Fluorine-18-Fluoroethylcholine PET/CT in the detection of prostate cancer: A South African experience

Mariza Vorster[1] MD, PhD, Moshe Modiselle[1] MD, Thomas enhan[1] PhD, Carl Wagener[2] PhD, That Sello[2] PhD, Jan Rijn Zeevaart[1,2] PhD , Evelyn Moshokwa[3] MD, Mike Machaba Sathekge[1] MD, PhD

[1]*Department of Nuclear Medicine, University of Pretoria and Steve Biko Academic Hospital, Pretoria, South Africa*

[2] *Radiochemistry, The South African Nuclear Energy Corpora-tion, Pelindaba, Pretoria, South Africa*

[3] *Department of Urology, University of Pretoria and Steve Biko Academic Hospital, Pretoria, South Africa*

Abstract

Objective: Imaging with fluorine-18-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) has, until recently provided disappointing results with low sensitivity rang-ing from 31%-64% in patients with well-differentiated prostate cancer (PC) at all prostatic specific antigen (PSA) levels while fluorine-18-fluoroethylcholine (^{18}F-FECh) PET/CT showed about 85% sensitivity in restag-ing patients after relapse. We present our experience of the sensitivity of ^{18}F-FECh PET/CT in the early stages of PC.

Subject and methods: Fifty patients were prospectively recruited and imaged, of which 40 fulfilled all inclusion criteria. Our patients had an average age of 65.5 years. Fifteen patients were referred for initial staging, with the remaining 25 referred for restaging and all patients had histologically confirmed adenocarcinoma. Patients were imaged by ^{18}F-FECh PET/CT. Findings were evaluated qualitatively and quantitatively and compared to the results of histology, PSA, Gleason score and bone scintigraphy. The prostate SUV max was also used.

Results: Thirty-one patients demonstrated abnormal pelvic- and or extra-pelvic findings on ^{18}F-FECh PET/CT, which was consistent with malignant or metastatic involvement. The prostate SUVmax could not be used to predict the presence or absence of metastatic disease.

Conclusion: Findings of this paper suggest that ^{18}F-FECh PET/CT in 30/40 cases (estimated as 75%) was helpful in the initial staging, restaging and lymph node detection of patients with PC. The SUVmax was not helpful. We diagnosed more PC cases in our African-American patients as compared to the Caucasian patients.

Keywords: Prostate cancer - PET/CT - Fluoroethylcholine

Correspondence address:
Mike Sathekge MD, PhD
University of Pretoria and
Steve Biko Academic Hospital
Private Bag X169, Pretoria,
0001, South Africa
Tel: +27 12 354 1794
Fax: +27 12 354 1219
mike.sathekge@up.ac.za

Introduction

Prostate cancer (PC) is one of the leading causes of morbidity and less of mortality worldwide, and the same is true in South Africa. Epidemiological evidence has demonstrated important racial differences in incidence and clinical behavior of PC among patients [1]. At a molecular level, the development of PC is considered to be a complex interaction between important genetic and cellular factors [2].

One of the well established risk factors is race with incidence and mortality rates in black American men almost twice those of white American men and 5 times higher than those of Asian men living in Asia [3]. The Southern African prostate cancer study (SAPCS) showed that black South African men present with higher PSA levels and histopathological tumor grade compared with Black Americans, which was further escalated in men from rural localities [4].

Early detection is crucial in the successful management of this disease with an increase in expected 5 years survival from 33% up to a 100% if treated at an organ-confined stage [5]. Biologically and clinically, PC is a heterogeneous disease that is characterized by states ranging from indolent to aggressive.

Current modalities used in the diagnosis, staging and re-staging of PC, all suffer from various limitations. Prostate-specific antigen (PSA) screening has resulted in increased detection of clinically insignificant PC through repeated standard and occasionally saturation biopsies (overdiagnosis and stage migration), which have inevitably led to early unnecessary therapy in many patients [5, 6].

The Gleason score is well-recognised for its predictive value in patient prognosis, and is used by clinicians in combination with the PSA and clinical information to select the most appropriate course of therapy. Recently, a score of 7 has been recognised as having a poorer outcome [7].

Imaging evaluation of prostate cancer remains challenging [8], but its role should in-

clude diagnosis, localization of suspected recurrence, characterization (indolent vs. lethal) of the primary tumor and determination of disease extent. Despite the usefulness of fluorine-18-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) in oncology it is however not recommended for staging and restaging in well differentiated PC due to its low sensitivity [9, 10]. Imaging by PET/CT with ^{18}F-fluoroethylcholine (^{18}F-FECh) could potentially provide physicians with a one-stop investigation, which could assist in selecting the most appropriate form of therapy, prediction and evaluation of treat-ment response as well as overall prognostication [11].

In order to stage PC according to the 7th American Joint Comitte of Cancer (AJCC) guidelines, the accurate assessment of extra-capsular involvement, lymph node detection and distant metastases is required [12].

The value of PET with radiolabeled choline in the staging of PC has been a subject of controversy, and varying results have been reported [13-17].

The application of ^{11}C or ^{18}F-labeled choline derivatives have been used with mixed results. The rationale for evaluating fluorocholine as an oncologic tracer applicable to PC is based on observations of increased choline and fluorocholine metabolism in malignant prostate tissue relative to normal tissue [18]. Previous studies have reported on the success of choline in PC relapse. A meta-analysis study provided a high sensitivity, of 85% and 92% specificity for the detection of locoregional and distant metastases in PC patients with recurrence of disease [19].

The aim of this study was to describe our experience in South Africa of the potential value of ^{18}F-FECh PET/CT in the detection of malignant lesions in various stages of PC with rising PSA levels.

Subjects and methods

Patients' population

Forty patients were included in the study with an average age of 65.5±6.71 years (range of 53-78) with the following demographics: Black 20/40, Caucasian 16/40, Indian 2/40 and coloured 2/40. Fifteen of the forty patients included in this study were referred for initial staging, with the remaining 25 referred for restaging and all patients had histologically confirmed adenocarcinoma. Regression analysis did not reveal any significant differences between races in terms of disease severity (P=0.49).

Study design

Approval for this study was granted by the University of Pretoria's Research and Ethics Committee and informed consent was obtained from all participants in this study prior to in-jection and imaging.

Fifty patients were prospectively recruited and imaged, of which 40 fulfilled all of the inclusion criteria. Patients with histologically proven PC were included as part of either ini-tial staging prior to surgery or suspected recurrence or restaging following therapy with curative intent (surgery or radiation therapy). All patients had a currently proven biochemical recurrence.

Patients were fasted for 4-6h with ample hydration both before and after administration of the ^{18}F-FECh and asked to empty the urine bladder just before imaging. Furosemide (20mg) was administered together with the tracer in all cases.

Radiochemistry

Fluorine-18-FECh was produced under Good manufacturing practice (GMP) conditions at the radiochemistry group at the Nuclear Energy Corporation of South Africa (NECSA) in a Raytest Synchrom R&D (Germany) remote synthesizer ac-cording to the published procedure by Schmaljohann et al (2011) [20]. No-carrier was added. Aqueous ^{18}F-fluoride (15- 26GBq) was trapped on a preconditioned (18mL 1M NaHCO3) Quaternary methyl ammonium SepPak light car-tridge (Waters). The ^{18}F-fluoride was eluted with a mixture of 900µL acetonitrile, 200µL aqueous 0.1M K2CO3 and 17- 18mg kryptofix 2.2.2 into the first reactor of the remote syn-thesizer. The residual water in the reactor was removed by azeotropic distillation by adding a further 2mL acetonitrile, and heating to 95°C under a stream of nitrogen under vac-uum. Fifteen-17mg of the 2-bromoethyl-4-nitrobenzenesulfonate precursor in 1mL acetonitrile was added to the reactor and the ^{18}F labeling [aliphatic nucleophilic substitution (SN2) substitution of 4-nitrobenzenesulfonate by ^{18}F-fluoride to give ^{18}F-bromofluoroethane (^{18}F-BFE)] reaction was carried out at 95°C for 10min. After cooling and the addition of 5mL of water to the reactor, the reaction mixture was pushed into a further 12mL of water, this cloudy mixture was purified and the intermediate product was trapped by sending it through three preconditioned cartridges con-nected in series and connected to waste: Firstly, an Interna-tional Commission on Harmonization cartridge (Alltech, Grace Davison Discovery Science, Deerfield, Illinois, USA) preconditioned with 10mL of water, then a C-18 SepPak plus cartridge (Waters Corporation, Milford, Massachusetts, USA), preconditioned with 10mL of ethanol and then 10mL of water, and thirdly a chromafix horseradish peroxidase (HRP) cartridge (Macherey-Nagel, Waters Corporation Milford, Massachusetts, USA), preconditioned with 10mL of ethanol and then 10mL of water. Only the HRP cartridge, where the ^{18}F-BFE intermediate product was trapped, was then eluted with 1.8mL of dry dimethyl sulfoxide (DMSO), through an unconditioned Silica (Si-60) light SepPak cartridge (Waters) into a second reactor that already contained 200µL dimethylaminoethanol (DMAE). The alkylation reaction between ^{18}F-BFE and DMAE to give ^{18}F-FECh, was carried out at 105°C for 10min. After cooling down, the ^{18}F-FECh product was purified and trapped by adding 5mL water to the reac-tor and sending the reaction mixture through two cartridge memory plus SepPak cartridges (Waters), connected in se-ries and each preconditioned with 10mL water. After wash-ing the cartridges with 5mL ethanol, followed by 15mL water, the ^{18}F-FECh product was eluted with 8mL of sterile saline solution to give 2.2-6.4GBq of final product solution, a radiochemical yield (RCY) of 15%-25%. This final product solution was aseptically dispensed in a biosafety cabinet, by passing the required

Quality control
The radiochemical purity and identity of the final product were determined by Agilent 1200 series instrument (Agilent Technologies International, Morges Switzerland), with refractive index (RI) and radioactive (Raytest Gabi Star-Raytest, Strabenhardt, Germany) detectors and an Agilent Zorbax stable bond (SB) C-18, 250x4.6mm 5µ column. Elution was carried out with mobile phase containing 10% acetonitrile and 6.4g/l of Organization for safety and asepsis procedures. The pH was adjusted to 2.2 with phosphoric acid. Flow was set on 1mL/min. All chemicals used, were of high performance liquid chromatography grade. The ^{18}F-ethylcholine was eluted with room temperature 16.40±1.20min and ^{18}F-FECh 30-60s later, due to delay time between RI and radio detector. Bacterial endotoxin, pH, appearance, radioactivity concentration, bubble point test and chemical purity were examined on every patient injection. All methods for analyses were validated.

Image acquisition
Study participants were imaged on a Siemens Biograph 40 PET/CT scanner 90min following intravenous administration of ^{18}F-FECh dosage of 5MBq/kg. Both oral (barium in water) and intravenously (i.v.) administered contrast (100mL Ultravist, at a rate of 2mL/s) were administered, except where a contra-indication existed, such as inadequate kidney function or known iodine allergy. Images were acquired in a three-dimensional mode with a 4min emissions scan for each of 7-9 bed positions (Matrix size 512x512) from pelvis to skull to have minimal bladder filling at the time of scanning. For the CT-attenuation correction (AC) scan, the recommendations provided by the manufacturer were followed. Generally, CT-AC scans were operated using at least 60mAs. Reconstruction of images with and without attenuation correction (CT based) was done using ordered subset expectation maximization (OSEM) to yield axial, sagittal and coronal slices. All images were first evaluated qualitatively for abnormal uptake, which if present, was then followed by semi-quantification analysis. This was done in the following way: a region of interest was manually drawn around any lesions and the size selected to correspond to the pathology on CT. This resulted in a standardized uptake value (SUV), which was representative of the relative concentration of radiotracer in a lesion of interest, normalized to the patient's weight and the dose of radiotracer administered, was calculated according to the formula: SUV=radiotracer activity×patient weight/injected dose. We used the maximum SUV (SUVmax) in this study, which represents the pixel with the highest tracer uptake in the lesion.

Data analysis
Fluorine-18-FECh PET/CT scans were interpreted independently from the results of other special investigations by two experienced nuclear physicians. These results were then compared to the PSA level, Gleason score, histopathology and/or clinical follow-up based on other imaging and non-imaging tests.

Statistical analysis
Descriptive statistics were used to describe the study population in terms of age, race, PSA and Gleason values. Where these were normally distributed, the results were expressed as percentages or means with standard deviations. Alternatively, where these were not normally distributed, it was expressed as median values and ranges. The statistical software package STATA version 12.0 (Freiburg, Germany) was used to perform linear and logistic regression, where applicable.

Results

Other investigations performed
Total PSA values were available in 28 patients and ranged from 0.11 to 563ng/mL with a median value of 19.85. The PSA value was demonstrated as an independent predictor of the presence of metastatic disease, with higher values associated with the presence of metastases (P=0.001).

The Gleason score was available in 30 patients, which ranged from 4 to 9 with the highest occurrence of Gleason 6 (20%) to 8 (20%). A detailed Gleason score was available in only 17 patients, with the highest frequencies noted in the following categories: 3+3, 3+4 and 4+4 (all 7.5%). Higher Gleason scores were statistically significantly associated with the presence of metastatic disease (P=0.025).

Twenty-six patients also underwent imaging with conventional bone scintigraphy with technetium-99m-methyl diphosphonate (^{99m}Tc-MDP). This corresponded to the PET/CT findings in 22/26. Typical uptake pattern indicative of osteoblastic skeletal metastases was demonstrated on ^{99m}Tc-MDP bone scintigraphy. Comparison between CT and PET, revealed the following: PET and CT correlated with local findings in 38/40; PET and CT correlated with distant metastases involving the lungs, liver and skeletal system in 31 patients. The majority of these metastatic lesions were located in the skeleton.

Image findings
Nine patients had no evidence of malignant or metastatic involvement (In all of these patients the uptake in the prostate was negligible). The rest of the study population (31 patients) demonstrated uptake in the prostate gland, which had a median SUVmax of 5.61. The SUVmax in the prostate gland could not be used to predict the presence or absence of metastatic disease involvement (P=0.2). Thirteen patients had disease restricted to the pelvis; eighteen had extra-pelvic disease, of which the majority also had concomitant pelvic involvement. The most common areas of metastases were skeletal involvement (12/31) and pelvic lymph nodes involvement (12/40), followed by bladder involvement (9/31), rectal involvement (7/31) and abdominal lymph nodes involvement (5/31). Regional lymph nodes involvement was present in 19 patients with a mean SUVmax of 7.7 (±3.2) compared to a lower median SUVmax of 5.9 noted in 18 patients with distant lymph nodes. Mediastinal lymph nodes involvement was noted in several patients with SUVmax around 3, which were characterized by both PET and CT as infective/inflammatory.

A more detailed Table with all laboratory data for each of the 40 patients is available on request.

***Table 1**. Risk group classification*

	Very low-risk	Low-risk	Intermediate-risk	High-risk	Locally advanced
D'Amico (32)		PSA≤10ng/mL and GS<7 and cT1-2a	PSA10-20ng/mL or GS ≤7, or cT2b	PSA>20ng/mL or GS<7, or cT2c-3a	
NCCN (33)	cT1c, GS <7, PSA <10ng/mL, PSAD <0.15, <3 positive biopsies	PSA<10ng/mL, GS<7, cT1-2a	PSA 10-20ng/mL or GS<7 or cT2b-2c	PSA >20ng/mL or GS<7, or cT3a	cT3b-4
CAPRA (34)		<3	3-5	6-10	
EAU (35)		PSA<10ng/mL, GS<7, cT1c	PSA 10-20ng/mL, or GS 7,or cT2b-2c	PSA <20ng/mL/ GS 8-10 or = > cT3a	

In these guidelines, the D'Amico risk-group classification is used to define high-risk PCa (high-risk or locally advanced PCa comprise stages T3 and T4). Low-risk, versus high-risk PCa is based on PSA findings only, or on Gleason score only.

Discussion

In the US, the African-American male group had the highest incidence rate for prostate cancer, at nearly twice that of Caucasians, while Asian men had the lowest incidence. The African-American males are more likely to develop PC at an earlier age, present with a higher stage at the time of diagnosis, and have a higher rate of metastases and poorer survival rate than the Caucasian men [21].

Several studies have explored potential differences in tumor growth determinants between African- American and Caucasian patients. Guo et al (2000) [22] demonstrated a down-regulation of Bcl-2 expression, which may be potentially responsible for the loss of apoptotic control in prostate tumors from African-American men.

Differences in diet, socio-economic circumstances, lifestyle, and access to medical care have been suggested as causative factors for the pronounced ethnic differences observed in the incidence and clinical behavior of PC, although the molecular mechanisms underlying this racial diversity in PC are not well defined [23]. A case control study performed in Soweto (South Africa) similarly suggested important differences between black and Caucasian men with prostate cancer [24].

Our local patient population consisted largely of black patients; and most of them had cancer at an advanced stage. So, we could not obtain statistical results among races.

Prostate cancer is biologically and clinically a heterogeneous disease that makes imaging evaluation challenging. Initial imaging diagnosis may be made with ultrasound or MRI using endorectal probes and image-guided biopsies when disease is suspected on the basis of a high serum PSA level or abnormal findings on digital rectal examination. Prostate cancer is often multifocal therefore a standard 10- to 12-core biopsy may miss 38% of cancers or underrepresent higher-grade tumor foci (which probably drive the overall cancer biologic behavior and outcome). This highlights the important role of imaging in localization and characterization of primary tumors [25]. Accurate depiction of the primary tumor foci may guide and evaluate the response to focal therapies ("male lumpectomy") of aggressive cancers (~15% of tumors) and avoid early treatment of indolent cancers, which should rather be followed by active surveillance [26].

Prostate-specific antigen screening has resulted in increased detection of clinically insignificant prostate cancers through repeated standard and occasionally saturation biopsies (overdiagnosis and stage migration), which have inevitably led to early unnecessary therapy in many patients [5, 6]. In order to increase the diagnostic specificity of PSA in detecting PC cases that need immediate attention, other researchers have suggested the use of PSA density, velocity, doubling time and free to total PSA ratio or combining PSA with Gleason score [27]. Despite highly successful treatments for localized prostate cancer, approximately 15%-40% of men will experience a detectable rise in the serum PSA level (biochemical failure) within 10 years from the primary treatment. This suggests that prostate cancer can metastasize relatively early in the course of the disease, probably as a result of genetic instability, including loss of metastase-suppressor genes [7]. About 25%-35% of men with an increasing serum PSA level will develop locally recurrent disease only, 20%-25% will develop metastatic disease only, and 45%-55% will develop both local recurrence and metastatic disease [5]. In our study, a higher PSA level was significantly associated with the presence of metastatic disease. Other researchers have demonstrated a statistically significant higher ^{18}F-CH PET/CT positive detection rate with a concomitant increase in the total PSA levels at the time of the scan [28].

The Gleason score is well-recognised for its predictive value in patient prognosis, and is used by clinicians in combination with the PSA, ^{99m}Tc-MDP bone scan and clinical information to select the most appropriate course of therapy [29]. Another researcher suggested that a quatitative whole body scan can eventully be used as a promising biomarker especially if used under proper standardized methodology [30]. In addition, other researchers demonstrated that a higher serum chromogranin A positively correlated with multiple bone metastases, higher Gleason score and PSA [31].

We also found a significant association between higher scores and metastatic disease. Recently, a score of 7 has been recognised as having a poorer outcome [7]. In future studies the risk group classification in Table1 might be helpful [32-35].

The accurate detection of disease confined to the prostate gland versus extraglandular spread to the lymph nodes or the skeleton is crucial when defining the most appropriate therapeutic approach. Imaging modalities play an important role in the staging of PC [36]. Imaging by PET/CT offers the advantages of whole body staging in one investigation, which combines morphological and functional imaging. It also allows for monitoring of treatment response and patient prognostication. However, the most commonly used PET tracer in oncology, ^{18}F-FDG, which represents glucose metabolism in cancer cells, is not useful in the imaging of PC

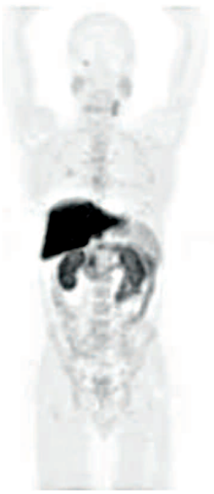

Figure 1. ^{18}F-Fluoro-ethyl-choline-biodistribution (185MBq) was i.v. injected, followed by PET image acquisition. Normal tracer bio-distribution was noted in the salivary glands, liver, kidneys and bladder at 90min post-injection.

due to various factors related to tumor growth and composition [37, 38].

Fluorine-18-FECh is a PET tracer which has recently been introduced in the evaluation of PC patients and its accuracy in staging and restaging of this disease has been assessed by previous studies [39, 40]. The rationale for evaluating fluorocholine as an oncologic tracer applicable to PC is based on observations of increased choline and fluorocholine metabolism in malignant prostate tissue relative to normal tissue. Choline is a component of phosphatidylcholine, which is an important element of cell membranes. Biosynthesis of the cell membrane increases in malignancy and together with the upregulation of choline, kinase activity induces a higher uptake of choline, especially in PC.

The various forms of choline (F-choline, F-ethylcholine and F-methylcholine) have comparable biodistribution, however because of the difference in their affinities, uptake tends to be lower if the methyl group is substituted by the ethyl group. The normal biodistribution of ^{18}F-FECh demonstrates relatively high accumulation in the pancreas, liver, spleen, and kidneys; variable uptake in the bowel; and excretion into urine (Figure 1).

The present study has demonstrated abnormal ^{18}F-FECh accumulation in 31 patients, which corresponded to malignant or metastatic disease involvement. Disease confined to the pelvis was present in thirteen patients, with 18 patients

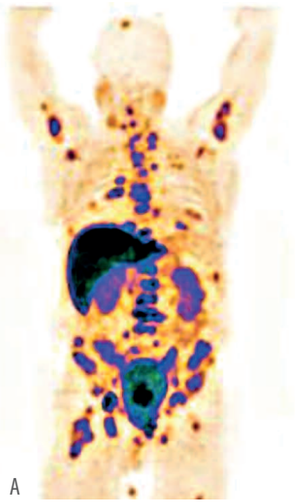

Figure 2. a) A 64 years old man with prostate cancer and rising PSA level. ^{18}F-Fluoro-ethyl-choline-biodistribution (185MBq) was i.v. injected, followed by imaging at 90min post-injection. Maximum Intensity PET Projection images demonstrate widespread skeletal metastases and inguinal lymph nodes involvement (b).

presenting with both pelvic-and extra-pelvic involvement. The most common sites of metastatic involvement were noted in the skeletal system (Figures 2 and 3) and pelvic lymph nodes (12/40), followed by bladder (9/40) and rectal (7/40) involvement. Regional lymph node involvement demonstrated a mean SUVmax of 7.7, with a median value of 3.9 noted in distant lymph nodes. The advantage of PET/CT to explore all anatomical sites and all tissues in one single examination was also demonstrated by other researchers with ^{11}C-choline PET/CT [41]. They suggested the use of this study soon after a rise in PSA for early detection of metastases [41]. However one of the limitations of our results are the false negative results, which could be related to the tumor size or micrometastases.

In 2008 other researchers [42] evaluated the role of ^{18}F-FECh PET/CT in the restaging of PC, which showed an overall sensitivity of 86% at any PSA level and 87% sensitivity at PSA levels of >2μg/L. Sensitivity without antihormonal therapy at any PSA level was 83%, and at PSA >2μg/L without antihormonal therapy, 86%. Sensitivity at any PSA level in patients with hormonal therapy was 84% and at >2μg/L, 88% [38].

Other studies showed an overall sensitivity of 74% in the detection of malignant lesions with biochemical recurrence after initial therapy, thus clearly supporting the previously published data concerning the feasibility of this modality in the restaging of PC patients [43, 44]. Similar results were also noted by others who demonstrated a high overall detection rate (80%), which is proportional to the trigger PSA (both for local and distant relapse). They proposed ^{18}F-FECh PET/CT as

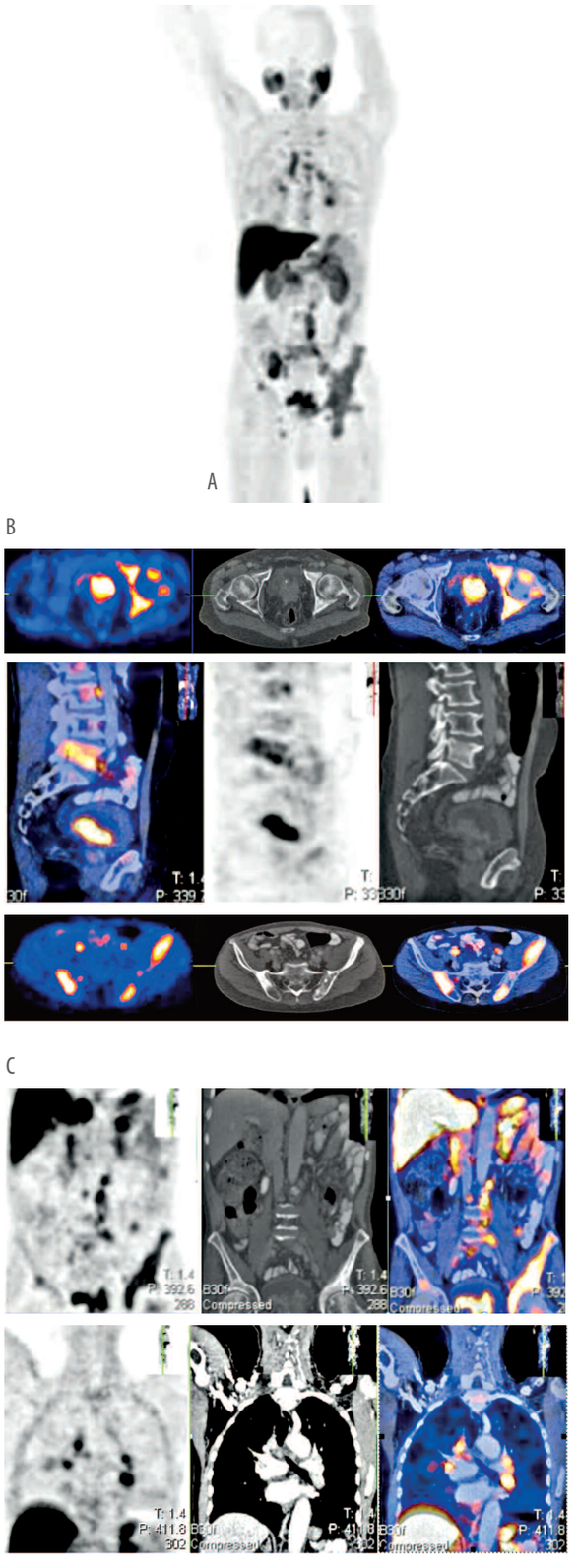

Figure 3. a) A 71 years old man with prostate cancer and rising PSA levels referred for initial staging.185MBq of ^{18}F-Fluoro-ethyl-Choline was i.v. injected and images acquired at 90min post-injection. b) PET/CT Images demonstrate widespread skeletal involvement, local and distant lymph nodes involvement. Lesion detection is higher on PET compared to CT. c) Local and distant metastatic lymph nodes involvements shown better appreciated on PET than on CT.

a first-line imaging procedure in the restaging of PC patients primarily treated with radiotherapy [26]. Compared to the previous published studies, our study was able to demostrate local soft tissue disease, nodal involvement, and distant metastases in PC patients, which influenced their treatment management.

In conclusion, although the number of our patients was limited, our study suggested that ^{18}F-FECh PET/CT in 30/40 cases (estimated as 75%) was helpful in the initial staging, restaging and lymph node detection of patients with PC. The SUVmax was not helpful. We diagnosed more PC cases in our African-American patients as compared to the Caucasian patients.

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The authors declare that they have no conflicts of interest.

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