VOLUME 9 | ISSUE 2

Oncologic imaging ORIGINAL ARTICLE

The Diagnostic Performance of PSMA PET/CT In Patients With Biochemically Recurrent Prostate Cancer After Radical Treatment

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SUBMISSION: 11/01/24 - ACCEPTANCE: 16/04/24

ABSTRACT

Purpose of the study: To assess the role of PSMA ligands Positron Emission Tomography and Computed Tomography (PET/CT) Scans in the biochemical recurrence of prostate cancer post-radical treatment.

Materials and methods: Our prospective study included 131 males with proven biochemical recurrent prostatic adenocarcinoma. The patients' images and data were analyzed for the rate of detection of recurrence based on PROMISE criteria. Also, the correlation between the level of serum PSA and the detection rate of PSMA PET/CT was analyzed. Moreover, the estimation of a cut-off value for the level of serum PSA to distinguish between positive and negative PSMA PET/CT was performed.

Results: The overall detection rate was 102/131 patients (77.8 %). There was a positive relation between serum PSA before the scan and the positivity of PSMA PET/CT. The most common sites of recurrence were operative bed/ radiated prostate, pelvic lymph nodes, osseous deposits, retro-peritoneal lymph nodes, and visceral deposits. The cut-off value for serum PSA level to differentiate between a positive PSMA PET/CT scan from a negative one is>0.73 ng/ml.

Conclusion: PSMA PET/CT has a pivotal role in cases with biochemical recurrence after radical treatment of prostate cancer.

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KEY WORDS
PSMA PET/CT, biochemically recurrent prostate cancer.

Introduction

Prostate cancer (PCa) ranks number one in terms of prevalence among males and the clinical management decisions depend on the patient's risk stratification and TNM staging. In nuclear medicine, prostate-specific membrane antigen (PSMA) is among the most promising imaging and therapeutic targets since it is expressed in prostatic adenocarcinoma 100–1000 times more than the benign prostatic cells and other tissues [1].

Elevation of PSA (prostate-specific antigen) after radical treatment (radiotherapy or radical prostatectomy (RP)) is known as biochemical recurrence (BCR) or biochemical failure and it accounts for approximately 20–40% of those patients who have undergone RP. In the case of RP, BCR is considered when there are two consecutive PSA levels above 0.2 ng/ml; whereas the Phoenix Consensus in 2006 defined biochemical recurrence following radiotherapy as an increased 2 ng/ml higher than the PSA nadir value [2].

The role of PSMA-PET includes local detection of primary tumors, initial staging of intermediate to high-risk prostate cancer, biochemical recurrence setting, assessment of response to therapy, and recently PSMA-ligands directed surgery and radiotherapy as well as guided theranostic pair therapy [3]. The levels of PSMA expression are elevated by increasing the tumor grade and stage, also with biochemical recurrence (BCR) and when castrate-resistant phenotype evolves [4].

Our objectives were to detect the positivity of PSMA PET/CT in recurrence using PROMISE criteria, sites of recurrence at PSMA PET/CT, the relation between pre-scan level of serum PSA and positivity of the PSMA PET/CT scan, and estimate a cut-off value for the level of serum PSA to distinguish between positive and negative PSMA PET/CT.

Materials and methods

This prospective trial recruited a total of 131 male cases who were referred to our center from March 2020 till March 2022 with prostatic adenocarcinoma who received radical treatment and presented with biochemical recurrence. The study took place in the Nuclear Medicine and Radiation Oncology Department, Kasr El-Ainy Hospital, Cairo University after the approval of our departmental and the university's ethical committee.

We excluded patients with claustrophobia, a history of second primary malignancy (though PSMA PET/CT is the most specific tracer available for imaging of prostate cancer till now, localization of PSMA PET/CT imaging in non-prostatic malignancies is also being reported in the literature. PSMA has been found in the neovasculature of a variety of other malignancies, these include clear cell renal carcinoma, breast cancer, gliomas, primary hepatocellular carcinoma, pancreatic cancer, differentiated thyroid cancer, and more indications are being added. Thus, we excluded other malignancies in our study to make sure that deposits and lesions encountered in our study are attributed to the prostate and not any other tumor), persistently elevated PSA after definitive therapy, PSA bounce phenomenon, previously received chemotherapy or androgen deprivation treatment (ADT) for a known metastatic PCa, patients referred for initial staging or PSMA radio-ligand therapy.

Patients' medical records were thoroughly reviewed, and medical history was taken to collect data on age, weight, height, type of radical treatment received, PSA nadir level after the radical treatment, duration to biochemical recurrence from radical treatment, serum PSA before the scan, whether or not patient received "androgen deprivation therapy" 6 months before the scan, and serum creatinine level performed maximum 2 weeks before the study (in patients who received IV contrast).

Study protocol:

The PSMA PET/CT scans were conducted utilizing the time of flight with 64 slices CT on a Philips Gemini TF camera (TOF). Patients were injected with a PSMA-ligand radio-active tracer according to their weight, in which 55 patients were injected with ^{68}Ga-PSMA (medi-

an of injected doses: 165 MBq, range: 88.8–314.5 MBq) and ^{18}F-PSMA-1007 was used in 76 patients (median of injected doses: 292.5 MBq, range: 111–518 MBq). Before the commencement of the trial, the patients were directed to void promptly, PET acquisition started after uptake time ranging from 45–90 minutes after PSMA ligands injection using 2–3 min frames over 12–14 frames; also, a low CT dose was acquired for attenuation correction and anatomical localization. A diagnostic CT with intra-venous contrast (dose ~ 70ml) was also conducted in patients eligible for contrast injection, for better delineation of metastatic lesions. The performed PET/CT scans started from below the knees to the tip of the skull.

Image Analysis:

The PET/CT scan is evaluated by two radiologists and two experienced nuclear medicine physicians, who determine whether it is positive or negative. The analysis of images was conducted utilizing the OsiriX software. Interpretation of positive neoplastic lesions are based on the PROMISE criteria where miPSMA Score was calculated. The definition of expression is contingent upon the amount of uptake in the parotid gland, liver/spleen, and blood pool. The liver SUV is quantified by locating a circular region of interest with a 3cm diameter in the normal inferior right lobe of the liver in the axial plane. For the blood pool, center a circular region of interest with a 2cm diameter in the aortic arch in the axial plane; for the parotid gland, center a circular region of interest with a 1.5cm diameter in the right parotid gland in the axial plane; and for a tumor lesion, center a circular region of interest measuring 1cm in diameter over the voxel with maximum uptake in the axial plane. The results for no, low, moderate, or high expression of PSMA are denoted as 0, 1, 2, or 3.

Response to treatment:

Analyses were conducted per patient. The results obtained from the pre-treatment and post-treatment PET/CT scans were compared, and the imaging response was classified into categories: "stable disease ", "progressive disease," or "improved disease (full or partial response to therapy)" based on the following criteria: –

– A "progressive disease" was characterized by the appearance of a novel lesion, an enlargement of existing lesions, or an escalation in the magnitude and scope of the pathological uptake.

– "improvement" was characterized by lesion elimination (complete imaging response), reduction in the number of lesions, or alteration in the intensity and breadth of pathologic uptake (partial response).

– No alteration in PET/CT results constituted "stable disease".

The biochemical response, as assessed by the fluctuations in the level of serum PSA (ng/ml) between pre-treatment and post-treatment levels, is as follows:

– An increase of ≥25% in PSA was deemed as a "progressive disease".

– A reduction of 50% or more in PSA was deemed a "partial response."

– The term "stable illness" was applied to any PSA variation between the aforementioned limits.

Statistical analysis:

Statistical Package for Social Sciences (SPSS) version 25 was used for data management and analysis. Qualitative variables were displayed as frequencies and percentages. Quantitative variables were displayed using medians and ranges or means and standard deviations, as appropriate. The following tests were used: Chi square, Student's t-test and Mann-Whitney test. Receiver operating characteristic curve (ROC curve) was done to determine the best cut-off point, specificity, sensitivity, and area under the curve (AUC). P-values<0.05 was deemed significant.

Results

This prospective study was conducted on 131 cases with biochemical recurrent PCa post radical treatment. Mean age was 67.4-year-old and ranged from 50–88 years old. Median level of serum PSA was 1.39 ng/ml, mean of serum PSA level is 6.4 ng/ml and range of (0.002–152.1 ng/ml) (Table 1).

There were total of 69 cases who were subjected to RP as method for radical treatment, 31 patients received radiotherapy and 31 patients received both modalities. A total of 38 (29%) patients received ADT 6 months prior to PSMA PET/CT scan (Table 1). Overall, 76 patients underwent ^{18}F-PSMA -1007 PET/CT with a median dose of 299.5 MBq and 55 patients underwent ^{68} Ga-PSMA PET/CT with a median dose of 165 MBq. A total of 111 pa-

Table 1: Distribution of studied patients regarding age, weight and modality of treatment

Demographic data		Cases
Age (Years)	Mean ±SD	67.4±8
	Range	50-88
Weight (Kg)	Mean ±SD	89±14
	Range	78 -93
Modality of treatment	radical prostatectomy	69 (52.4%)
	radiotherapy	31 (23.7%)
	Both	31 (23.7%)
ADT 6 months prior to PSMA PET/CT scan	No (%)	38 (29%)

Table 2: Scoring and diagnosis of recurrence at operative bed/ radiated prostate:

Scoring and diagnosis of recurrence at operative bed/ radiated prostate	Cases No (%)
Scoring of operative bed/ radiated prostate (n=76)	
0	1 (1.3)
1	49 (64.5)
2	13 (17.1)
3	13 (17.1)
Diagnosis of recurrence of operative bed/radiated prostate (n=76)	
Negative	17 (22.4)
Equivocal	9 (11.8)
Positive	50 (65.8)

tients received IV contrast whereas 20 patients did not.

The overall detection rate of at least one positive lesion at PSMA PET/CT suggestive of recurrence was 102/131 patients representing 77.86%.

Among the PSMA PET/CT positive patients, the overall most common sites of recurrence were operative bed/ radiated prostate (49%), pelvic lymph nodes (48%), bone metastases (34.3%), retro-peritoneal lymph nodes (10.8%), visceral deposits (7.8%) and supradiaphragmatic lymph node (0.98%).

The median PSA value for a positive PSMA PET/CT scan is 2.1 ng/ml, (range of 0.02–152 ng/ml) whereas the median PSA value for a negative PSMA PET/CT scan is 0.4 ng/ml (range of 0.002–15 ng/ml). A significant variation (p value<0.001) was reported between serum PSA values for PSMA positive and PSMA negative scans.

In a total of 62 patients, there were operative bed lesions. The most common site of recurrence at prostatectomy operative bed was left lateral, constituting 40.4% of all operative bed sites. The median for operative bed SUVmax is 6.4, mean of 13.3 and a range of 1.8–65, whereas the median for the size of operative bed lesion is 1.5 cm, mean of 1.9 cm and a range of 0.4-6 cm. In a total of 14 patients, there was PSMA avid lesion/s at the site of the radiated prostate. The median value of SUVmax of lesion/s detected in radiated prostate is 4.6, mean of 8.2 and a range of 2.5–57.5 whereas the median value for size of lesion/s in radiated prostate is 2.05 cm, mean of 1.95 cm and range of 1.1–2.7 cm (Table 2).

A total of 52 patients presented with pelvic lymph nodes, where 49 of them were positive for recurrence based on PROMISE criteria. Many of the lymph nodes were bilateral (26 patients). The most common lymph node encountered is the “left external iliac lymph node”. The median value for SUVmax is 4.85, mean val-

Table 3: Scoring and diagnosis of recurrence at regional, retro-peritoneal and other LNs

Scoring of lymph nodes	Cases No (%)
Scoring of regional LNs (n=52)	
0	3 (5.8)
1	34 (65.4)
2	2 (3.8)
3	13 (25)
Diagnosis of recurrence in regional LNs (n=52)	
Positive	49 (94.2)
Negative	3 (5.8)
Retro-peritoneal LNs (n=131)	
Yes	11 (8.4)
No	120 (91.6)
Scoring of retro-peritoneal LNs (n=11)	
1	5 (45.5)
2	3 (27.3)
3	3 (27.3)
Other LNs (n=131)	
Yes	22 (16.8)
No	109 (83.2)
Scoring of other LNs (n=22)	
1	17 (77.3)
2	5 (22.7)
Diagnosis of recurrence of other LNs (n=22)	
Negative	19 (86.4)
Equivocal	2 (9.1)
Positive	1 (4.5)

ue of 11.22 and a range of 1.4–72. The median value for the size of pelvic nodes is 1 cm, mean value of 1.2 cm and a range of 0.4–3.3 cm. In addition, retro-peritoneal lymph nodes were found in a total of 11 patients (8.4%). The most common group was "left para-aortic lymph nodes". Median SUVmax was 10.3 and median size of 1.2 cm. Also, other lymph nodes were found in 22 patients out of 131; however, only one (left supraclavicular lymph node) was considered positive for recurrence according to PROMISE criteria (Table 3).

Table 4: Scoring and diagnosis of osseous lesions.

Scoring of osseous lesions	Cases No (%)
Bone lesions (n=131)	
Yes	46 (35.1)
No	85 (64.9)
CT changes in bone (n=46)	
Yes	38 (82.6)
No	8 (17.4)
Scoring of bone lesions (n=46)	
0	3 (6.5)
1	23 (50)
2	10 (21.7)
3	10 (21.7)
Diagnosis of recurrence in bone (n=46)	
Positive	35 (76.1)
Negative	11 (23.9)

A total of 46 patients (35.1%) presented with osseous lesions. According to PROMISE criteria, 35 patients were diagnosed positive for deposits. The majority presented with multiple osseous lesions (21 patients). The median value for SUVmax of osseous lesion is 8.9, mean value of 15.1 and a range of 2.2–141.4 (Table 4).

A total of 12 patients (9.2 %) presented with pulmonary lesions, where 7 patients were positive for recurrence based on PROMISE criteria. The median value for SUVmax is 5 and range of 1.4–1.3 whereas the median value of size is 1 cm and range of 0.5–3 cm (Table 5).

The validation of results of PSMA PET/CT was done through following-up of 99 (75.6%) patients through: - Clinical follow-up with serum PSA was available in 87 patients. - PSMA PET/CT as a follow-up performed in 39 patients. - Other imaging modalities such as MRI, and bone scans were performed on 7 patients. - Only 1 patient had a biopsy from an operative bed lesion and that showed specificity, sensitivity, PPV, and NPV of 84.6%, 90.1%, 97.3%, and 58%, respectively. Other studies in the bibliography used histopathology as a method of

Table 5: Data about lung lesions.

Lung lesions data	n=131 (%)*
Lung lesions (n=131)	
Yes	12 (9.2)
No	119 (90.8)
Scoring of lung lesions (n=12)	
0	4 (33.3)
1	6 (50)
2	2 (16.7)
Diagnosis of recurrence in lung lesions (n=12)	
Positive	7 (58.3)
Negative	5 (41.7)

Table 6: ROC Curve for PSA before scan:

Variable	Cut off point	Sn (%)	Sp (%)	PPV (%)	NPV (%)	AUC	95% CI for AUC	P value
PSA	>0.73	70.4	85	97	31.5	0.79	0.70-0.87	<0.001

Sn:Sensetivity. Sp:Specificity, CI: Confidence interval, AUC: Area under the curve, PPV: Positive predictive value, NPV: Negative predictive value, p value <0.05 is deemed significant, PSA: Prostatic specific antigen

verification of lesions and follow-up which is why their negative predictive value (NPV) is higher than ours.

Also, the cutoff value for serum PSA to predict a positive PSMA PET/CT scan was >0.73 ng/ml with specificity, sensitivity, and AUC of 85%, 70.4%, and 0.79, respectively (Table 6) (Fig. 1).

There were 33 patients (25.2%) who were followed up using serum PSA level as well as PSMA PET/CT. There were 26 patients out of 33 (78.7%) who had compatible imaging response and biochemical response as follows: 15 patients (45.5%) showed improvement, 10 patients (30.3%) had progressive disease and one patient (3%) had stable disease. This results in significant moderate agreement of kappa value of (0.63) and this was significant (P<0.001).

In our study, there was no aim to investigate the added value of diagnostic contrast-enhanced computed tomography to PSMA PET/CT studies, however, contrast surely helped in better delineation of lesions. Other studies stated that contrast-enhanced CT increases diagnostic certainty and interobserver agreement in PSMA PET/CT studies.

Discussion

Recurrent disease may occur in as many as 50% of cases with PCa after ten years of radical treatment **[5].** For the patient's treatment choices, precise disease localization is critical at biochemical recurrence; PSMA PET has been identified as having a high recurrence detection rate [6].

Nowadays, The American Urology Association Radiographic Assessments for Detection of Advanced Recurrence (RADAR III) consensus group [7] as well as the European Association of Urology [2] have incorporated ^{68}Ga-PSMA-11 PET into principles for biochemical recurrence management guidelines. PSMA PET is also included in the American Society of Clinical Oncology's most current consensus recommendations for imaging advanced PCa. [8].

In this trial, we assessed the findings of PSMA ligands PET/CT in the included 131 cases with biochemical recurrent PCa.

In our study, the overall detection rate of at least one positive lesion at PSMA PET/CT suggestive of recurrence was 102/131 patients representing 77.86%.

We had a similar detection rate to Akdemir et al. [9] retrospective study that used ^{68}Ga PSMA PET/CT in 121 cases with BCR post-radical treatment. The median pre-scan level of serum PSA was 3.87 ng/ml and the detection rate was 76%. Also, Afshar-Oromieh et al. [10] retrospective study that using ^{68}Ga PSMA PET/CT in 1007 cases with BCR post-RP showed that the median pre-scan serum PSA level was 2.2 ng/ml and detection rate of 79.5%. Hoffmann et al. [11]revealed that the median pre-scan level of serum PSA was 2.98 ng/ml and the detection rate was 77.4%. In addition, Zhou et al. [12] showed that the median pre-scan serum PSA level was 1.27 ng/ml and a detection rate of 79%.

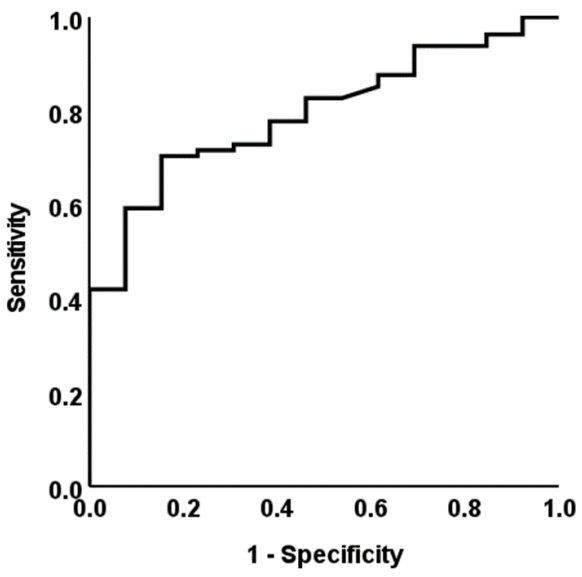

Figure 1: *ROC curve for PSA*

However, the rate of detection of recurrence in our trial was higher than that of Ceci et al [13]retrospective study that used ^{68}Ga PSMA PET/CT in 119 cases with BCR after RP and the level of serum PSA<0.5 ng/ml showed that the median pre-scan serum PSA level was 0.34 ng/ml and the rate of detection was 34.4%. Also, Lengana et al. [14] revealed that the median pre-scan level of serum PSA was 1.6 ng/ml and the rate of detection was 52.2%.

Moreover, our detection rate was lower than that of Rahbar et al. [15]retrospective study using ^{18}F PSMA -1007 PET/CT in 100 cases with BCR after radical treatment. The median pre-scan level of serum PSA was 1.34 ng/ml and the rate of detection was 95%. Also, Ilhan et al. [16]concluded that the median pre-scan level of serum PSA was 4.19 ng/ml and the rate of detection was 94%.

We should take into consideration the use of different PSMA ligands in the other studies, differences in imaging protocols, differences regarding the definition of BCR in different studies, differences in number of patients enrolled in every study, the different levels/ range of PSA at the time of the scan also the different radical treatments methods included in each study.

In the current study, the overall most common sites of recurrence among the PSMA PET/CT positive patients were operative bed/ prostate (49%), pelvic lymph nodes (48%), bone metastases (34.3%), retro-peritoneal lymph nodes (10.8%), visceral deposits (7.8%) and supradiaphragmatic lymph node (0.98%).

Our study was congruent with Watabe et al. [17] and Giesel et al. [18]who revealed most common sites of recurrence be local recurrence (43.7), pelvic lymph nodal deposits (40.6%), osseous deposits (40.2%), retro-peritoneal lymph nodal deposits (19.5%), supra-diaphragmatic lymph nodal deposit (19.5) and visceral deposits (3.6 %).

However, our study was incongruent with Eisenhauera et al [19]where the sites of recurrence were as follows: lymph nodal (43%), bone deposits (33%), local recurrence (23%), and visceral/ soft tissue deposits (11%). Lengana et al. [14] stated that the most common sites of recurrence were lymph nodal (45.8%), local recurrence (37.5%) and bone deposits (8.3%). The difference in sites of recurrence could be due to the use of different PSMA ligands in the other studies, difference in number of cases enrolled in every study, the different levels of PSA at the time of the scan also the different radical treatments methods included in each study, also the subdivision of sites of recurrence where some studies divided lymph nodes as pelvic, retro-peritoneal and supradiaphragmatic whereas other papers did not.

In our study validation of results of PSMA PET/CT was done through following-up of 99 (75.6%) patients where clinical follow-up using serum PSA was available in 87 patients, PSMA PET/CT as a follow-up performed in 39 patients, other imaging modalities including MRI, bone scans were performed in 7 patients and only one patient has a biopsy from an operative bed lesion. This resulted in specificity, sensitivity, PPV and NPV of 84.6%, 90.1%, 97.3% and 58% respectively.

Not many studies focused on calculating the specificity, sensitivity, PPV and NPV, but Witkowska-Patena et al [20]included 40 patients with serum PSA level ≤2, where PSMA PET/CT results were verified during 10.3 months (±4.7 months) follow-up. Verification of 40 lesions resulted in sensitivity, specificity, PPV and NPV of 100%, 94.4%, 66.7% and 100%. Also Mingels et al. [21] included total of 177 patients where detection rate was 91%. Confirmation of positivity was done by: histopathology, reduction of serum PSA>50% after target therapy, or confirmatory imaging (such as MRI and/or bone scan). Follow-up of 81 patients resulted in specificity,

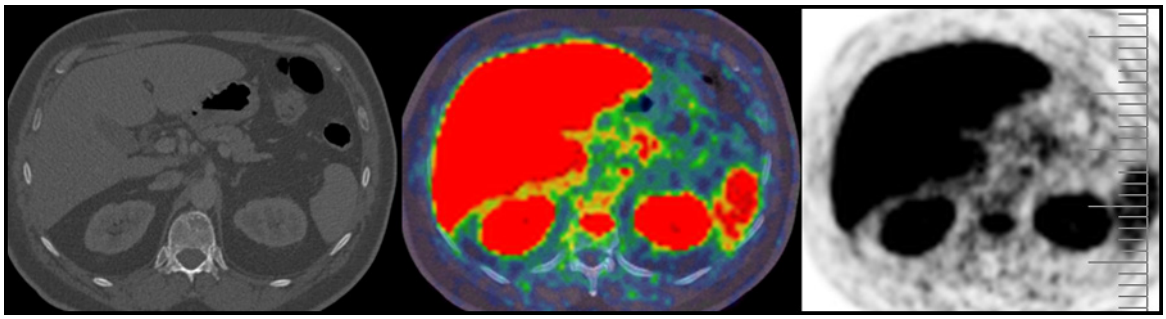

Figure 2a

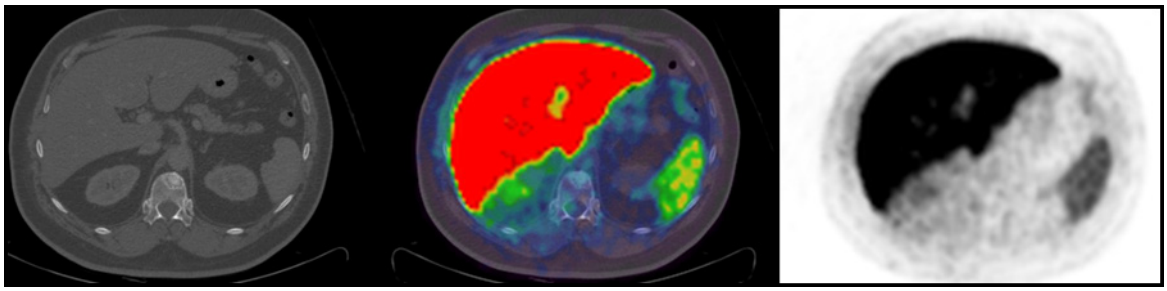

Figure 2b

Figure 2: *PSMA PET/CT of case 4 shows osseous lesion in D12 vertebra in prior image (a) and in current image (b).*

sensitivity, PPV and NPV of 89%, 95%, 86% and 96%.

Considering optimal cut off for serum PSA for predicting positive PSMA scan, we found that the optimal cut-off for serum PSA level for anticipating PSMA positive and PMSA negative scan to be>0.75 ng/ml with specificity, sensitivity, PPV and NPV of 85%, 70.4%, 97% and 31.5% (AUC = 0.79; 95% CI 0.70–0.87).

Hoffmann et al. [11]with a total 581 patients resulted in a The best PSA level for predicting positive and negative scans, as determined by ROC analysis (95% CI 0.746–0.831; AUC=0.788), was 1.24 ng/mL in all patients predominantly treated with RP and RT. Aydin, A., et al [22]included 51 patients where 72.5 % has positive PSMA PET/CT scans. The optimal cut-off for pre-scan PSA to distinguish between positive and negative scans was ≥0.71 ng/ml (AUC 0.759, 95% CI 0.609–0.909). Akdemir et al. [9]included total of 121 patients with detection rate of 76 %.On ROC analysis, the optimal cutoff for serum PSA before the scan to distinguish positive from negative scan was ≥0.5 ng/ml (AUC=0.816, 56.2% specificity and 98.7% sensitivity),and Lengana et al. [14] included total of 46 patients and the detection rate was 52.2%. An optimal serum PSA cut off level was found to be 1.3 ng/ml.

Eventually, we know that our study has some limitations. Firstly, diagnosis was done based on follow-up of many patients due to absence of histopathological confirmation because of ethical and practical issues. Secondly, lack of data regarding PSA kinetics. Finally, we did not report the impact of PSMA PET/CT on treatment strategies; however, this was not among aims of this study.

Conclusion

PSMA PET-CT offers a very precise approach to identify recurrence when used in biochemically recurrent PCa. On the basis of serum PSA levels exceeding 0.73 ng/ml, recurrence can be detected by PSMA PET/CT.

A 58-year-old patient with prostatic adenocarcinoma performed PSMA PET/CT for BCR had been treated with RP and presented with serum PSA of 8 ng/mL PSMA PET/CT showed that positive PSMA uptake by lytic osseous lesion at D12 vertebra. The SUVmax of the lesion was higher than the blood pool activity thus making a score of 1 and resulting in positive lesion for recurrence based on PROMISE criteria. Follow-up of the patient was done where he received hormonal treatment for 6 months. His PSA level be-

came 0.16 ng/mL and performed another PSMA PET/CT ,6 months following the initial one, and the results were regression of the previously noted D12 osseous deposit with SUVmax 3.1 (Fig. 2 a and b). **R**

Ethical approval:

All procedures used in trials involving human subjects were in conformity with the institutional research committee's ethical standards as well as the 1964 Helsinki statement and its subsequent amendments. All patients provided a written consent to expose the data that has been used for research purposes.

Acknowledgements, sponsorships and grants:
This project did not receive any specific funding.
Conflicts of interest to disclose:
None

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Ahmed Tawakol, Sherif El-Refaei, Mohamed Houseni, Eman Ashraf Mousa, Mohamed Abdel latif Shahin. The Diagnostic Performance of PSMA PET/CT In Patients With Biochemically Recurrent Prostate Cancer After Radical Treatment. *Hell J Radiol* 2024; 9(2): 21-30.