	95.2%
Specificity	66.7%	63.6%	95.3%	100.0%	100.0%	100.0%
Positive predictive value	33.3%	33.3%	83.3%	100.0%	100.0%	100.0%
Negative predictive value	88.9%	100.0%	91.0%	100.0%	100.0%	98.5%
False positive	33.3%	36.4%	4.7%	0.0%	0.0%	4.8%
False negative	33.3%	0.0%	28.6%	0.0%	0.0%	0.0%
Accuracy	66.7%	69.2%	89.4%	100.0%	100.0%	98.8%

χ^2: Chi square; Fisher's exact *p* value used; *: *p* value <0.05

Table 6: Characteristics of the bone scan false negative and false positive lesions on 68Ga-PSMA PET/CT

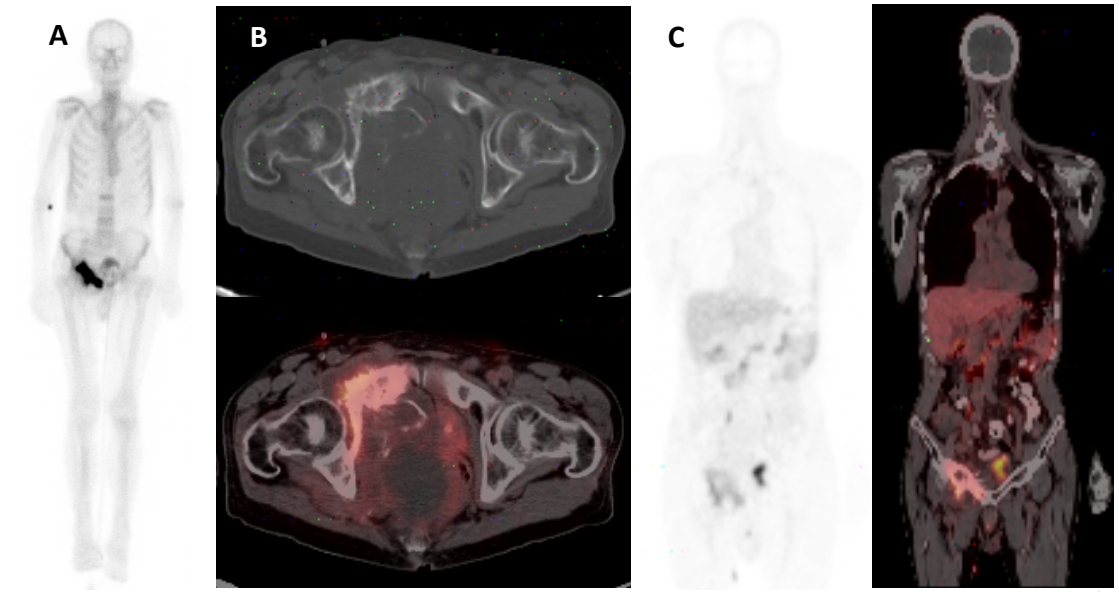
	No
False negative lesions	11
Marrow lesions	3 (27%)
Lytic lesions	3 (27%)
Equivocal sclerotic lesions	5 (46%)
Additional soft tissue lesions	13
False positive lesions	18
Osteo-degenerative	13 (72%)
No significant morphological finding	5 (28%)
Additional soft tissue lesions	0

Fig 1.



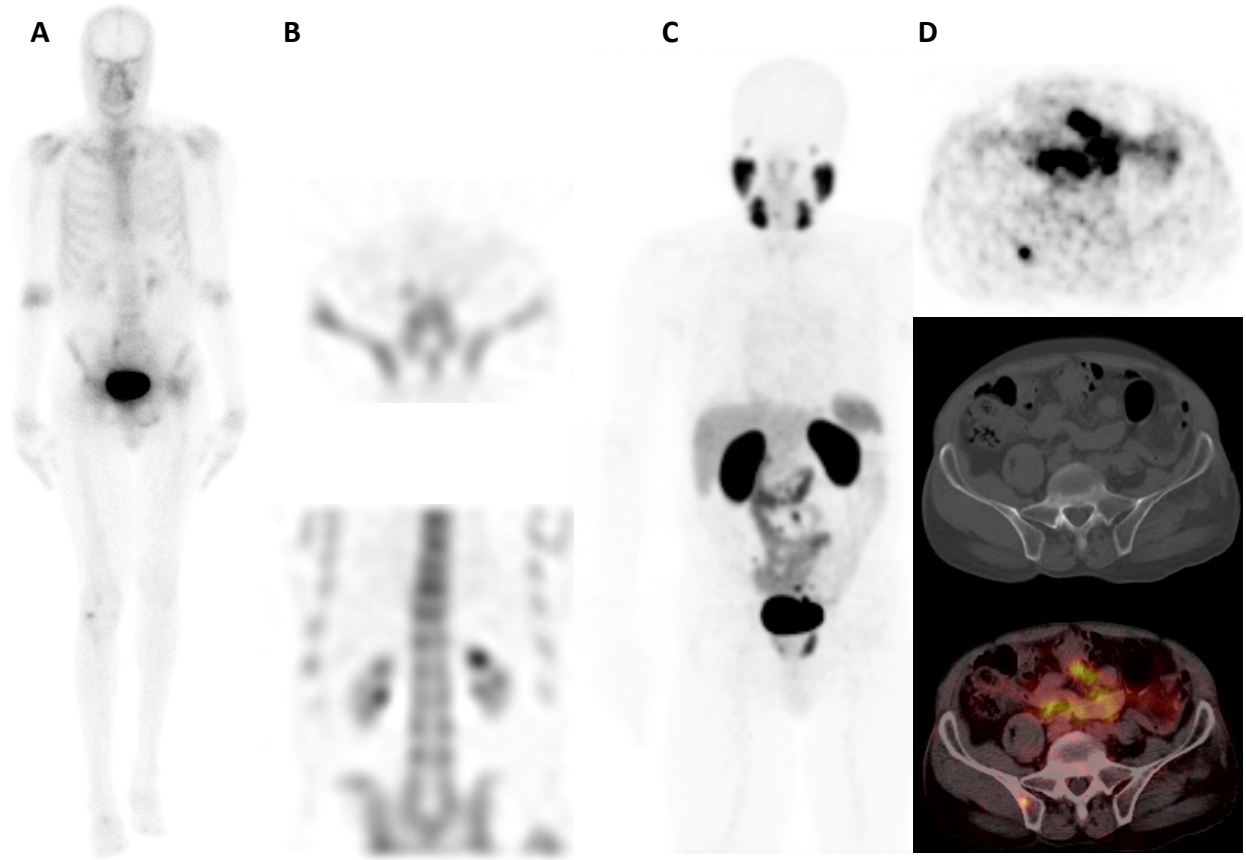
58-year-old male, Gleason 4+5, Bone Scan (A) demonstrated a single osteoblastic skeletal lesion in the thoracic vertebrae. ^{68}Ga-PSMA-11 PET/CT MIP (B), fused coronal and sagittal images (C, D) demonstrated widespread skeletal and nodal lesions, which were not visualized on the bone scan, this is why ^{68}Ga-PSMA PET/CT should replace bone scan.

Fig 2.



73-year-old male with Gleason 5+5, bone scan (A) demonstrated pelvic osteoblastic skeletal metastases. ^{68}Ga-PSMA-11 PET/CT pelvic CT bone window and PET/CT fused axial (B) and coronal PET and PET/CT fused (C) images demonstrated low-grade tracer uptake in pelvic skeletal lesion, less than liver uptake, which was deemed negative.

Fig 3.



54-year-old male with Gleason score of 4+4, Bone scan whole body image (A) and SPECT images (B) axial and coronal did not demonstrate uptake typical for osteoblastic skeletal metastases. ^{68}GA-PSMA PET/CT MIP image (C) and axial PET (D) PET, CT and fused PET/CT image demonstrated a marrow metastases in the right ilium

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4 ^{68}Ga-PSMA-HBED-CC PET/CT Imaging in Black Versus White South-African Prostate Carcinoma Patients Presenting with A Low-Volume, Androgen Dependent Biochemical Recurrence: A Prospective Study

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ABSTRACT

Objectives: To compare the diagnostic accuracy of ^{68}Ga-PSMA-HBED-CC PET/CT imaging for the detection of androgen-dependent recurrent prostate carcinoma (ADPC) in black South-Africans (BSAs) versus white South-Africans (WSAs) with rising serum PSA values below or equal to 10 ng/ml.

Patients and methods: Sixty-one ADPC patients were prospectively included in the study (mean age: 66.7 years), 38 WSAs and 23 bBSAs. ^{68}Ga-PSMA-HEBD-CC PET/CT imaging results obtained were related to serum PSA levels and to ethnicity.

Results: Forty-one patients (67%) had a positive ^{68}Ga-PSMA-HBED-CC scan result. ^{68}Ga-PSMA-HEBD-CC PET/CT positivity was significantly higher in patients with PSA values > 2 ng/ml (32/38 patients (84%)) when compared to patients with PSA values < 0.5 ng/ml (6/11 patients

(55%) or PSA values of 0.5-2 ng/ml (3/12 patients (25%)) (p= 0.0001). Mean PSA values proved not significantly different in patients presenting with extra-pelvic involvement when compared to those with intra-pelvic involvement nor between patients that presented with bone involvement versus those that did not on ^{68}Ga-PSMA-HBED-CC PET/CT) ($p \geq 0.147$). Age, Gleason-scores, median PSA-values, the frequency of a positive scan result, the frequency of bone involvement and extra-pelvic involvement proved similar in WSAs and BSAs ($p \geq 0.417$). ***Conclusion:*** ^{68}Ga-PSMA-HBED-CC PET/CT imaging identified a recurrence in 67% of the patients under study. Higher PSA levels were associated with ^{68}Ga-PSMA-HBED-CC PET/CT positivity and the detection rate. Imaging results obtained proved similar in BSAs and WSAs suggesting that the tumor burden and growth rate of androgen dependent prostate carcinoma is similar in both races.

Key Words: ^{68}Ga-PSMA, PET/CT, Prostate Cancer, African, mCRPC

INTRODUCTION

Following treatment with curative intent of prostate carcinoma, 20–40% of patients undergoing radical prostatectomy (RP) and 30–50% of patients undergoing EBRT will experience biochemical recurrence (a rise in prostate-specific antigen (PSA) levels) within 10 years [1-5].

Standard imaging in prostate carcinoma patients presenting with a biochemical recurrence include trans-rectal ultrasound guided biopsy, CT, MRI, and bone scintigraphy. However, while these techniques may detect macroscopic disease, they have poor sensitivity for detecting very low volume disease, or when PSA is <10 ng/ml [6,7]. Aside from standard imaging techniques, choline based (i.e. either ^{18}F-Choline or ^{11}C-Choline) PET/CT is currently also widely used in clinical routine for the detection of recurrent prostate carcinoma. However, in patients with prostate-specific antigen (PSA)-values below 3 ng/ml the detection rate is reported to be only 40–60 % [8]. More recently, studies using the novel PET-tracer ^{68}Ga-PSMA-HBED-CC targeting the prostate specific membrane antigen (PSMA) that is overexpressed on prostate carcinoma have demonstrated promising sensitivity and specificity for the detection of recurrent prostate carcinoma with detection rates surpassing those of choline-based PET/CT imaging whilst impacting significantly overall patient

management [9,10].

Many aspects of prostate carcinoma have been shown to differ between black and white men, including incidence, grade, sensitivities and specificities of serum prostate-specific antigen (PSA) and survival [11,12,13]. In this prospective study, we compare the diagnostic accuracy of ^{68}Ga-PSMA-HBED-CC PET/CT for the detection of recurrent prostate carcinoma in black versus white South-Africans with rising serum PSA values below or equal to 10 ng/ml, suggestive of low-volume recurrence, that previously had undergone either radical prostatectomy or external beam radiation therapy with curative intent for an underlying prostate carcinoma, who were not yet on hormonal or systemic therapy and were being considered for further targeted therapy

PATIENTS

Sixty-one patients, 23 black and 38 white South-Africans, presenting with a rising PSA level that previously had undergone either radical prostatectomy or external beam radiation therapy with curative intent for an underlying prostate carcinoma or salvage radiation therapy after radical prostatectomy, who were not yet on hormonal or systemic therapy and were being considered for further targeted therapy were prospectively included in the study following written informed consent. No target had been identified for treatment through clinical examination or imaging. Clinical, biochemical and imaging data were collected at the time of inclusion. All patients included presented with a PSA level $\leq$ 10 ng/ml and all underwent ^{68}Ga-PSMA-HBED-CC PET/CT imaging. Data obtained by ^{68}Ga-PSMA-HBED-CC PET/CT imaging were collected and related to PSA levels and race and their impact on patient management was assessed

METHODS

This study was approved by the Ethics committee of the University Hospital of Pretoria. The protocol number was 368/2016 and was approved on the 21st of September 2016. Informed consent was obtained from all patients prior to participating.

^{68}Ga-PSMA-HEBD-CC PET/CT IMAGING

^{68}Ga-PSMA-HBED-CC PET imaging from mid-thigh to vertex was performed in all patients following the injection of a body weight adjusted dose of 2 MBq/kg. All ^{68}Ga-PSMA-HBED-CC injections contained 2 mmol PSMA ligand resulting in a median specific radioactivity of 66GBq/micromol [9].

Acquired ^{68}Ga-PSMA-HBED-CC PET/CT 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. ^{68}Ga-PSMA-HBED-CC PET/CT images were visually analyzed for the presence of sites of abnormal ^{68}Ga-PSMA-HBED-CC uptake. Uptake higher than background-activity in lymph nodes and tissues, not corresponding to physiologic tracer accumulation, was considered pathologic and compatible with malignancy. The number of ^{68}Ga-PSMA-HBED-CC avid lesions and their location were defined for all ^{68}Ga-PSMA-HBED-CC PET/CT patient studies. The detection rate of recurrence by ^{68}Ga-PSMA-HBED-CC PET/CT was defined in the entire group of patients, for black and white South-Africans separately and for different levels of PSA, respectively < 0.5 ng/ml, between 0.5 and 2 ng/ml and above 2 ng/ml.

STATISTICAL ANALYSIS

Statistical analysis was performed using SPSS software, version 23.0 (IBM Corp., Armonk, NY). Normalcy of data was assesses using the Kolmogorov-Smirnov test. For comparison of groups, the parametric Student t-test and the non-parametric Mann-Whitney U test and Kruskal-Wallis test were used where appropriate. For comparison of frequencies, the Chi-square test or McNemar test was used. Finally, accuracy of ^{68}Ga-PSMA-HEBD-CC PET/CT imaging was assessed using ROC-curve analysis. The significance level used was $p \leq 0.05$ (two-tailed).

RESULTS

Patient data are shown in table 1. Of the sixty-one patients prospectively included in the study, 38 were white South Africans and 23 were black South-Africans. Mean age was 66.7 yrs. (sd: 8.9 yrs.).

Twenty-eight patients had undergone radical prostatectomy (46%), twelve patients had undergone primary radiation therapy (20%) and 21 patients had undergone salvage radiotherapy after radical prostatectomy (34%).

Median Gleason score of the primary prostate carcinoma was 7.0 (range 6-9).

Median PSA value of the entire group of patients under study was 2.93 ng/ml (range: 0.01 ng/ml - 9.7 ng/ml).

Overall, 41 patients (67%) had a positive ^{68}Ga-PSMA-HBED-CC scan result. ^{68}Ga-PSMA-HBED-CC PET/CT positivity was significantly higher in patients with PSA values > 2 ng/ml (32/38 patients (84%)) when compared to patients with PSA values < 0.5 ng/ml (6/11 patients (55%) or PSA values of 0.5-2 ng/ml (3/12 patients (25%)) (p= 0.0001). Based on ROC-curve analysis (AUC = 0.729 (p=0.004) (see Figure 1), using a PSA cut-off value of 2 ng/ml, a sensitivity of 78% and a specificity of 65% was found. Of the 41 patients presenting with a positive ^{68}Ga-PSMA-HBED-CC PET/CT scan (see Figures 2 and 3), 37 patients presented with 5 or fewer lesions (oligo-metastatic diseases), 21 patients presented with 1 lesion, 7 patients with 2 lesions, 4 patients presented with 3 lesions, 4 patients presented with 4 lesions, 1 patient presented with 5 lesions) and 4 patients presented with more than 5 lesions. Median PSA-values in patients presenting with oligo-metastatic disease and patients presenting with more than 5 lesions proved not significantly different, respectively 4.0 ng/ml (range: 0.01-9.7 ng/ml) versus 5.5 ng/ml (range 2.16-7.53 ng/ml) (p=0.471). Of the 41 ^{68}GA-PSMA-HBED-CC positive patients, 13 patients presented with extra-pelvic involvement. Mean PSA values proved not significantly different in these patients when compared to the remaining 28 ^{68}GA-PSMA-HBED-CC positive patients presenting with intra-pelvic involvement (5.21 ng/ml (SD:1.99 ng/ml) versus 3.82 ng/ml (SD: 3.11 ng/ml) (p= 0.147)). Likewise, mean PSA-values proved not significantly different between patients that presented with bone involvement (n=10) versus those that did not (n=31) on ^{68}Ga-PSMA-HBED-CC PET/CT (respectively 4.07 ng/ml(SD: 3.16 ng/ml) versus 4.83 ng/ml(1.77 ng/ml) (p=0.340).

Black versus white South-Africans: Age proved not significantly different between black (mean age 67.3 yrs. (SD:10.01 yrs.) and white (mean age 66.4 yrs. (SD:8.4 yrs.) South-Africans (p=0.717). Gleason-scores of the primary tumor were similar in white and black South-African men under study, respectively a median of 7.0 (range: 6-9) (p= 0.594). Median PSA-values proved not significantly different between black and white South-Africans, respectively 2.83 ng/ml (range: 0.1-9.7 ng/Ml) versus 3.0 ng/ml (range: 0.25-9.4 ng/ml) (p=0.530). Also, the

frequency of positive scan results was similar in black men (17/23 scans (63%)) when compared to that obtained in white men (24/38 scans (74%)) (p=0.417). Additionally, the frequency of white and black South-African patients presenting with PSA values < 0.5 ng/ml, with PSA-values > 0.5 ng/ml and < 2ng/ml and with PSA values > 2 ng/ml proved similar (P $\geq$ 0.143). Finally, the frequency of bone involvement (4/17 in black – versus 6/24 in white South-Africans) and extra-pelvic involvement (6/17 in black- versus 7/24 in white South-Africans) on ^{68}Ga-PSMA-HBED-CC PET/CT imaging proved similar in white and black South-African men (respectively p=0.606 and p= 0.742), see table 2.

DISCUSSION

In this series, 67% of the patients (41 out of 61) under study presented a positive ^{68}Ga-PSMA-HBED-CC scan. This figure is comparable to the result of a recent meta-analysis by Perera et al. including sixteen articles and 1309 patients, in which the overall percentage of positive ^{68}Ga-PSMA PET findings in prostate carcinoma patients presenting with a biochemical recurrence (rising PSA-values) was 76% [14]. In this meta-analysis, however, studies including both patients that did as well as that did not undergo medical or surgical castration or combination androgen deprivation therapy were included and no restriction was put on the level of increase of serum PSA values. Contrariwise, in the series presented, we studied patients suffering from prostate carcinoma with rising PSA values below 10 ng/ml, suggestive of low volume recurrence, that had previously undergone either radical prostatectomy or external beam radiation therapy with curative intent and who were not yet on hormonal or systemic therapy which may be responsible for the slightly lower disease detection rate in our series. As shown previously by other authors, the lower the PSA value, the less likely the ^{68}Ga-PSMA-HBED-CC scan will be positive [15,16]. Furthermore, ^{68}GA-PSMA PET/CT imaging has also been reported to be less frequently positive in patients that are not under androgen-deprivation, either surgical or medical, when compared to patients that undergo medical or surgical castration or combination androgen-deprivation therapy [16.] A possible explanation for this finding is that PSMA is up-regulated by anti-androgen therapy. In this regard, in a series of 20 patients suffering from prostate cancer undergoing medical or surgical castration or combination androgen-deprivation therapy in whom matched pretreatment and post-treatment specimens were available, an enhanced expression of PSMA was found in the post-

treatment specimens [17]. Neither type of androgen deprivation treatment nor tissue sensitivity to androgen deprivation appeared to influence the degree of biomarker expression. The same study also reported on the up-regulation of PSMA and down-regulation of PSA expression in the prostate carcinoma cell line LNCaP in the absence of androgens. On the other hand, androgen deprivation therapy may reduce tumor size thereby reducing detectability of prostate carcinoma lesions [18].

In line with the results from the meta-analysis by Perera et al., positive ^{68}Ga-PSMA PET scan findings proved highest in those patients presenting with a PSA value $\geq$ 2 ng/ml. Inversely, PSA-values proved not significantly different between patients presenting with bone metastases versus those that did not on ^{68}Ga-PSMA-HBED-CC PET/CT or in patients presenting with extra-pelvic involvement versus those with intra-pelvic involvement on ^{68}Ga-PSMA-HBED-CC PET/CT. Hypothetically, this finding may relate to the selective inclusion of low-volume recurrences (PSA values > 10 ng/ml) and the predominant oligo-metastatic character of the tumor recurrences identified using ^{68}GA-PSMA-HBED-CC PET/CT in the patient population under study with only 4 out of the 41 recurrences presenting with more than 5 lesions suggestive of a relatively homogenous population in terms of tumour aggressiveness. The concept of oligometastatic disease, first postulated by Hellmann and Weichselbaum in 1995, suggest tumor progression is a stepwise process and that a malignancy initially metastases in a limited way, before acquiring widespread metastatic behaviour [19,20,21]. It is suggested that initially, the tumor microenvironment in the primary lesion remains sufficiently hospitable so that evolutionary clonal pressure is low. A significant body of predominant retrospective studies suggests that survival rates in these patients are significantly better and their confirmation by randomized controlled trials is ongoing [21]. Given the rapid adoption of G68-PSMA-HBED-CC PET/CT imaging in routine clinical practice, this imaging modality is likely to impact on the number of patients diagnosed with oligo-metastatic disease (37 out of 61 in the series presented or 61%) as well as on their treatment and survival [22].

Following radical prostatectomy or external beam radiation therapy with curative intent for an underlying prostate carcinoma, as was the case for the patients included in the study, the increase in serum PSA level reflects the mass of recurrent prostate carcinoma tissue present. When normalized for age, clinical stage, pathological stage, Gleason score, benign prostate gland volume and prostate tumor volume, black men present with significantly higher PSA

tumor density and levels of prostate specific antigen PSA (on average 20% higher) both before screening and under treatment when compared to white men [23,24,25,26]. Thus, for a comparable serum PSA value, the recurrent tumor volume in black men is likely to be smaller than that in white men. Accordingly, a lower sensitivity of ^{68}Ga-PSMA-HBED-CC PET/CT detection rate may be anticipated in black when compared to white men presenting with low volume prostate carcinoma recurrence. This was however not corroborated by the series presented, evidencing a similar detection rate for prostate tumor recurrence in both black and white men with comparable Gleason scores irrespective of the PSA-value category. Also, the distribution pattern (intra-pelvic versus extra-pelvic) as well as the median number of lesions identified was similar in black men and white man suggesting that the tumor burden and growth rate of androgen dependent prostate carcinoma is similar in black and white men. In androgen independent prostate carcinoma, Fowler et al. previously demonstrated that PSA nadir, pretreatment PSA values and PSA doubling time controlled for clinical stage after gonadal androgen withdrawal are not significantly different in black when compared to white man [27]. Likewise, the biochemical response to deferred flutamide therapy and flutamide withdrawal proved the same in black and white men. Thus it seems that burden and growth rate of both androgen dependent and independent prostate carcinoma does not contribute to the well documented inferior survival of black men suffering from prostate carcinoma when compared to white man.

Positive uptake of ^{68}Ga-PSMA-HBED-CC were assumed pathological (metastatic) based on 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 [28, 29]. Our study is also limited by the small patient numbers included in both the WSA and BSA groups, a large sample size would be required to confirm our findings

In conclusion, in this prospective study including patients with rising serum PSA values suggestive of a low-volume recurrence that had undergone either radical prostatectomy or external beam radiation therapy with curative intent for an underlying prostate carcinoma, and who were not yet on hormonal or systemic therapy, ^{68}Ga-PSMA-HBED-CC PET/CT imaging identified a recurrence in 67% of the patients under study. Higher PSA levels were associated with better detection of site of recurrence on ^{68}Ga-PSMA-HBED-CC PET/CT. Finally the

detection rate, the distribution pattern (intra-pelvic versus extra-pelvic) and median number of lesions identified on ^{68}Ga-PSMA-HBED-CC PET/CT imaging proved similar in black men when compared to white men suggesting that the tumor burden and growth rate of androgen dependent prostate carcinoma is similar in both races.

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Table 1. Patient characteristics

Mean age		66.7 yrs. (sd: 8.9 yrs)
Prior Treatment	Radical Prostatectomy (RP)	n = 28(46%)
	RP + salvage radiotherapy	n = 21(34%)
	Primary radiation therapy	n = 12(20%)
Gleason score of the primary prostate carcinoma		7 ; range: 6-9
PSA values (median and range)		2.93ng/ml(0.01-9.7ng/ml)
PSMA positive scans		n=41(68%)

Table 2. Findings in black versus white South-Africans

	Black	White	p-value
Number of patients	23	38	
Age (mean +/-sd)	67.3(10.01)yrs	66.4(8.4)yrs	p=0.717
Gleason score(median and range)	7(6-9)	7(6-9)	p=0.594
PSA (median and range)	2.83(0.1-9.7)ng/ml	3.0(0.25-9.4)ng/ml	p=0.530
PSMA scan positivity	17/23(63%)	24/38(74%)	p=0.417
Intra-/extrapelvic disease	11/6	17/7	p=0.742
Bone involvement	4/17	6/24	p=0.606

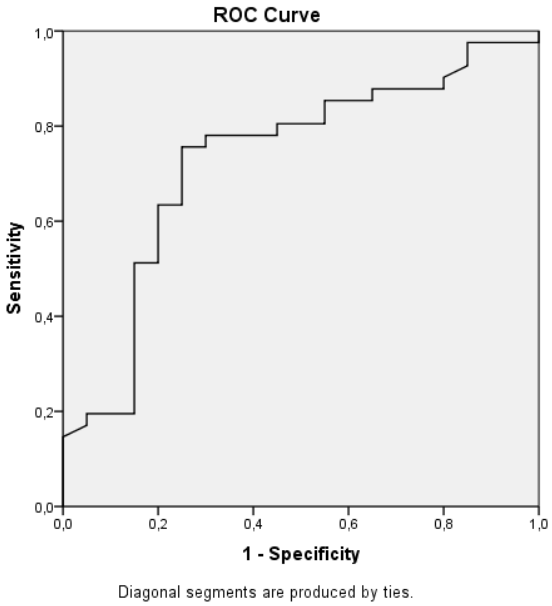

Figure 1. ROC-curve of PSA values for PSMA-positivity (AUC= 0.729(p=0.004)).

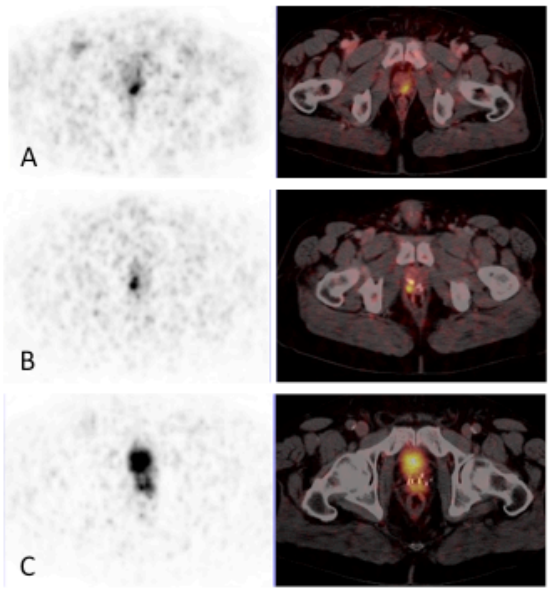

Figure 2. (A) 61yrs, previous radical prostatectomy. PSA 0,15. (B) 65yrs, previous radical prostatectomy. PSA 1,2. (C) 58yrs, previous brachytherapy and pelvic EBRT. PSA 3,13. White arrow indicates site of local recurrence.

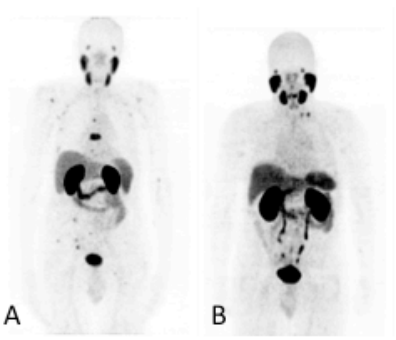

Figure 3. (A) 83yrs, previous radical prostatectomy and EBRT. PSA 6,2. Widespread skeletal and nodal metastases. (B) 66yrs, previous brachytherapy. PSA 5,62. Left supraclavicular lymph node involvement only.

5 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.

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ABSTRACT

Background: Accurate early assessment of biochemical recurrence is essential in determining the correct treatment plan for patients with prostate cancer. ^{68}Ga-PSMA-11 targeting prostate-specific membrane antigen (PSMA) has been at the forefront of imaging in

biochemical recurrence however the emergence of ^{18}F-PSM-1007 may prove to be advantageous over the ^{68}Ga-PSMA-11 molecule due to its physical and physiologic al 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.

Methods: Twenty-one patients with biochemical recurrence prostate cancer were prospectively enrolled into the study. ^{18}F-PSMA-1007 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: ^{68}Ga-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. ^{18}F-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. ^{18}F-PSMA-1007 demonstrated a sensitivity, specificity, positive and negative predictive value of 88.9%, 100%, 100%, and 92.3% respectively whilst 68Ga-PSMA-11 demonstrated a sensitivity, specificity, positive and negative predictive value of 44.4%, 83.3%, 80%, and 66.6% respectively

Conclusions: 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.

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 re-present with a detectable rise in serum PSA value[2].

Localization of source of PSA recurrence especially when the PSA value is still low has an impact on survival in prostate cancer patients as the treating doctor is able to direct potentially curative salvage therapy to this site of production whilst also reducing the potential harmful effects of unnecessary over treatment[3-5].

^{68}Ga-PSMA-11 has emerged as the leading PET imaging agent of choice in biochemical recurrence demonstrating good sensitivity and specificity in the setting of low serum PSA values[6]. Studies on the impact of ^{68}Ga-PSMA PET CT imaging on treatment intent have consistently demonstrated significant management changes as a result of positive findings on PSMA PET CT scans[7,8].

^{68}Ga-PSMA-11 though does have significant challenges. ^{68}Ga 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[9]. ^{68}Ga 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[10]. On the other hand ^{18}F-PSMA-1007 under goes hepatobiliary clearance resulting in minimal tracer accumulation in the ureters and bladder[11]. ^{18}F-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 a higher activity of ^{18}F-PSMA-1007 can be administered as compared to ^{68}Ga-PSMA-11 and due to its long half life of 110 minutes delayed imaging may be acquired to improve target to background clearance[12].

The aim of our study was to assess 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 local research ethics committee.

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).

^{68}Ga-PSMA-11 was prepared in-house as we have previously described whilst ^{18}F-PSMA-1007 was supplied by NTP [13].

Whole body PET/CT images from 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.

The median injected activity was 3.7mCi (range 1.24 – 8.25 mCi) 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 simultaneously acquired for all studies for attenuation correction and anatomical localization.

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. PET/CT images were visually analyzed for the presence of sites of abnormal ^{18}F-PSMA-1007 and ^{68}Ga-PSMA-11. Uptake higher than background-activity in lymph nodes and tissues, 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 defined for all PET/CT patient studies. 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 < 0.5 ng/ml, between 0.5ng/ml and 1ng/ml, between 1ng/m and 2 ng/ml, and above 2 ng/ml.

Metastasis diagnosed on each of these studies was compared against a 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 was 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

^{68}Ga-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. ^{18}F-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.

Local recurrence was identified in 5 of the positive patients on ^{68}Ga-PSMA-11, with only a single nodal metastases being identified. No skeletal lesions were identified on ^{68}Ga-PSMA-11 (Table 2).

Seventeen patients had had previous prostatectomy. ^{18}F-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.

Four of the patients had primary radiotherapy. ^{18}F-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).

^{18}F-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 (Table 3).

Discussion

The early localization of source of PSA is extremely crucial for the treating doctor of patients who present with biochemical recurrence after definitive therapy for prostate cancer. Localization of source of PSA recurrence especially when the PSA value is still low has an impact on survival in prostate cancer patients as the treating doctor is able to direct potentially curative salvage therapy to this site of production whilst also reducing the potential harmful effects of unnecessary over treatment[5]. ^{68}Ga-PSMA -11has emerged as a leading PET imaging agent in biochemical recurrence.

In a meta analyses ^{68}Ga-PSMA-11 PET/CT demonstrated an overall 86% detection rate in biochemical recurrence. The detection rate though was significantly lower as PSA levels dropped and was found to be 50% for PSA of 0.2 - 0.49ng/ml and 53% for PSA levels of 0.50-0.99 ng/ml. Prostate local recurrence was only identified in 10% of the cases whilst the majority of the sites of recurrence included the lymph nodes[14].

Though demonstrating very good detection rates in biochemical recurrence ^{68}Ga-PSMA is not without its shortcomings. 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 PSA production may be missed in the prostate bed or in close association to the ureters due to the adjacent urinary activity[15]. To mitigate this forced diuresis and subsequent delayed imaging has been researched in an attempt to get a better

view of this area[16].

The introduction of ^{18}F-PSMA-1007 PET/CT imaging was anticipated to yield increased sensitivity as the pelvis can be reviewed unobstructed due to its minimal renal clearance[17]. Geisel et al 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[18]. Similar detection rates in the setting of low PSA were also seen by other researchers[19].

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 researchers this was still higher than that of ^{68}Ga-PSMA (23.8%) in the same patients. ^{18}F-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 doubtful findings noted on ^{18}F-PSMA-1007 PET CT imaging.

Mc Carthy et al 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[20]. 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 its better visualization of the pelvis.

<u>Limitations</u>

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 [21-23].

The study was a small pilot study and findings would need to corroborated in a larger cohort study.

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.

Acknowledgements:

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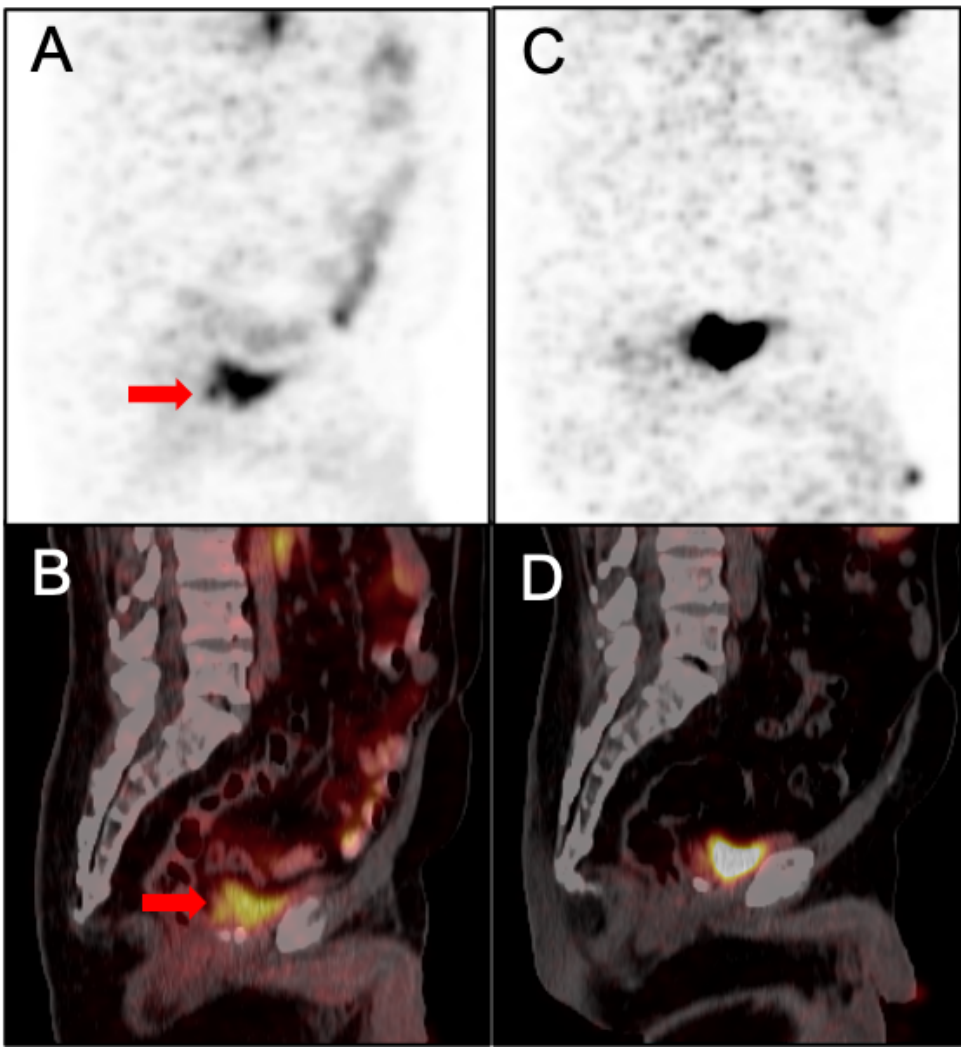
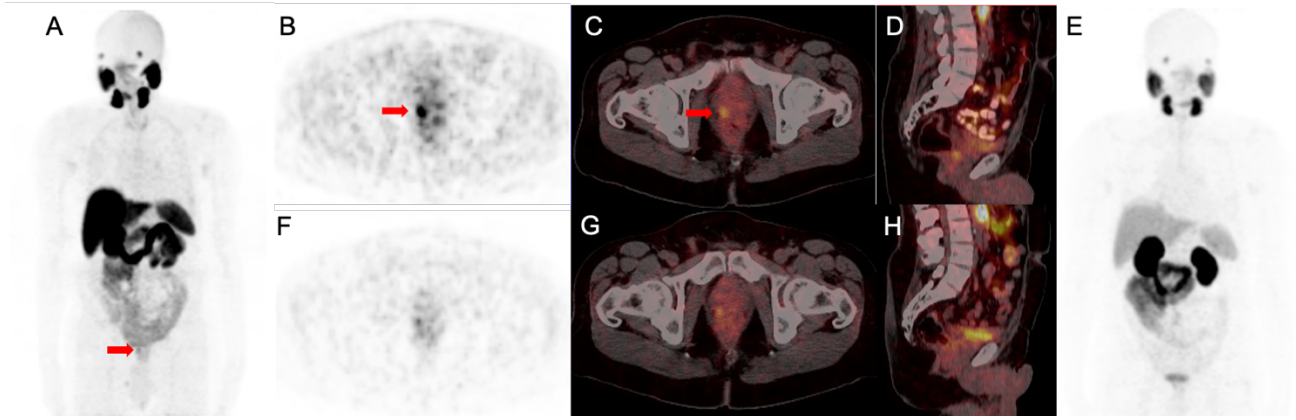
Figure 1.



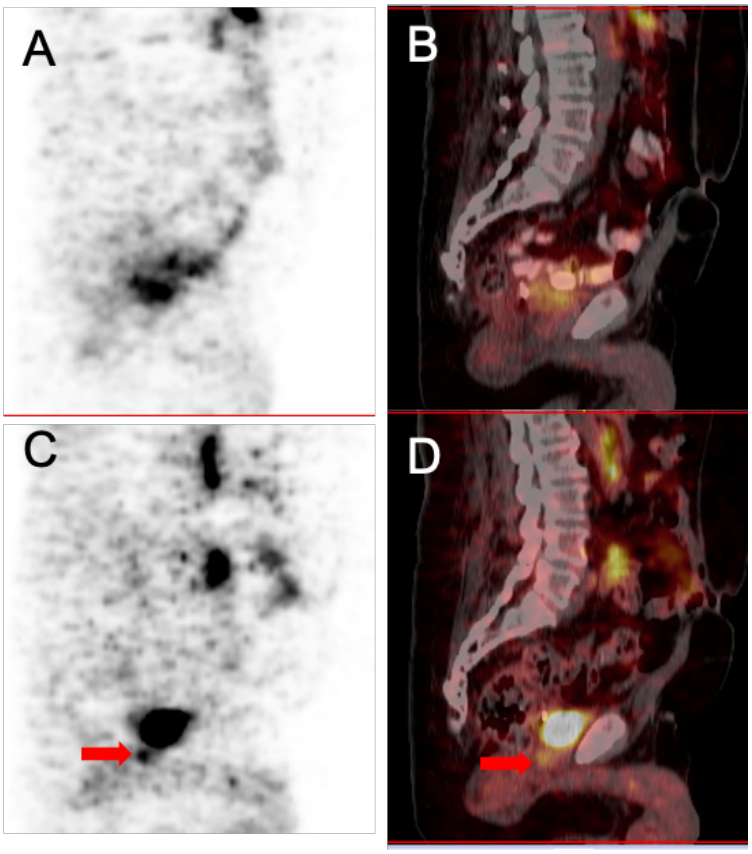
75 year old male, Gleason grade 1, with PSA of 1.51ng/ml. Sagittal ^{18}F-1007-PSMA PET (A) and fused (B) images demonstrating prostatic recurrence (arrow). ^{68}Ga-PSMA-11 sagittal PET (C) and fused (D) images demonstrating negative uptake.

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).

Table 1
Age distribution, Gleason scores, PSA and image findings 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
PRIMARY THERAPY		
Prostatectomy	15	71.4
Prostatectomy + EBRT	2	9.5
Radiotherapy	4	19.1

SD: Standard deviation; EBRT: External Beam Radiotherapy

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

	^{18}F-1007-PSMA PET/CT	**^{68}Ga-PSMA PET/CT**
Variable	**N (%)**	**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	--

Table 3
Comparing the diagnostic performance of ^{18}F-1007-PSMA and ^{68}Ga-PSMA PET/CT

	Positive	Negative	Total
Variables	**n = 9 (%)**	**n = 12 (%)**	**N = 21 (%)**
^{18}F-1007-PSMA			
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	0	1 (100)	1

Evaluation	**^{18}F-1007-PSMA**	**^{68}Ga-PSMA PETCT**
Sensitivity	88.9%	44.4%
Specificity	100%	83.3%
Positive predictive value	100%	80.0%
Negative predictive value	92.3%	66.6%

***p* = 0.3750**

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6 The Diagnostic Performance of ^{18}F-PSMA-1007 PET/CT In Prostate Cancer Patients With Suspected Early Recurrence After Definitive Therapy With A PSA <10ng/ml

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Submitted

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Keywords: ^{18}F-PSMA-1007 PET/CT, early biochemical recurrence, prostate cancer, PSA kinetics

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AIMS

The prostate bed is the commonest site of early recurrence of prostate gland. The currently used PSMA ligands (^{68}Ga-PSMA and ^{99m}Tc-PSMA) undergo early urinary clearance resulting in interfering physiological activity within and surrounding the prostate. This can result in sites of cancer recurrence being obscured. ^{18}F-PSMA-1007 has an advantage of delayed urinary clearance thus the prostate region is reviewed without any interfering physiological activity.

The aim of this study was to determine the diagnostic performance of ^{18}F-PSMA-1007 PET/CT in patients with early biochemical recurrence after definitive therapy.

MATERIALS AND METHODS

Forty-six Prostate cancer patients prostate (mean age 66.6±7.66, range 48-87 years) presenting with biochemical recurrence (median PSA 1.59ng/ml, range 0.05 – 9.97) underwent non-contrast-enhanced ^{18}F-PSMA-1007 PET/CT. Area of abnormal tracer uptake above background activity outside of organs with physiologic tracer biodistribution were considered as suggestive of prostate cancer recurrence. PET/CT findings were evaluated qualitatively and semiquantitatively (SUVmax) and compared to the results of histology, Gleason score, and conventional imaging.

RESULTS

Twenty-four of the 46 (52.2%) patients demonstrated a site of recurrence on ^{18}F-PSMA-1007 PET/CT. Oligometastatic disease was detected in 15 (32.6%) of these patients. Of these 10 (37.5%) demonstrated intra-prostatic recurrence, whilst lymph node disease was noted in 11 (45.8%) whilst two patients demonstrated skeletal recurrence. The detection rates for PSA levels 0 - <0.5, 0.5-<1, 1-2, >2 were 31.25%, 33.33%, 55.56% and 72.22% respectively. 7 (29,2%) of the positive patients had been described as negative or equivocal on conventional imaging. Optimal PSA cutoff level of 1.26ng/ml

CONCLUSION

^{18}F-PSMA-1007 demonstrated good diagnostic performance detecting sites of recurrence at PSA values as low as 0.19ng/ml. Its superior ability to detect recurrence missed by conventional imaging will have a significant impact on patient management.

Introduction

According to Globocan 2018 prostate cancer has the second highest rate of incidence of all cancers in males after lung cancer[1]. Prostate confined disease can have extremely favourable

outcomes with 5 years survival rates of nearly 100% however up to a third of these patients will represent with a detectable rise in PSA levels suggestive of prostate cancer recurrence[2,3]. In these patients biochemical recurrence is defined as a PSA value of >0.2 ng/ml after radical prostatectomy or a PSA of >2ng/ml from nadir after radiotherapy[4].

Localization of early recurrence (low PSA) has a high impact on survival and morbidity as potentially curative salvage therapy may be directed to a specific site thus eliminating the unwanted harmful effects of unguided routine treatment[5-7].

Nomograms have shown a good sensitivity in predicting local recurrence however they are still unable to distinguish the type of extra-prostatic recurrence[6].
^{18}F-Flourocholine had initially gained traction in PET imaging of biochemical recurrence due to increased phosphatidylcholine metabolism in malignant cells however it grew out of favour due to a low detection rate for prostate cancer recurrence in the setting of low PSA[8,9].

^{68}Ga-PSMA-11 has emerged as a leading PET imaging tracer in biochemical recurrence replacing ^{18}F-Flourocholine due to its good sensitivity and specificity in the setting of low PSA values[9-11].
Though successful as an imaging agent in prostate cancer recurrence ^{68}Ga-PSMA-11 still suffers from significant challenges including the fact that the number of patients which can be imaged on a daily basis are limited by the number of eluates from the ^{68}Germinium/^{68}Gallium generator[12].

^{18}F-PSMA-1007 has a few advantages over ^{68}Ga-PSMA-11 due to the following physical properties. It is cyclotron produced resulting in more doses being available for patients to be imaged. Its half life of 110 minutes allows for delayed imaging for better target to background clearance[13]. ^{18}F-PSMA-1007 undergoes delayed urinary clearance which allows for examination of the prostate bed without interference from adjacent physiological urinary bladder activity which is seen with ^{68}Ga-PSMA[14,15].

The aim of our study was to assess the diagnostic performance of ^{18}F-PSMA-1007 in patients who presented with early biochemical recurrence of PSA $\leq$2.0ng/ml.

Materials and Methods

The study was approved by the local research ethics committee.

Forty-six patients (mean age, 66.65 years, range, 48 – 87 years) with biochemical recurrence prostate cancer were prospectively enrolled into the study (Table 1).

^{18}F-PSMA-1007 was supplied by NTP [16].

Whole body PET/CT images from vertex to mid thigh were acquired on a Siemens Biograph 40 PET/CT scanner 120 minutes after injection of ^{18}F-PSMA-1007 respectively.

The median injected activity was 3.7mCi (range 1.24 – 8.25 mCi) for ^{18}F-PSMA-1007.

Non-contrasted low dose CT scans were simultaneously acquired for attenuation correction and anatomical localization.

Image Analysis

Acquired ^{18}F-PSMA-1007 PET/CT 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. PET/CT images were visually analyzed for the presence of sites of abnormal ^{18}F-PSMA-1007. Uptake higher than background-activity in lymph nodes and tissues, not corresponding to physiologic tracer accumulation, was considered pathologic and compatible with malignancy. The number of ^{18}F-PSMA-1007 avid lesions and their location were defined for all PET/CT patient studies. The detection rate of recurrence by ^{18}F-PSMA-1007 PET/CT was defined in the entire group of patients and for different levels of PSA, respectively < 0.5 ng/ml, between 0.5ng/ml and 1ng/ml, between 1ng/m and 2 ng/ml, and above 2 ng/ml.

Metastasis diagnosed on the studies was compared against a 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. The diagnostic performances of ^{18}F-PSMA-1007 PET/CT at different Gleason grade, PSA doubling time and PSA velocity was determined. Similar evaluation was done for the diagnostic performances of ^{18}F-PSMA-1007 PET/CT at different PSA levels (PSA <0.5, 0.5-1.0, 1.0-2.0, >2.0). The diagnostic performances for the entire cohort of ^{18}F-PSMA-1007 for the detection of recurrence was determined. The statistical significant level was set at a p value of <0.05. Statistical analysis was done using STATA 14.

Results

Twenty-nine patients had undergone radical prostatectomy (80.43%), nine patients had undergone primary radiation therapy (19.1%) and eight patients had undergone salvage radiotherapy after radical prostatectomy (9.5%).

Median Gleason grade of the primary prostate carcinoma was 2.0 (range 1-5).

Median PSA value of the entire group of patients under study was 1.59 ng/ml (range: 0.05 ng/ml – 8.93 ng/ml) (Table 1).

^{18}F-PSMA-1007 identified twenty-four (52.2%) patients' scans as being positive whilst twenty-two (47.8%) were identified as negative for recurrence.

Single metastatic disease was detected in fifteen (32.6%) of the positive patients. Of these patients ten (37.5%) demonstrated intra-prostatic recurrence whilst lymph node only disease was noted in three (6.5%) patients. In total eleven patients demonstrated nodal metastasis. Of these eleven patients nine demonstrated intra pelvic nodal disease recurrence. Two patients demonstrated skeletal recurrence.

Seven (29,2%) of the positive patients had been described as negative or equivocal on conventional imaging (Table 2).

Forty of the forty-six patients had PSAdt data available at imaging. Twenty-one patients presented with PSAdt ≤6 months, whilst nineteen patients presented with PSAdt >6 months.

The detection rates PSAdt ≤6 months and >6 months were 47.62% and 52.5% respectively (Table 3).

PSA velocity data was only available in thirty-nine of the patients. Of the thirty-nine patients twenty-one, seven and eleven had PSA velocities of <1, 1-2 and >2 years respectively. The detection rates for PSA velocity <1, 1-2, >2 were 38,1%, 42,86 % and 81.82% respectively (Table 3).

The detection rates for PSA levels 0 - <0.5, 0.5-<1, 1-2, >2 were 31.25%, 33.33%, 55.56% and 72.22% respectively (Table 3).

Based on ROC-curve analysis (AUC = 0.724), using a PSA cut-off value of 1.26 ng/ml, a sensitivity of 75% and a specificity of 68% was found (Figure 1).

Table 1: Age distribution, Gleason scores, PSA and previous therapy

Variable	Frequency	Percentage
Age (years)		
Mean ± SD	68.04 ± 7.54	
Range	48 – 87	
Gleason Grade		
Median	2	
Range	1-5	
PSA		
Median	1.59	
Range	0.05 – 8.93	
PRIMARY THERAPY		
Prostatectomy only	29	80.43
Prostatectomy + EBRT	8	9.5
Primary Radiotherapy	9	19.1

Table 2: Study participant PET CT study image findings of ^{18}F-PSMA-1007

	^{18}F-1007-PSMA PET/CT
Variable	**N (%)**
Positive	24 (52.17)
Previously negative on conventional imaging	7
Negative	22 (47.83)
Uncertain	--
Prostatic Bed Disease Only	10 (21.74)
Prostatic Bed Disease with nodal disease	11
Extra Prostatic Disease	14 (30.43)
Oligometastatic Disease	15 (32)
Nodal Metastatic Disease	11
Location nodal	9 pelvic / 2 extra-pelvic
Skeletal Metastatic Disease	2
Soft Tissue Metastatic Disease	3

Table 3: Comparing the diagnostic performance of ^{18}F-1007-PSMA and PSA doubling time, PSA velocity and PSA

PSA Doubling Time (months)	**Negative n(%)**	**Prostatic Only n(%)**	**Extra Prostatic n(%)**	**Total**	
≤ 6	11 (52.38)	0	10 (47.62)	21 (52.50)	
>6	8 (42.11)	7 (36.84)	4 (21.05)	19 (47.50)	
Total	19 (47.50)	7 (17.50)	14 (35.0)	40	*p = 0.004*
PSA Velocity (years)	**Negative**	**Prostatic Only**	**Extra Prostatic**	**Total**	
<1 n(%)	13 (61.90)	3 (14.29)	5 (23.81)	21 (53.85)	
1-2 n(%)	3 (42.86)	1 (14.29)	3 (42.86)	7 (17.95)	
>2 n(%)	2 (18.18)	3 (27.27)	6 (54.55)	11 (28.21)	
Total n(%)	18 (46.15)	7 (17.95)	14 (35.90)	39	*p=0.179*
PSA (ug/L)	**Negative**	**Positive**		**Total**	
<0.5 n(%)	11 (68.75)	5 (31.25)		16	
0.5-1 n(%)	2 (66.67)	1 (33.33)		3	
1-2 n(%)	4 (44.44)	5 (55.56)		9	
>2 n(%)	5 (27.78)	13 (72.22)		18	*p=0.90*

Discussion

Prostate cancer patients who present with early biochemical recurrence after primary curative therapy may potentially still have an opportunity for further curative salvage therapy should the site of recurrence be accurately identified[7]. Salvage radiotherapy outcomes have been demonstrated to show an inverse relationship with PSA value with the most benefit demonstrated in patients who present with a PSA value of <1.0ng/ml[5,17]. This highlights the clinical value of accurate early assessment of biochemical recurrence.

^{68}Ga-PSMA has played a leading role in the PET imaging of not only biochemical recurrence but also in the initial staging of prostate cancer and has been demonstrated to have a high impact on treatment plans for patients[18-20].

Afshar-Oromieh et al reported an overall detection rate of 82.8% for ^{68}Ga-PSMA in biochemical recurrence[21]. In a prospective study in biochemical recurrence ^{68}Ga-PSMA demonstrated an overall detection rate of 75%, the detection rates for PSA groups were 38%, 57%, 84%, 86% and 97% for PSA groups <0.5ng/ml, 0.5 to <1.0ng/ml, 1.0 to <2.0ng/ml, 2.0 to <5.0ng/ml and >5.0ng/ml respectively[22].

In a prospective study of ^{18}F-PSMA-1007 in biochemical recurrence Giesel et demonstrated a detection rate of 61.5%, 74.5%, 90.9%, and 94% for PSA groups 0.2-0.5ng/ml, 0.5-1.0ng/ml, 1.0-2.0ng/ml and >2.0ng/ml respectively[23].

In our study we found comparatively lower detection rates for ^{18}F-PSMA-1007 which were 31.25%, 33.33%, 55.56% and 72.22% for PSA groups 0 - <0.5ng/ml, 0.5-<1.0ng/ml, 1-2, >2ng/ml respectively. This is was probably due to the low PSA values that were seen in our cohort, 28 (60.9%) patients in our cohort presented with a PSA value of <2.0ng/ml. A number of studies have demonstrated a reduction in detection rate as the pre-scan PSA value reduced[24-26]. Giesel et al had found that the patients with negative imaging findings in their cohort had a median PSA of 1.56ng/ml[23]. The median PSA for our study was 1.59ng/ml which may further explain the low overall detection rate.

We found that a pre-scan PSA with optimal cut-off of 1.26ng/ml was a predictor for a positive scan which is also comparable with what other authors have found[27].

Normograms have been reported to predict intra-prostatic vs exra-prostatic recurrence however they are unable to distinguish from the type of extra-prostatic recurrence[4,6,28].

Mestre et al demonstrated that the detection rate of PSMA-PET correlated with PSAdt with an increase in the detection rate seen in association with a PSAdt ≤6 months as compared to those with a PSAdt >6 months[29].

Verburg et al was able to demonstrate with ^{68}Ga-PSMA in biochemical recurrence that a short PSAdt of <6 months was significantly associated with extra-prostatic disease recurrence[30]. We also observed in our paper that only extra prostatic disease recurrence was seen in the patients who had a PSAdt of <6 months. We could not see a significant relationship between PSA velocity and PSMA PET outcomes.

^{68}Ga-PSMA has been demonstrated to have a high impact on the management of recurrent prostate cancer including the direction of salvage radiotherapy after radical prostatectomy[31,32]. One of the more common sites for prostate cancer recurrence after radical prostatectomy is the prostate bed[33]. There have been concerns that local prostate cancer recurrence may be missed with ^{68}Ga-PSMA PET imaging due to its physiological urinary bio-excretion which may result in bladder and ureter activity obscuring prostate bed locoregional pelvic node assessment[34]. This limitation was noted in the 14% detection rate for local prostatic recurrence seen in ^{68}Ga-PSMA[26]. The physical attributes of ^{18}F-PSMA-1007 favour biliary excretion thus allowing for better assessment of the prostate bed and pelvis without interfering activity from the urinary bladder[13]. In our study eleven (45%) of the twentyfour patients who were identified as positive for recurrence on imaging had prostatic bed recurrence. Similar detection rates for local disease recurrence especially in low PSA was seen with ^{18}F-PSMA-1007[23]. The detection rates we reported for local disease recurrence were also higher in comparison to those reported for ^{68}Ga-PSMA[35]. This may likely contribute to increased reporter confidence in interpreting findings in the prostate bed resulting in less findings[36].

Improved sensitivity for the detection of local recurrence may prove vital for treating doctors as treatment options for salvage therapy for local recurrence including reirradiation using stereotactic radiation therapy become available to patients[37].

Limitations

It was not possible to get histopathological correlation of all detected metastatic lesions. Positive uptake of ^{18}F-PSMA-1007 was 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 [38-40]. The study had a limited population size and findings would need to be corroborated in a larger cohort study.

Conclusion

Though limited by a small study population ^{18}F-PSMA-1007, when compared to a similar patient cohort of very low PSA recurrence, performed well and was able to demonstrate a good detection rate for local intraprostatic bed recurrence. This will be potentially crucial as

more potential curative treatment options become available needing more accurate localization of PSA source whilst still at very low volumes. Further research in a larger population to this end is recommended.

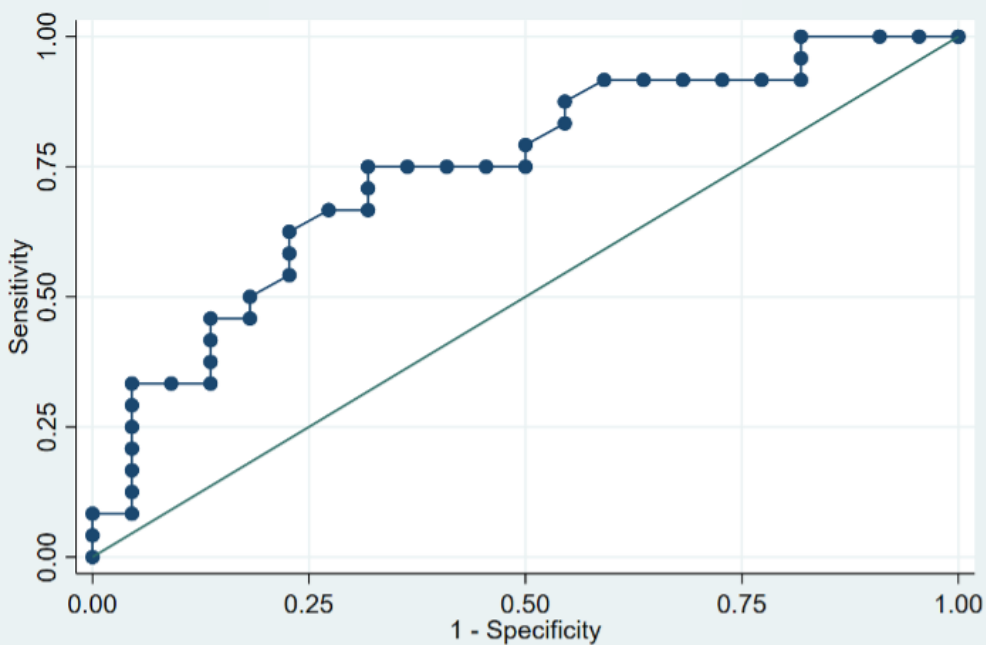

Figure 1: Receiver-operating-characteristic (ROC) curve for PSA with an optimal cutoff level of 1.26ng/ml.

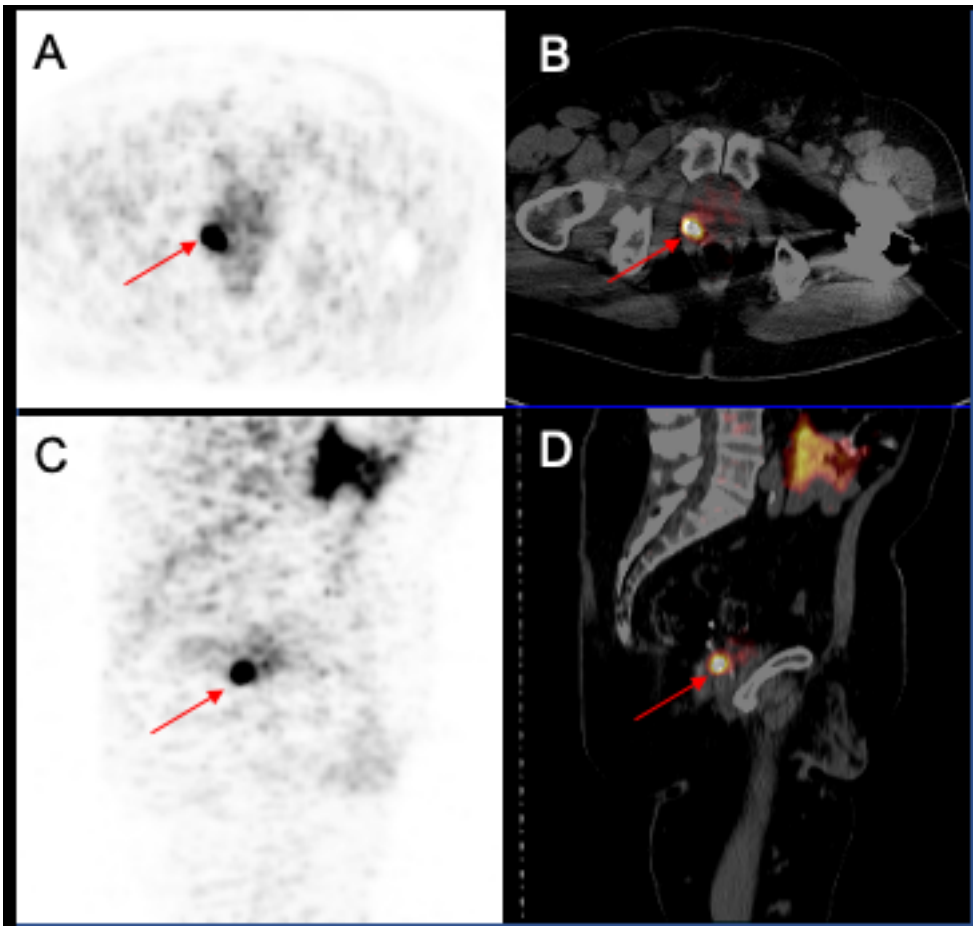

Figure 2: 68-year-old patient, previous radical prostatectomy, Gleason grade 3, PSA before PET 2.7ng/ml. Axial ^{18}F-1007-PSMA PET (A) and fused (B) images demonstrating prostatic recurrence (arrow). Sagittal ^{18}F-1007-PSMA PET (C) and fused (D) images demonstrating prostatic recurrence (arrow).

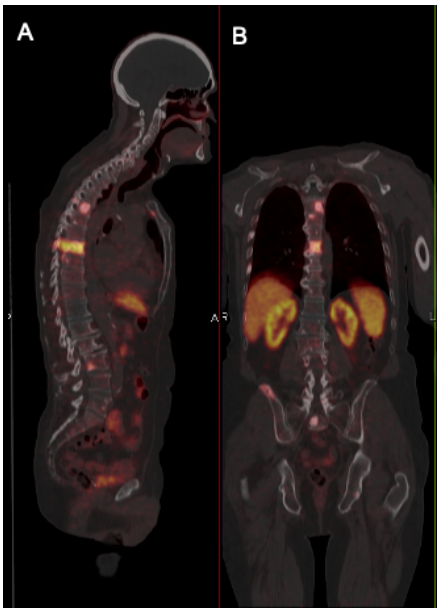

Figure 3: 87-year-old patient, previous radical prostatectomy, Gleason grade 5, PSA before PET 2.64ng/ml. ^{18}F-1007-PSMA fused sagittal (A) and coronal (B) images demonstrating skeletal metastases in the thoracic and lumbar spine, sacrum and pelvis.

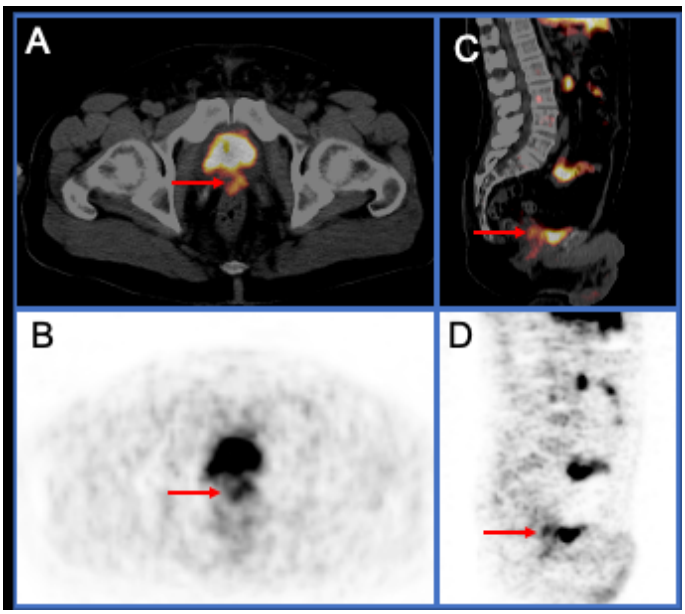

Figure 4: 61-year-old patient, previous radical prostatectomy, Gleason grade 3, PSA before PET 0.19ng/ml. Axial ^{18}F-1007-PSMA fused (A) and PET (B) images demonstrating prostatic recurrence (arrow). Sagittal ^{18}F-1007-PSMA fused (C) and PET (D) images demonstrating prostatic recurrence (arrow).

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7 Focal Hematopoietic Hyperplasia of the Rib, a false positive on ^{18}F-PSMA-1007 PET/CT imaging

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Submitted

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Abstract

We report a case of a 60 year old man with prostate cancer who presented with biochemical recurrence. ^{18}F-PSMA-1007 PET/CT study performed for suspected biochemical recurrence demonstrated focal uptake in the 4th right rib. No other sites of abnormal tracer uptake were noted in the study. Biopsy of the rib lesion demonstrated focal hematopoietic hyperplasia of the rib.

Keywords:
^{18}F-PSMA-1007, Prostate cancer, bone metastases, biochemical recurrence, focal hematopoietic hyperplasia of the rib

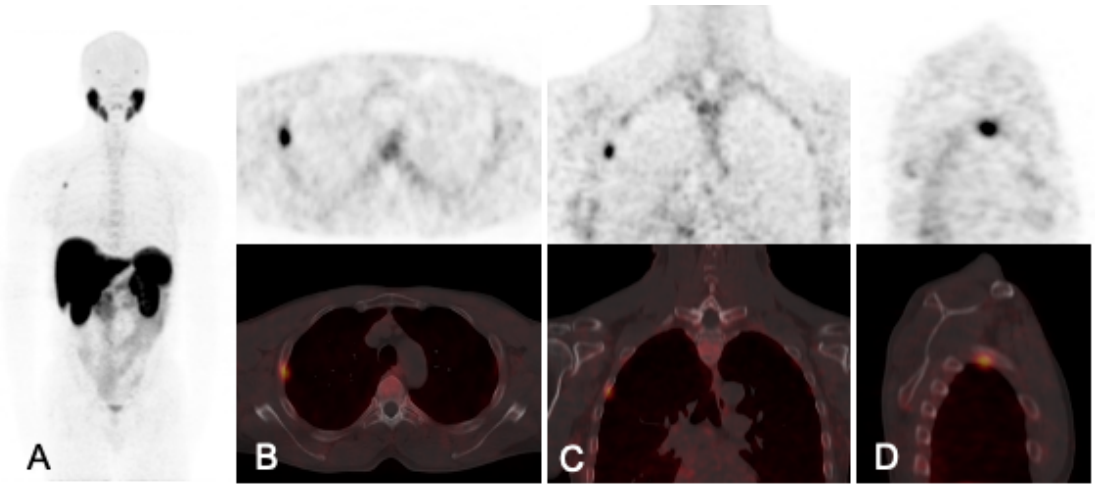

Figure 1. 60 year old male with prostate cancer, Gleason3+3, presenting with history of rising PSA (0.33ng/ml). His treatment history included radical prostatectomy with clear margins. No further therapy has been given. ^{18}F-PSMA-1007 PET/CT study was performed for suspected biochemical recurrence. The MIP image (A) demonstrated uptake that localized to the rib lesion. on the CT, PET/CT PET and fused axial, coronal and sagittal images (B-D respectively). Prostate specific membrane antigen (PSMA) is a type II membrane antigen with high expression in prostate cancer cells resulting in increasing interest in its targeting with PSMA ligands in prostate cancer imaging [1,2]. ^{18}F-PSMA-1007 has demonstrated great sensitivity and specificity in its ability to detect prostate cancer metastases even at low PSA levels [3]. The PSMA molecule is not only overexpressed in prostate cancer but may also be overexpressed in other cancers and benign conditions leading to interpretation errors [4-6].

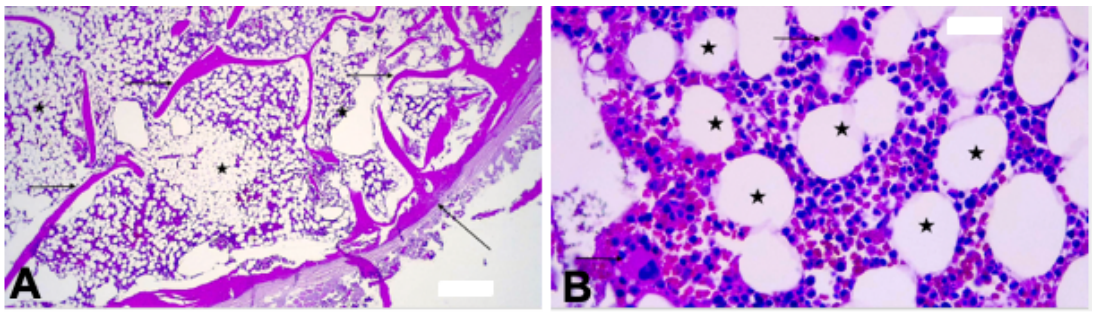

Figure 2. Biopsy of the rib lesion demonstrated confirmed focal hematopoietic hyperplasia. Histology , low power view, H&E x25 (A) demonstrated cortical bone and periosteal fibrous tissue on the bottom right (diagonal arrow), trabeculae of normal bone and enclosed anatomically normal medullary space containing haematopoietic tissue (**). On the high power view of the marrow component (B) adipocytes (**) and trilineage haematopoietic elements including megakaryocytes (arrowed) were noted, H&E x400. No malignant cells were noted. Focal hematopoietic hyperplasia is a rare pseudotumor of the ribs due to the abnormal expansion of marrow [7]. To date only 6 of these cases have been reported in the literature. They are mainly discovered incidentally on radiological imaging presenting as an

expansile solitary osteolytic rib lesion, which had a thin and intact cortex [8]. To date no case has been reported in nuclear medicine imaging.

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8 Conclusion and Recommendations

Prostate cancer remains the leading cancer diagnosed in men worldwide. Its is a biologically heterogenous disease that makes imaging evaluation challenging. The role of imaging in prostate cancer is to characterize the primary tumour and accurately detect prostate confined and extra-prostatic spread of disease including the identification of skeletal metastases. Imaging is of utmost as it ultimately defines the therapeutic approach. Though a disproportionate burden of disease, disease recurrence rate and mortality has been reported in prostate cancer in black versus white patients in our thesis we were not able to demonstrate a significant difference in the detection rate, distribution pattern and median number of lesions between the two racial groups in biochemical recurrence after definitive therapy. To our knowledge this is the first time that such a comparison on imaging has been made.

The current imaging methods in the staging of prostate cancer (bone scan, computed tomography and magnetic resonance) have varying sensitivity and specificity and thus there has been a debate on the imaging modality of choice in the staging of prostate cancer.
In our thesis we demonstrated that ^{68}Ga-PSMA PET-CT was superior to bone scan in the detection of skeletal metastases. ^{68}Ga-PSMA PET-CT demonstrated a reduced false positive rate and significantly high sensitivity and accuracy as compared to bone scan.

The leading PET imaging agent of choice in prostate cancer is ^{68}Ga-PSMA and has demonstrated high detection rates in biochemical recurrence and resulted in significant impact on therapeutic plans for the treating physician. ^{68}Ga-PSMA however suffers from limitations. Its physiological urinary clearance may result in prostate bed and pelvic sites of recurrence being missed. ^{18}F-PSMA-1007 was anticipated to have superior sensitivity to ^{68}Ga-PSMA. In our thesis ^{18}F-PSMA-1007 demonstrated a good detection rate for local intraprostatic bed disease recurrence. We were however unable to reproduce the reported detection rates of other PSMA PET agents in biochemical recurrence and this may due to the fact that a large majority of our patient cohort presented with very low PSA values. In fact when compared to patients of similar low PSA recurrence our detection rates proved to be similar. We found that PSA doubling time was significantly related to ^{18}F-PSMA-1007

detection rate whilst there was no significant relationship with PSA velocity. We found an optimal PSA cut-off value of 1.26ng/ml.

In our thesis, to our knowledge we were the first to investigate a direct comparison between ^{18}F-PSMA and ^{68}Ga-PSMA findings in the same patients presenting with biochemical recurrent prostate cancer. Though limited by a small study population ^{18}F-PSMA was able to detect more sites of recurrence as compared to ^{68}Ga-PSMA. ^{18}F-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.

We then highlighted a rare case of focal hematopoietic hyperplasia of the rib presenting as a false positive for skeletal metastases. This serves an important case for reporting physicians to keep in mind that not all positive uptake on ^{18}F-PSMA-1007 PET-CT imaging is due to metastatic disease and that the reading physician should interpret findings taking into account all available supportive information including clinical history, previous imaging reports and PSA trends.

Even though ultimately ^{18}F-PSMA-1007 performed similarly to other reported PSMA PET agents given the fact that ^{18}F-PSMA-1007 is cyclotron produced with a half-life of 110 minutes, it may prove a significant additional advantage over ^{68}Ga-PSMA as more doses for imaging may be made available for patients with an even greater reach for prostate cancer patients in who are in distant towns from major cities. Our research was limited by a small study population and therefor we recommend further research in a larger population of patients with a very early biochemical recurrent prostate cancer.

The accurate detection of localized intraprostatic disease is essential in biochemical recurrence and is crucial in the treatment planning of newly diagnosed prostate cancer patients. MRI has played a leading role in the T staging of the intraprostatic tumour due to its excellent anatomical resolution. However, better visualization of the tumour in the prostate bed with increased sensitivity is possible with ^{18}F-PSMA-1007 as it undergoes minimal urinary clearance. The advent of combined PET-MRI promises to revolutionize cancer staging as it

combines the best of both worlds – molecular and anatomical imaging. Imaging prostate cancer patients with ^{18}F-PSMA-1007 PET-MRI may prove to be the best combination when reviewing the whole body, including the prostate bed. I would recommend further studies to this end.

9 Appendix

9.1 Appendix 1: University of Pretoria PhD Committee Approval

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Faculty of Health Sciences

12 July 2018

Prof MM Sathekge
HoD: Nuclear Medicine
University of Pretoria

Dear Prof Sathekge

STUDENT : T LENGANA (PhD MEDICAL NUCLEAR SCIENCE)

^{18}F-PSMA-1007 in recurrent prostate cancer, a new frontier in prostate cancer PET imaging

The above-mentioned student's protocol has been approved by the PhD committee.

We wish the student all the best with his studies.

Kind regards

PROF V STEENKAMP
CHAIR: PhD COMMITTEE

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University of Pretoria, Private Bag X323
Arcadia 0007, South Africa
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Fakulteit Gesondheidswetenskappe
Lefapha la Disaense tša Maphelo

9.2 Appendix 2: University of Pretoria Research Ethics Approval

The Research Ethics Committee, Faculty Health Sciences, University of Pretoria complies with ICH-GCP guidelines and has US Federal wide Assurance.
- FWA 00002567, Approved dd 22 May 2002 and Expires 03/20/2022.
- IRB 0000 2235 IORG0001762 Approved dd 22/04/2014 and Expires 03/14/2020.

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Faculty of Health Sciences Research Ethics Committee

31/05/2018

Approval Certificate
New Application

Ethics Reference No: 217/2018

Title: 18F-PSMA-1007 in Recurrent Prostate Cancer, a new frontier in Prostate Cancer PET imaging.

Dear Dr Thabo Lengana

The **New Application** as supported by documents specified in your cover letter dated 2/05/2018 for your research received on the 2/05/2018, was approved by the Faculty of Health Sciences Research Ethics Committee on its quorate meeting of 30/05/2018.

Please note the following about your ethics approval:
- Ethics Approval is valid for 2 years
- Please remember to use your protocol number (**217/2018**) on any documents or correspondence with the Research Ethics Committee regarding your research.
- Please note that the Research Ethics Committee may ask further questions, seek additional information, require further modification, or monitor the conduct of your research.

Ethics approval is subject to the following:
- The ethics approval is conditional on the receipt of **6 monthly written Progress Reports**, and
- The ethics approval is conditional on the research being conducted as stipulated by the details of all documents submitted to the Committee. In the event that a further need arises to change who the investigators are, the methods or any other aspect, such changes must be submitted as an Amendment for approval by the Committee.

We wish you the best with your research.

Yours sincerely

Dr R Sommers, MBChB; MMed (Int); MPharMed,PhD
Deputy Chairperson of the Faculty of Health Sciences Research Ethics Committee, University of Pretoria

The Faculty of Health Sciences Research Ethics Committee complies with the SA National Act 61 of 2003 as it pertains to health research and the United States Code of Federal Regulations Title 45 and 46. This committee abides by the ethical norms and principles for research, established by the Declaration of Helsinki, the South African Medical Research Council Guidelines as well as the Guidelines for Ethical Research: Principles Structures and Processes, Second Edition 2015 (Department of Health).

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