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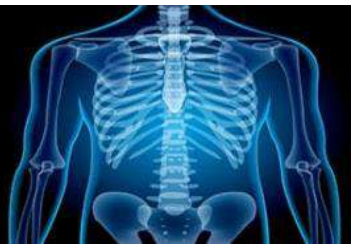

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Using of 18 fluorine labeled prostatic specific membrane antigen positron emission tomography-computed tomography in staging of prostatic cancer in correlation with prostate specific antigen level

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Abstract
Background: Due to its biological properties, Prostate-specific membrane antigen (PSMA) is a good target for prostate cancer molecular imaging. The aim of this work was to evaluate the role of 18F PSMA Tomography–Computed Tomography (PET CT) in the diagnosis and staging of cancer prostate in association with prostate specific antigen serum level.
Methods: This prospective cohort work was performed on 30 individuals pathologically proven prostate cancer patients, seven patients were recently diagnosed and were referred for primary staging of the disease, and 27 patients were long term patients who received initial treatment and were referred due to high prostate-specific antigen (PSA) level.
Results: There was positive association between PSA values and maximum standardized uptake values (SUV max) of PSMA expression at prostate with insignificant correlations between PSA and age or SUV max of PSMA expression of metastatic lesions of prostate cancer. At 3.4 cut-off value, SUV max of PSMA expression at prostate had 100% sensitivity and specificity win diagnosis of active local cancer prostatic lesions with higher AUC than PSA. PSA was higher among metastatic prostate cancer patients with statistically significant difference. At cut-off value equal to 5.3, PSA had 95% sensitivity and 71.4% specificity in prediction of metastasis.
Conclusions: PSMA PET/CT is the modality of choice in recurrent cancer prostate, it can assess the site of recurrence and determine the disease burden. It can detect cancer prostate metastasis in non-enlarged lymph nodes, bony deposits even with no apparent CT morphological changes.

Keywords: 18f PSMA positron emission, tomography–computed tomography, cancer prostate, prostate specific antigen

Introduction
Prostate cancer is the second most common malignancy in males and the fifth most common cause mortality worldwide. Since treatment choices change depending on whether the prostate cancer is localized, locally progressed, or has spread to other parts of the body, an accurate prostate cancer staging using imaging techniques is crucial for effective disease management [1].
The sensitivity of conventional imaging techniques to identify metastases of cancer of the prostate has been proven to be low [2]. Including magnetic resonance imaging (MRI), computed tomography (CT), and bone scintigraphy. Lesions of prostate cancer have been seen with favorable outcomes utilizing molecular imaging and several radiopharmaceuticals. In positron emission tomography (PET) imaging, 18F-FDG continues to be the mainstay. FDGPET avidity in prostate cancer is modest and varied, and it may be an accidental discovery caused by a benign condition. Thus, a demand for precise targeting emerged [3].
Choline-labeled tracers, using 11C or 18F, have been utilized as potentially useful markers up until recently. Because of its poor sensitivity, this radiotracer has essentially been forgotten. When examined, other tracers including 11C-acetate and 18F-uorocyclobutane-1-carboxylic acid failed to live up to predictions or exhibit qualities comparable to choline. Similarly to the prior mentioned tracers, 18F-Uciclovire had the same outcome [4].

A cell surface protein called Prostate-specific membrane antigen (PSMA), which is also expressed in the proximal small intestine, kidney, and salivary glands, is considerably more expressed in prostate cancer cells compared to in other PSMA-expressing organs. With increasing pathological Gleason grade, PSMA expression often rises [5]. Most PSMA ligands have been either 68Ga or 18F labeled for diagnosis reasons. Even at reduced PSA levels, research suggests that PSMA-ligand PET/CT is sensitive and extremely specific in detecting prostatic metastasis [6].

In contrast to 68Ga-labelled tracers, 18F-PSMA can provide a longer half-life, better energy features, and greater picture quality. The urinary system excretes 18F-PSMA very little, which is advantageous for pelvic imaging [7]. Currently, serum PSA is the most used biomarker for prostate cancer screening and a trustworthy indicator of disease recurrence after first therapy [8]. The levels of PSA, together with other factors, may predict the probability of developing bone metastases, but they should be considered with the results of clinical and diagnostic imaging studies since they do not necessarily correlate with the severity of the illness [7].

The objective of this study was to evaluate the contribution of 18F PSMA PET CT for determining the stage and diagnosis of prostate cancer in relation to serum levels of prostate specific antigen.

Patients and Methods

This prospective cohort work was performed on 30 individuals, both sexes, pathologically proven prostate cancer patients, seven patients were recently diagnosed and were referred for primary staging of the disease, and 27 patients were long term patients who received initial treatment and were referred due to high PSA level, with clinical criteria prostate cancer based on previous histopathology with elevated serum PSA, recently diagnosed prostate cancer patients with elevated PSA blood level with no detectable lesions to explain this by conventional imaging and patient with very high PSA blood level refusing to be biopsied.

After receiving clearance from the Ethical Committee International Medical Center in Cairo, the research was carried out. All patients provided written permission after being fully briefed.

Criteria of exclusion were severe illness, instability of vital signs, active infection, and inability to remain supine for 30 minutes.

All patients were subjected to: history taking, data related to prostate cancer (Prostate biopsy results, surgical intervention, and medical intervention (radiotherapy, chemotherapy, hormonal therapy) and PSA level evaluation.

18f PSMA PET/CT

Different coaxial imagery ranges may be covered during a PET/CT test. The "base of the skull to mid-thigh" was our goal range for torso imaging.

Patient preparation

The day before the scan, the participant ought to obtain a call to confirm their presence, make sure they understand every part of the procedure, and go over any special instructions. From 2 hours before the injection till the end of the scan, participants must fast. Ordinary medications may be taken as directed. There's not a requirement to stop the patient's hormone medication if they are already taking it. Schedule 18-F PSMA in close coordination with the PET-CT service lead. Patients were intravenously administered by Fluorine-18 (PSMA-1007) 300 MB`+/- 10%.

Technical points

Place the individual on the scanning settee (supine, headfirst) alongside his or her head supported by the headrest. Participants should lay a small cushion under both arms and raise their arms over their heads while utilizing the headrest's wings as support. The supra-orbits are used to acquire the upper thigh to skull base acquisitions. Throughout the 20-to-45-minute examination, the participant ought to be capable to lay still in the PET/CT equipment. The participant should raise his arms over his head if at all possible, and if practical, the manufacturer's recommended support equipment (such as foam pallets) should be used. The imaging was done by non-contrast 64 multi-slice CT.

Table 1: Parameters of CT scan

Scan range	kVp	Ref mAs	Slice width	Rotation	Pitch	Safire
Upper thigh to skull base	120	60	3-5mm	0.5 secs	0.95	3

Table 2: Reconstruction parameters of PET

Series	Recon method	Scatter correction	Iterations	Subsets	Output image type
PET WB AC PSF	TrueS+ TOF	Relative	2	21	Corrected
PET WB NAC	Iterative+ TOF	None	3	21	Uncorrected
PET AC	Iterative+ TOF	Relative	2	21	Corrected

Calculations of SUV and image analysis

Both attenuation correction and without it were used to present 18F PET pictures. Quantitative findings about size and PSMA uptake may be obtained for all slices (of the attenuation-corrected datasets). Software that can show combined PET and CT information utilizing an SUV scale was employed to assess the images.

Description of the findings

The 18F PSMA PET /CT study's quality was hindered by artifacts of motion, an aberrant tracer bio-distribution (18F buildup in muscles and/or brown fat), and penetration of the tracer at the sites of injection, for example. Location, size, and SUV intensity of pathological PSMA labeled 18F build-up in relation to normal tissue are described. Describe the relevant CT results and how they relate to abnormal PSMA buildup. When contrasted with background uptake in, for instance, the liver parenchyma (mean SUV 2.0 - 3.0, maximum SUV 3.0 - 4.0), 18F uptake may be described as mild, moderate, or severe. All pertinent anatomical observations were described in the CT section of the report of the 18F PET/CT.

Sample Size Calculation

Utilizing the Windows version 11.0.8 of the PASS program (pass. ncss, llc. Kaysville, Utah, USA). Utilizing a two-sided, two-sample unequal-variance t-test, a group with a sample size of 30 has 90.463% power for rejecting the null hypothesis of equal means whenever the population's mean difference is μl - μ2= 7604.0 – 5411.0 =2193.0 with a

standard deviation of 0103.0 and a significant level (alpha) of 0.020.

Statistical analysis

SPSS v26 (IBM Inc., Chicago, IL, USA), a statistical analysis program, was used. Histograms and the Shapiro-Wilks test were utilized to assess the normality of the data distribution. Using an unpaired Student's t-test, quantitative parametric parameters were provided as mean and standard deviation (SD) to contrast between the two groups. Interquartile range (IQR) and median were used to show and evaluate quantitative non-parametric variables. The Chi-square test or Fisher's exact test was used to examine qualitative parameters that were reported as frequency and percentage (%). Statistical significance was defined as a two-tailed P value < 0.05.

Results

The mean age of the studied cases was 71.7±7.05 years with median PSA 56.2 ng/ml. Prostate cancer-related lesions (local and metastatic) were found in 27 patients. Metastasis was found in 20 patients. Median SUV max of PSMA expression at prostate was 7.75 while median SUV max of PSMA expression at metastatic lesions 6.1. Table 3

Table 3: Characteristics of the included patients

	Total cohort (n=30 patients)
Age (years)	71.7±7.05
PSA (ng/mL)	56.2
Patients with prostatic activity	27 (90%)
Patients with metastatic lesions	20 (66.7%)
SUV max of prostate activity	7.75
SUV max of metastatic lesions	6.1

Data presented as mean ± SD, median or frequency (%). PSA: Prostate-specific antigen. SUV max: maximum standardized uptake value

No statistically substantial variation was existed among the 2 groups as regard PSA blood level or SUV max of PSMA expression at metastatic lesions. SUV max of PSMA expression at prostate was higher with statistically significant difference among recently diagnosed patients. No statistically substantial variation was existed among the 2 groups as regard SUV max of PSMA expression at prostatic lesions. PSA was higher with statistically significant difference among metastatic group. Table 4

Table 4: Comparison between patients with recently diagnosed cancer prostate and cancer prostate follow up patients and between metastatic and non-metastatic prostate cancer groups regarding PSA level and SUV max of PSMA expression at prostate and metastatic lesions

	Recently diagnosed cancer prostate patients (n=7)	Follow up patients (n=23)	P value
PSA (ng/mL)	65.1 (43-120)	27.7 (4.6-81.1)	0.069
SUV max prostatic lesions	18 (5.10-40)	6.3 (4.2-14)	0.021*
SUV max metastatic lesions	15.5 (8.5-31.8)	12.9 (6.9-18.8)	0.494
	Metastatic Prostate cancer (n=20)	Non- metastatic- prostate cancer (n=7)	
PSA (ng/mL)	55.5 (4.57-211)	12.4 (0.02-81.07)	0.034
SUV max prostatic lesions	9.15 (3-40)	5.6 (4.2-14)	0.056

Data are presented as median (IQR). PSA: Prostate-specific antigen. SUV max: maximum standardized uptake value. * Level of significance <0.05.

A statistically substantial association was existed among PSA blood level and SUV max of PSMA expression at prostate and metastasis at patients with recently diagnosed prostate cancer. But no statistically substantial was existed in patients with cancer prostate coming for follow up and expression at metastasis. A statistically substantial association was existed among PSA and SUV max of PSMA expression at prostate. Table 5

Table 5: Correlation between PSA blood levels, SUV max of PSMA expression at prostate and at metastasis of the patients with recently diagnosed cancer prostate, patients with cancer prostate coming for follow up and at metastatic lesions

		PSA blood level		SUV max of PSMA expression at prostate	
		r	P value	r	P value
Patients with recently diagnosed cancer prostate					
PSA blood level		-	-	0.901	0.006*
SUV Max of PSMA expression at metastatic lesions		0.725	0.103	0.831	0.040*
SUV Max of PSMA expression at prostate		0.901	0.006*	-	-
Follow up cancer prostate patients					
PSA blood, level		-	-	- 0.071	0.773
SUV Max of PSMA expression at metastatic lesions		0.321	0.264	0.281	0.264
SUV Max of PSMA expression at prostate		- 0.071	0.773	-	-
Metastatic lesions (all the thirty patients included)					
		r (correlation co-efficient)		P value*	
PSA	Age	0.032		0.867	
	SUV max prostatic activity	0.352		*0.04*	
	SUV max metastasis	0.2		0.29	

PSA: prostate-specific antigen. SUV max: maximum standardized uptake value. PSMA: prostate-specific membrane antigen. * Spearman correlation; r: correlation coefficient; level of significance.

At cut-off value equal to 3.4, SUV max of PSMA expression at prostate had 100% sensitivity and specificity win diagnosis of active prostatic lesions. Figure 1

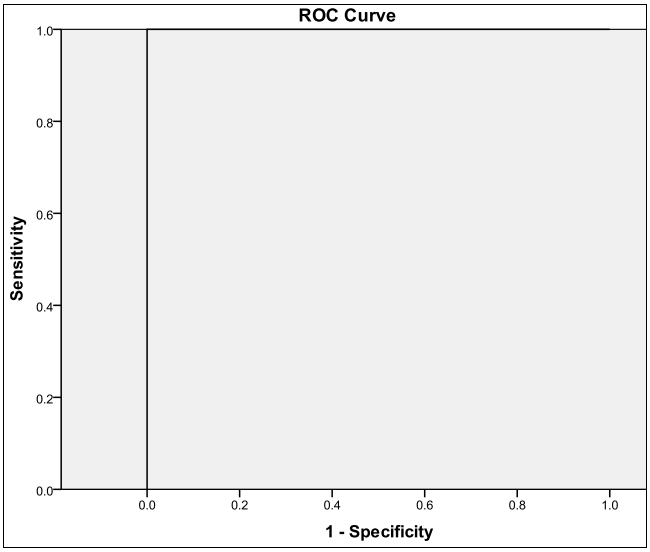

Fig 1: ROC curve illustrating accuracy of SUV max of PSMA expression at prostate in diagnosis of active prostatic lesions

At cut-off value equal to 5.3, PSA had 95% sensitivity and 71.4% specificity in prediction of metastasis. Figure 2

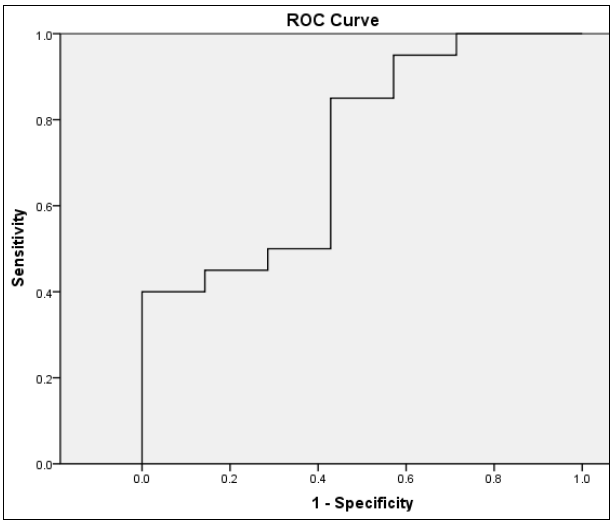

Fig 2: ROC curve illustrating the accuracy of PSA to predict metastasis

Case (1)

PSMA PET/CT findings

A. Average sized prostate showing bilateral basal, mid, and apical peripheral zonal lesions (up to about 1.7 cm); that are seen eliciting increased tracer uptake with SUV max up to 6.1; as well as; abutting the related adjacent portions of both seminal vesicles. Few tiny concretions are also noted.

B. Enlarged bilateral internal iliac LN. s (up to 1.4 cm) are seen eliciting mildly increased tracer uptake with SUV max up to 3.2.(not suspected in MRI).

C. Sclerotic osseous lesions; involving sacral bodies and both sacral alar; are seen eliciting mildly increased tracer uptake with SUV max of 3.6.

D. Lt. humeral proximal shaft medullary-based focal mildly increased tracer uptake with SUV max of 2.4 is seen; yet no corresponding sclerotic or lytic osseous lesions detected.

No other significant foci of PSMA expression could be noticed at the rest of the surveyed body on scintigraphic bases. Physiological tracer bio-distribution is noticed at the liver, spleen, colon, lacrimal and salivary glands as well as the urinary system. Figure 3

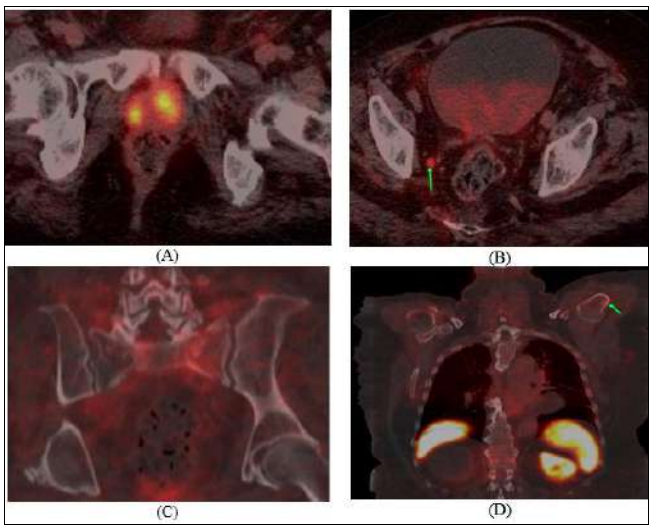

Fig 3: Case (1)

Case (2)

PSMA PET/CT findings

A. Metabolically active enlarged prostate is seen measuring 6.0x6.5 cm with estimated SUV max of PSMA expression up to 29.3.

B. Few metabolically active peri-anal and right internal iliac nodal lesion are seen, the largest measuring 13.2 mm with estimated SUV max of PSMA expression up to 15.1.(MRI findings for these lymph nodes were not conclusive).

No other significant foci of PSMA expression could be noticed at the rest of the surveyed body on scintigraphic bases. Physiological tracer bio-distribution is noticed at the liver, spleen, colon, lacrimal and salivary glands as well as the urinary system. Figure 4

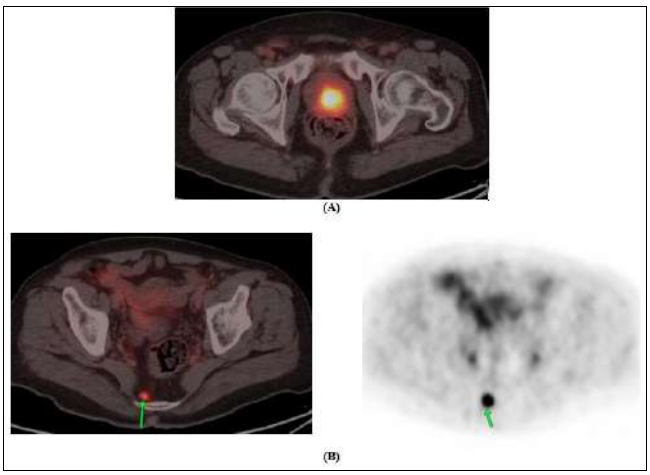

Fig 4: Case (2)

Discussion

The cytoplasm and the epithelial apical side that surrounding the prostatic ducts are where PSMA expression and localisation are found in the normal human prostate, but not the neuroendocrine cells, basal epithelium, or stromal cells. [9].

Our results revealed that three prostate cancer cases had normal PSA (10% false negative cases). It was reported that up to 25% of individuals with prostate cancer may have PSA that is within the normal range (false negative). [10]. In

a study by Ferraro *et al*. [11] PSA was positive in 75% of total prostate cancer patients. SUV max of PSMA expression at prostatic lesions median in our study was 7.7 and higher than that for metastatic prostatic lesion which was 6.1. This comes in line with a study by Domachevsky *et al*. [12] who reported SUV max of PSMA expression in prostatic lesions median was 7.65 and in metastatic lesions was 4.76. Higher SUV max values of PSMA expression in prostatic lesions equal to 13.1±10.1 were reported in another study [13]. Previous study by Werner *et al*. [14] also found SUV max of PSMA expression in prostatic lesions equal to 12.3±8.4.

Also, Tian *et al*. [15] reported higher SUV max of PSMA expression in prostatic lesions than our results as he proposed that early SUV max equal to 10.9±12.5 and late SUV max equal to 14.6±16.7 in malignant prostatic lesions. In another study [16], mean SUV max of PSMA expression in prostatic lesions was much lower than what we reported (2.43±0.44). Chiu *et al*. [17] indicated that prostate SUV max >4.4 has highly specificity and sensitivity for prostate cancer and lower values were reported with metastatic lesions. Uprimary *et al*. [18] found that SUV max for metastatic tumors was higher than non-metastatic tumors and this was found against the results of our study.

In our study we found small iliac lymph nodes, and ischio-anal lymph node, which showed equivocal findings on MRI, showing high PSMA uptake confirming their metastatic nature upgrading the TNM staging of the disease and consequently changes the treatment plan. This result is consistent with several studies that have validated PSMA PET/CT's diagnosis performance in primary nodal staging using histopathology. According to Hofman *et al*. [19], their imaging method greatly outperformed traditional imaging in terms of sensitivity (0.85 vs 0.38), as well as specificity (0.98 vs 0.91).

We found small lymph nodes <8mm (the anatomical cut off short diameter utilized in CT and MRI) with increased PSMA expression. This comes hand in hand with many studies [20, 21] performed to assess the role of PSMA PET /CT in assessment metastases of lymph nodes.

In another participant recently diagnosed with cancer prostate with negative bone scan, we found mild increased tracer uptake at single rib with no underlying morphological CT changes, suspicious for metastatic process. This agrees with many studies that found PSMA PET /CT has higher specificity and sensitivity than bone scan. Pyka *et al*. [22] revealed a specificity and sensitivity of PSMA PET/CT of 100% at primary staging.

We discovered that SUV max of PSMA expression at prostate was greater with statistically significant difference among recently diagnosed patients. A statistically substantial association was existed among PSA blood level and SUV max of PSMA expression at prostate. This come in hand with many studies that have shown that in the primary tumor, a correlation between radiotracer accumulating intensity and PSA, Gleason, and d'Amico risk scores (i.e., the larger the PSA, Gleason, and d'Amico hazard scores are, the higher the PSMA uptake on PET). [23]. Like the current study, Barakate *et al*., proposed that a positive association was existed among PSA value and SUV max of PSMA expression at prostate. The Pearson correlation factor r for the connection between PSA readings and SUV max discovered during early imaging was 0.413 ($p< 0.001$). According to conventional imaging, the connection between PSA levels and SUV max of PSMA expression was comparable, with $r = 0.408$ ($p < 0.001$). [24]. Other studies also confirmed the presence of positive association between PSA and SUV max of PSMA expression. On a study by Sachpekidis *et al*. [25] Their examination of the link between PSA levels and SUV average and SUV maximum found a modest but substantial association ($r = 0.60$ and $r = 0.57$) (205). A positive association was determined among PSA level and SUV max value ($p < 0.001$ and $r = 0.49$) in another study. Against our study, Turkbey *et al*. [26] did not find statistically substantial association among SUV max of PSMA expression and PSA levels. Also, Schmuck *et al*. [27] could not find substantial association among PSA and prostate SUV max of PSMA expression.

We found that PSMA PET/CT had 100% specificity and sensitivity win diagnosis of active prostatic and metastatic lesions at SUV max cut off 3.4. Our usage PSMA PET/CT in recurrence staging changed the therapeutic planning due to detection of lesions not apparent in conventional imaging. This agrees with results obtained by Roach PJ *et al*. [28] who reported that in 62% of participants included in their study, the management strategies have changed. Also, Bianchi L *et al* [29] reported that in 42% of participants included in their study, the management strategies have changed after performing PSMA PET/CT scanning.

no statistically substantial association was existed among PSA blood level and SUV max of PSMA expression at prostate and metastasis in patients with cancer prostate coming for follow up. This comes agrees with Kwee *et al*. [30] who proposed that no statistically substantial association was existed among the highest body tumor SUV max and PSA.

In contrast to our study, Violet *et al*. [31] reported statistically significant association among metastasis SUV max and PSA and correlated the SUV max of PSMA expression of metastatic tumor with PSA decline after receiving therapy.

no statistically substantial association was existed among PSA and patient age. Like the current study, there was no association between patient age and PSA in a study by Erdogan *et al*. [32] despite the existence of strong association between prostate volume and age.

In our study we failed to find an association between age and PSA, and this may be explained by that we included old age patients with small age range and most of them were malignant cases which causes increase of PSA and affects the association. We performed Flourine-based PSMA PET/CT scan for pathologically proven cancer prostate patients thus it exhibited 100% sensitivity and specificity at cut-off value of SUV max equal to 3.4. Gaur *et al*. [33] reported statistically significant difference between biopsy proven malignancy and non- malignancy groups. Similarly, Koerber *et al*. [34] reported statistically significant difference between malignant (10.77±8.45) and non- malignant (1.88±0.44) prostate lesions regarding SUV max.

A statistically substantial variation was existed among individuals with metastasis and non-metastatic patients regarding PSA. In agreement with the current study, Dotan *et al*. [35] stated that PSA is a good prognostic factor for bony metastasis of prostate cancer. As proposed by Antonarakis *et al*. [36] Alterations in PSA kinetics predict disease progression in prostatic cancer patients.

At cut-off value 5.3, PSA had 95% sensitivity and 71.4% specificity in predicting metastasis after prostate cancer.

Lojanapiwat *et al*. [37] reported increased specificity and sensitivity of PSA in diagnosis of metastasis with increased the PSA cut-off value. In another study, PSA had a specificity of 94%, but only 20% sensitivity in detecting metastasis [38]. The specificity and sensitivity of PSA for the identification of metastasis of lymph node were 75% and 44.4%, correspondingly in study by Yi c *et al*. [39].
Limitations: lack of randomization, small number of patients, lack of other imaging data for comparison, and absence of patients with nonmalignant prostatic diseases.

Conclusions

PSMA PET/CT can detect cancer prostate metastasis in non-enlarged lymph nodes which can be missed on conventional imaging (CT and MRI), bony deposits even with no apparent CT morphological changes and performed for recently diagnosed cancer prostate patients changed the staging made by other conventional modalities. PSMA PET/CT is the modality of choice in recurrent cancer prostate, it can assess the site of recurrence and determine the disease burden, so it is essential for adequate treatment plan.

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Conflict of Interest: Nil

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