ABSTRACT:

Background: Prostate cancer is regarded as the second cause of cancer related mortality in males globally. Radiation therapy and/or radical prostatectomy are effective forms of treatment. Nevertheless, between 15 and 53% of the treated individuals experienced a biochemical recurrence within ten years.

Aim of the Work: To evaluate 18F PSMA PET/CT imaging's diagnostic efficacy in the biochemical prostatic cancer recurrence after radical prostatectomy, hormonal therapy, and radiotherapy.

Patients and Methods: The study is conducted in the radiology department at a tertiary hospital. Twenty six patients with treated cancer prostate cancer were referred to our study who had their PSA levels rising to assess the risk of local recurrence.

Results: Twenty out of twenty-six patients revealed a positive study suggestive of recurrent prostate carcinoma 18F PSMA PET/CT with no definite positive scans detected at PSA level < 0.2 ng/ml. Patients were divided into 3 groups according to their PSA level distribution by the 25th and 5th percentiles. Statistically strong positive correlation between the PSA level and number of local or distant recurrences with p-value (<0.001). However, there was no strong correlation between PSA level and recurrence in osseous regions with p-value (>0.05).

Conclusion: Our results verified the utility of 18F-PSMA-PET/CT in identifying prostatic cancerous biochemical recurrence at various PSA levels. An elevated PSA increases the likelihood of a pathogenic 18F PSMA PET/CT among patients.

Keywords: PSA, cancer prostate, PET CT PSMA, SUV max.

INTRODUCTION:

Prostate cancer is the second most common cancer worldwide and the fifth cause of cancer related mortality among men (1). Even with successful radical prostatic surgery or radical external radiation, biochemical recurrence is common. This frequently happens years before recurrence manifests clinically. Thus, early detection of metastasis or localized recurrence is significant and would aid in modifying treatment plans (2).

Even if the PSA level is a sensitive sign of disease recurrence, it is important to differentiate as soon as possible between loco-regional and systemic recurrence. PSA readings more than 0.2 ng/ml, as confirmed by two consequent measurements and any increase in PSA level over 2.0 ng/ml above nadir following brachytherapy or external beam radiation therapy can be consistently linked to recurrence or residual neoplasia (3&4).

Standard imaging modalities such as Pelvic MRI and contrast enhanced CT
studies have a limited role in the early recurrence of the disease with insufficient sensitivity in detecting lymph node metastases (5).

Bone scintigraphy is of little value in evaluating recurrence and is often done for individuals whose PSA is rising quickly or who have levels higher than 10 to 20 ng/mL (6).

These limitations of computed tomography, MRI and bone scan imaging modalities have encouraged the adoption of positron emission tomography (PET). However, conventional PET/CT studies using choline or FDG-based tracers also have limitations, especially in the early phases of metastatic spread and BCR (7).

Recently, PET/CT using various radioisotope labeled ligands of prostate-specific membrane antigen (PSMA) such as Ga68 and F 18 has shown to be more selective than choline derivatives and recently acquired recognition as a sensitive and targeted imaging technique for assessing the degree of illness in individuals suffering from prostate cancer (8).

68Ga-PSMA-11 is currently a commonly utilized tracer for PET/CT imaging to identify recurrences of prostate cancer. Nonetheless, the longer half-life of 18F-labeled radiotracers over 68Ga (110 min vs 68 min) makes them more suitable for centralized production and distribution. As a result, there is a lot of interest in using PSMA compounds with 18F labels (9&10).

PATIENTS AND METHODS:

Study Tools:

a cross-sectional study conducted at the radiology department at a tertiary Hospital. Our study included twenty-six previously treated prostate cancer patients referred with rising PSA levels. The main source of data was the prospectively conducted PSMA PET/CT scans and the clinical history of the patients referred to the nuclear imaging unit, at a tertiary hospital for evaluation of the possibility of disease recurrence from March 2023 to August 2023.

Inclusion Criteria:

All patients with prostatic cancer received curative treatment in the form of radical prostatectomy and/or external beam radiotherapy, hormonal or chemotherapy presenting for follow-up with rising PSA levels.

Exclusion Criteria:

➢ Any patient referred for initial staging.
➢ Any patient with no primary therapy with curative intent (on palliative therapy).
➢ Patient with incomplete clinical data and labs.
➢ Patients with elevated serum creatinine levels in case of iodinated IV contrast injection.

METHODS:

Full history was taken including name, age, sex, symptoms, comorbidities, and current serum creatinine and PSA level. Before the procedure, patients were advised to fast from all forms of food and liquids (except water) for at least four to six hours. They were asked to be well hydrated before the study and during the uptake time and then to empty their urinary bladder before the study.

Technique:

The PET/CT scan was performed at a Tertiary hospital at the radiology department using a hybrid PET/CT system (Discovery IQ 5-ring, GE healthcare) with about 0.08-0.11 mci/kg of 18F-PSMA-1007 was injected intravenously with saline infusion followed by 60 minutes rest, then the PET scan was taken.

PET scan started from the mid-thigh to the skull base with several bed positions, each performed with a 15 cm axial field of view/bed position with 4 mm in plane spatial
resolution and covered the same field of view of the CT. The emission data will be acquired during a period of between 13 and 17 minutes, averaging 2 to 4 minutes for every bed position.

Two nuclear medicine radiologists with five to ten years of experience worked as a team to analyze and interpret PET, CT and fused PET/CT images.

**Statistical analysis:**

Such a study included 26 patients referred to the nuclear imaging unit of Ain Shams University Hospitals with re-rising PSA levels for the possibility of recurrent cancer prostate. The study was conducted over a period from March 2022 to August 2023. Data were input into the Statistical Package for Social Science (IBM SPSS 25) after being collected, reviewed, and coded. The quantitative data were reported as mean, standard deviations, and ranges when parametric, median, and interquartile range (IQR) when data was found non-parametric. Additionally, percentages and figures were used to represent qualitative characteristics. The following p-value was regarded as significant: Significant (S) is defined as P-value < 0.05 and non-significant (NS) as P-value > 0.05.

**Ethical Considerations:**

The study protocol was approved by the Research Ethics Committee of the Faculty of Medicine, Ain Shams University. Number: [FMASU MS 154/2023]

At every stage of the trial, patient privacy and data confidentiality were protected.

**RESULTS:**

The median age and PSA level of the 26 patients were 69 years (58–83 years) and 1.43 ng/mL (0.01–43.7 ng/ml) respectively. Six (23.1%) of the patients had negative results from 18F-PSMA-1007 PET/CT, while 20 (76.9%) had positive results.

Lesions characteristic of recurrent prostate cancer were as follows; 46.2 % local relapses, 50 % nodal metastasis (26.9% were in regional LN and 23.1% were in the extra-regional/distant lymph nodes), 23.1% osseous metastasis and 11.5 % visceral metastasis were detected (33.3% of which were in the lung, liver, and peritoneum, each) Table (1)

In a total of 20 patients with biochemical recurrence, a Single site recurrence was detected in 13 patients (65 %), recurrence in two sites was detected in 4 patients (20%), remaining 10% and 5% had recurrence in three sites and above, respectively.

In a total of 13 patients with single-site recurrence, exclusive local recurrence was detected in 5 patients (38.64%). Specifically, 2 patients (15.38%) developed bone metastases, while 5 patients (38.64%) developed lymph node metastases. One patient (7.69%) had exclusive visceral metastasis to the peritoneum.

<table>
<thead>
<tr>
<th>Count</th>
<th>Percentage %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local recurrence</td>
<td>12</td>
</tr>
<tr>
<td>Regional Lymph node spread</td>
<td>7</td>
</tr>
<tr>
<td>Extra regional/distant nodal</td>
<td>6</td>
</tr>
<tr>
<td>Osseus lesion</td>
<td>6</td>
</tr>
<tr>
<td>Visceral lesion</td>
<td>3</td>
</tr>
<tr>
<td>Lung</td>
<td>1</td>
</tr>
<tr>
<td>Liver</td>
<td>1</td>
</tr>
<tr>
<td>Peritoneum</td>
<td>1</td>
</tr>
</tbody>
</table>

All patients provided informed written consent outlining the specifics of the procedure prior to their inclusion in this study.
Participants were divided into three groups based on their PSA level distribution by the 25th and 75th percentiles. The first group with a PSA level < 0.2. The second group with PSA level ranging from 0.2 to 4.5. The third group with PSA level ≥ 4.5.

Group 1 included 6 patients and the PSMA scan was negative in all of them, meanwhile, group 2 included 14 Patients and group 3 included 6 patients with 100% positive scans with recurrence in different sites.

There was a statistically significant strong positive correlation between PSA value and regional recurrence, also there was a strong positive correlation with several recurrences in Regional Lymph nodes, extra-regional Lymph nodes, and viscera with p-value (<0.001). However, no significant correlation between the PSA value and bony recurrence with a p-value (>0.05) Table (2).

<table>
<thead>
<tr>
<th>PSA level</th>
<th>Local Recurrence</th>
<th>Regional LN spread</th>
<th>Extra regional nodal spread</th>
<th>Osseus lesion</th>
<th>Visceral lesion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rho correlation</td>
<td>0.815</td>
<td>0.748</td>
<td>0.695</td>
<td>0.111</td>
<td>0.646</td>
</tr>
<tr>
<td>p-Value</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.605</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

There was a statistically significant association between PSA level and local recurrence, regional, extra-regional/distant nodal spread, and bone metastasis detected by Fischer exact test, with p=0.001,0.004,0.028 and 0.028 respectively being more evident within group 3 which includes highest PSA values.

There was no statistically significant association between PSA level and visceral metastasis detected by the Fischer exact test with a p-value (>0.05).

Maximum standardized uptake values (SUV max) were assessed in different sites of recurrence. The maximum SUV max was detected in extra-regional nodal recurrence, and it was 56. The mean and median SUV max values were at the highest levels at visceral lesions and were about 19.16 and 13.58 respectively Table (3).

Significant positive moderate correlation found between SUV max values and PSA levels with a p-value (0.031).

<table>
<thead>
<tr>
<th>Average SUV max of all lesions</th>
<th>Mean ±SD</th>
<th>Median (IQR)</th>
<th>Min- Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>SUV max of local recurrence</td>
<td>7.43 ± 5.31</td>
<td>5.7 (3.5 - 10.51)</td>
<td>2 - 18.1</td>
</tr>
<tr>
<td>SUV max regional LN lesions</td>
<td>8.41 ± 6.82</td>
<td>7 (2.79 - 12.99)</td>
<td>2.6 - 21.2</td>
</tr>
<tr>
<td>SUV max of extra-regional nodal lesions</td>
<td>14.89 ± 20.64</td>
<td>7.23 (4.01 - 13.57)</td>
<td>1.3 – 56</td>
</tr>
<tr>
<td>SUV max of Osseus lesions</td>
<td>9.54 ± 4.59</td>
<td>7.53 (7.1 - 14.34)</td>
<td>4.6 - 16.2</td>
</tr>
<tr>
<td>SUV max of Visceral lesions</td>
<td>19.16 ± 16.76</td>
<td>13.58 (5.9 - 38)</td>
<td>5.9 – 38</td>
</tr>
</tbody>
</table>

Cases:

**Case 1:**
A male patient 60 years old with history of cancer prostate underwent Transurethral radical prostatectomy (TURP) 2 months before the study and presented with an elevated PSA level reaching 7.88ng/ml Figure (1&2).
Case 2:

A male patient 71 years old with a history of cancer prostate, received radiotherapy, now presenting with an elevated PSA level reaching 43.7 ng/ml, referred for evaluation Figure (3&4).

Figure 2: Maximum intensity projection (MIP) coronal (A) and sagittal (B) images showing physiological tracer activity with PSMA avid lesion at the anatomical site of the prostate(arrow), yet no other nodal, osseous, or visceral avid lesions noted (Stage T2 N0 M0).

Figure 1: (A, C) Axial CT and (B, D) Axial fused PET/CT images of the prostatic bed showing PSMA avid residual/recurrent tissue indenting bladder base achieving SUV max of 17.98.
Figure 3: Sagittal CT (B) Sagittal and axial fused PET/CT (A, C) images showing multiple metabolically active osseous lesions with the most avid one seen at L2 vertebra being sclerotic on CT image(A) and achieving SUV max of 14.34 on fused PET/CT image (B) (blue arrow). A small PSMA avid left supraclavicular lymph node is seen on the axial fused PET/CT image (C) (red arrow).

Figure 4: Sagittal fused PET/CT image(A) and Maximum intensity projection (MIP) coronal image (B) showing clear prostatic bed with widespread disseminated PSMA avid osseous lesions.

Case 3:
A male patient 59 years old known to have prostatic carcinoma 3 years ago, managed by radiotherapy, presented with an elevated PSA level of 15.8 ng/ml Figure (5&6).
Figure 5: Axial CT (A) and fused axial PET/CT (B) images of the pelvis showing normal physiological uptake of the prostate with no PSMA avid lesions to account for recurrent active neoplasia.

Figure 6: (A) Axial fused PET/CT image of the pelvis showing no avid prostatic lesions. (B) Axial fused PET/CT image of the upper chest showing PSMA avid retro-clavicular lymph node achieving SUV max of 8.31 (red arrow). (C) Axial CT image mediastinal window with corresponding axial fused PET/CT image (D) showing PSMA avid subcarinal lymph node achieving SUV max of 10.25 (blue arrows). (E) Maximum intensity projection (MIP) coronal image showing the same multiple enlarged PSMA avid mediastinal and hilar lymph nodes (yellow circle and red arrow).

DISCUSSION:

The effectiveness of 18F-PSMA-1007 PET/CT in identifying the biochemical recurrence of prostatic cancer was validated by our findings among several PSA levels. Twenty of the twenty-six individuals (76.9%) had at least one lesion on 18F that appeared to be indicative of recurrent prostate cancer. The patient based sensitivity was therefore 76.9%. Our overall detection rate was consistent with a study performed by Giesel et al., 2019 on the effectiveness of 18F-PSMA-1007 PET/CT in detecting biochemical recurrence in 251 patients, with a patient-based sensitivity of 81.3% (11).

In a recent case series of 12 patients Giesel et al., 2018 reported an 18F PSMA
1007 PET/CT detection rate of 75%, which is also in line with our results (12).

Our results are incompatible with a published study by Rahbar et al., 2018 on the patient-based sensitivity of 18 F PSMA PET CT, which demonstrated 95% diagnostic efficacy in individuals with biochemically recurrent prostate cancer. The difference could be attributed to the limited number of patients in our study (13).

Our study’s PET positive rate was higher than Fendler’s study by about 75% in 635 patients with average PSA level 2.1 ng/mL for 68 Ga PSMA PET/CT as compared to 76.9 % (with a median PSA of 1.46) for 18 F PSMA in our study. This could be attributed to the higher positron yield of 18F (18F 96.86 % versus 68Ga 89.14 %) and lower positron energy (18F 633 keV versus 68Ga 1,899 keV) which may improve image quality and affect diagnostic performance. In addition, image spatial resolution with 68Ga is lower than with 18F (2.4 versus 1.4 mm in all directions) (14).

Our study found that 46.2% (12/26) of patients had a local recurrence, which is consistent with the findings of Rahbar et al., 2018, who reported a local recurrence of 37% (37/100). Nevertheless, our detection rate was higher than that of Afshar Oromieh et al., 2017, who used 68Ga-PSMA and found that 4% of individuals had a local recurrence (13/319) (13&15).

Our research revealed a direct relationship between PSA levels, the detection rate and sensitivity of 18F-PSMA in local recurrence. We detected a statistically significant association between PSA level and local recurrence (p=0.001). A statistically significant positive correlation was found (p=0.001, r=0.815).

In our study, local recurrence was detected in 5 patients (38.64%) while 2 patients (15.38%) had bone metastases and 5 patients (38.64) had isolated lymph node metastases. This is consistent with Rahbar et al., 2018 study whose exclusive local recurrence was detected in 15 patients (15%), lymph node metastasis in 29 patients (29%), and bone metastasis in 16 patients (16%) (13).

According to our findings, 18F-PSMA may be preferable to 68Ga-PSMA, particularly in those with low PSA levels. The higher detection rate may be explained by the ability to distinguish between locoregional lymph node metastases and ureter/bladder activity, giving greater confidence when diagnosing local recurrence.

This wide range of PSA values in our subgroups is considered a limitation for our results to be correlated with other studies found in literature discussing the significance of cut-off values for 18 F PSMA PET/CT in biochemical recurrence at various PSA levels ranged between <0.5, 0.5-1, 1-2 and >2 ng.

In our study, there was no evidence of recurrence detected in group 1 patients with PSA level <0.2.

This is consistent with the American Urological Association's definition of biochemical recurrence as an increase in serum PSA of at least 0.2 ng/ml over two subsequent measurements.

We found that the detection rate and sensitivity of 18F PSMA in nodal recurrence are directly proportionate with PSA levels. We detected a statistically significant association between PSA level and regional and distant nodal recurrence (p=0.004 and p=0.028 respectively ), and a statistically significant strong positive correlation as well (p=0.001, r=0.748 and r=0.695 respectively)

Conclusion:

Our results verified the utility of 18F-PSMA PET/CT in identifying prostatic cancerous biochemical recurrence at various PSA levels. An elevated PSA increases the likelihood of a pathogenic 18F PSMA PET CT among patients, however, the detection rate is higher than other methods in patients with low PSA levels. Examining
lesions close to the urinary tract, including local recurrence and pelvic nodal lesions, is made easier by not visualizing the bladder's activity among prostate cancer patients with biochemical recurrence. With greater detection rates than 68Ga-PSMA, 18F-PSMA PET/CT seems to be a dependable and affordable substitute for 68Ga-PSMA PET/CT, particularly in patients who have local recurrence at low PSA levels.

**Study limitations:**

Single image acquisition at 90 minutes after radiotracer injection, inability to correlate results with Gleason score or PSA doubling time, and lack of histopathological confirmation of the detected lesions and follow-up studies are all considered as limitations of our study.

**Declarations:**

**Consent for publication**

Written informed consent was obtained from all patients for publication of the study.

**Availability of data and material**

All data generated or analyzed during this study are included in this article.

**Competing interests**

The authors declare that they have no competing interests.

**Funding**

This work has not received any funding.

**Authors' contributions**

The authors contributed to the study conception and design. Material preparation, data collection and data analysis were performed by all authors. The first draft of the manuscript was written by MMA and HA. TMR and BMR read and approved the final manuscript. All the authors read and approved the final manuscript.

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Not applicable

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**REFERENCES:**


Diagnostic Value Of 18f Labelled Psma Pet/Ct Imaging In Biochemical Recurrence

القيمة التشخيصية للتصوير بالمسح الذرى البوزيتروني باستخدام مادة الفلورين في الارتداد البيوكيميائي لأورام البروستاتا بعد العلاج الشفائي

بنت محمد رئيف مسعد، تقي السيد محمد السيد عمر، منة الله حاتم شلبى

قسم الأشعة التشخيصية – كلية الطب جامعة عين شمس

الخلفية: يعد سرطان البروستاتا ثاني أكثر الأورام الخبيثة شيوعا وسبب رئيسى للوفاة بين الرجال في جميع أنحاء العالم. يعطى الرجال المصابين بسرطان البروستاتا خيار تلقى العلاج الجذري في صورة استئصال البروستاتا؛ العلاج الهرموني أو العلاج الإشعاعي بهدف علاج المرض؛ ولكن تصل نسبة الارتداد البيوكيميائي إلى 53% من المرضى في غضون 10 سنوات.

النواص في البحث: تقييم الأداء التشخيصي التصويري F-PSMA PET/CT18 في الارتداد الكيميائي الحيوي لسرطان البروستاتا بعد استئصال البروستاتا الجذري، والعلاج الهرموني و/أو الإشعاع الخارجي.

المرضى و طرق الدراسة: هذه الدراسة هي دراسة مقطعية أجريت في قسم الأشعة مستشفى جامعة عين شمس. شملت دراستنا ستة وعشرين من مرضى سرطان البروستاتا الذين تم علاجهم سابقاً والمصابون بارتفاع مستوى PSA لتقييم إمكانية ارتداد المرض.

النتائج: أظهر عشرون من أصل ستة وعشرين من المرضى المتميزة في الفحص إيجاباً مع وجود أفة واحدة على الأقل تشير إلى الإصابة بسرطان البروستاتا المترددة F-PSMA-PET/CT18 مع عدم اكتشاف فحوصات إيجابية عند مستوى PSA ناطعة. تم تقسيم المشاركين إلى ثلاث مجموعات بناءً على توزيع مستوى PSA بقيم 25 و50؛ كان هناك ارتباط إيجابي قوي جداً ذو دلالة إحصائية بين مستوى PSA والتردد في المنطقة المحلية والإقليمية والغدد الليمفاوية البعيدة والحصانات. ومع ذلك، لم يكن هناك ارتباط ذو دلالة إحصائية بين مستوى PSA والتردد في مناطق العضم مع قيمة p (>0.05).

الخلاصة: أكملت نتائجنا كفاءة F-PSMA-PET/CT18 في اكتشاف التردد الكيميائي الحيوي لسرطان البروستاتا عند مستويات PSA مختلفة. يبدو أن احتماليت الإصابة بـ F-PSMA PET/CT18 أعلى من PSA. 