# Role of Fluorine-18 Labelled PSMA PET/CT Imaging in Prostatic Cancer Patients with Biochemical Recurrence



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## Abstract

**Background:** The second most common type of cancer in men is prostate cancer and the sixth most frequent cancer-related mortality cause in the world. The goal of curative treatment for patients with localized advanced prostate cancer is to completely eradicate the condition, although within ten years, up to 32% of individuals would get a biochemical recurrence. It has been demonstrated that the PSMA ligand is more sensitive and focused. The ability to detect cancers, including minute visceral, osseous, and lymph node metastases, even at low PSA levels is the major advantage.

**Results:** 76 (91.6%) of the 83 patients had one or more abnormality on the 18F-PSMA PET/CT. According to their PSA values, the patients are divided into four groups: G1 for PSA levels below 0.5 ng/ml, G2 for PSA levels between 0.5 and 1 ng/ml, G3 for PSA levels between 1:2 ng/ml, and G4 for PSA levels greater than 2 ng/ml. Among the 10 patients, four in G1 had a PSMA scan that was positive (40%). G2 had 12 patients, of whom 11 had a PSMA scan that was positive (91.6%), G3 had 19 patients, all of whom had a PSMA scan that was positive (100%) and G4 had 42 patients, all of whom had a PSMA scan that was positive (100%). According to the pathological results, the median SUVmax values rise with increasing PSA levels. Patients with PSA levels in G1 had median SUVmax values of 2.6, G2 of 3.9, G3 of 6, and G4 of 7.9.

**Conclusions:** With 18F-PSMA-PET/CT, relapsed prostate cancer can be detected. The detection rate is still higher than other approaches in individuals with PSA values as low as 0.5 ng/ml, despite the fact that the possibility of a pathogenic 18F-PSMA PET/CT is thought to be greater in people with higher PSA levels..

**Keywords:** prostate cancer- PET/CT- PSMA- SUVmax- PSA

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## Introduction

Males with localized prostate cancer possess the choice of receiving intense therapy (localized treatment, either a prostatectomy or intense radiation treatment) with the goal of curing the illness, however 32% or more of patients will experience biochemical recurrence within ten years **(1).** Blood PSA levels of 0.2 ng/ml or greater with a second verified rise after prostatectomy are classified as a biochemical recurrence. Following radical radiation treatment, a PSA increase of 2 ng/ml over the nadir is recognized as a biochemical recurrence **(2).**

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It is essential to diagnose recurring illnesses early in order to administer curative salvage therapy. On the other hand, in the presence of a biochemical recurrence, bone scans and CT or MRI on abdomen and pelvis only provide a modest rate of detection for metastatic or recurrent prostate cancer lesions **(3).** The large transmembrane glycoprotein known as PSMA is composed of a significant extracellular component, a small intracellular component, and a transmembrane component **(4).**

PSMA overexpression has been discovered to be much higher in prostate cancer than in normal prostatic tissue, and it also increases with tumour grade and castrate resistance, making it one of the most attractive targets for PET imaging **(5).**

The vast majority of PSMA-targeted PET radiotracers currently used in clinical practise are 68Ga-labeled imaging agents **(6).** Researchers found that 68Ga-PSMA PET/CT enabled the identification of one or more lesions in 83% of patients overall in a sizable study involving 319 individuals with biochemical recurrence, that even in patients with low PSA levels has great detection rates: 50% of cases were detected for individuals in the study with a serum PSA level of less than 0.5 ng/ml **(7).**

Since 68Ga-PSMA PET/CT is unfortunately not generally accessible, research is currently being done on radiolabeled 18F-PSMA ligands. Benefits of 18F-PSMA and 68Ga-prolonged PSMA's half-lives, which enable them to be transferred to nearby sites, exceed some of the practical restrictions of non-urinary excretion. **(4).**

The ability to diagnose lesions beneath or close to the urinary bladder that are local recurrences or pelvic small lymph node metastases, especially if they are situated along the ureters, is improved by the significantly decreased renal excretion of 18F-PSMA (**8).**

Giesel et al. 2018, reported on the diagnostic effectiveness of 18F PSMA in more than 250 cases with biochemical recurrence following radical prostatectomy: overall detection rates improved, especially at low and very low PSA values of 0.5-1 and 0.2-0.5 ng/ml, with rates of detection of 74.5% and 61.5%, respectively. **(9).**

The main aim of this study is to evaluate the role of 18F-PSMA PET/CT imaging in prostatic cancer patients who experience a biochemical recurrence after prostatectomy and/or radiation therapy.

## Patients and Methods

The local ethical committee authorized the design of the study as an across-sectional study. Following primary therapy with curative intent, 83 individuals with prostate cancer were referred for follow-up to assess for the likelihood of recurring illness since their PSA levels were increasing. Their ages range from 47 to 86. The patients came from urology and oncology departments during the period from 2019 to 2021, referred to the PET/CT unit in our hospital for assessment.



These individuals had 18F-PSMA PET/CT. Multiple patients had undergone Computed tomography, Magnetic resonance imaging, or bone scans prior to PSMA PET imaging. However, it was not possible to compare these data in a systematic manner due to the varying time in between these procedures and the variable approaches that done.

The inclusion criteria include any prostate cancer patients who undergone a prostatectomy and/or radiation therapy and showed up for follow-up with a rising PSA level.

Patients without primary treatment with curative purpose and those with increased blood creatinine levels are excluded from receiving an iodinated IV contrast injection.

Imaging protocol

For the investigation, a Siemens Bio-graph true point scanner was employed.

Patient preparation: Prior to the assessment, patients are requested to void and observe a 6-hour fast.

Dosage administration: A dose of 2-4 MBq/kg up to 400 MBq of 18F-PSMA IV injection was given 60 min before the examination.

Examination time: Low dose non-contrast CT scan done first, then a whole body PET investigation followed by a complete body enhanced CT scan. The entire study session lasted 20 to 30 minutes.

Technique: By automatically infusing 100-120 mL of non-ionic contrast into the vein at a rate of 4 ml/sec, we were able to create contrast-enhanced CT images. To account for attenuation, a CT image taken before the PET pictures is used. Then, from the

head to mid-thigh, an image reconstruction PET-CT examination was conducted.

PET/CT fusion: To make image interpretation simpler, sagittal and coronal pictures were created from axial PET and CT scans. Attenuation correction is either manual or automatic.

PET/CT interpretation:

At multidisciplinary conference for reporting, all studies were evaluated by two nuclear medicine specialists and radiologists, as per institutional standards. Bone metastases and local recurrence were both characterized as the absence of morphological alterations. Because The CT detecting ability for these metastases is poor, increased localized tracer absorption in these areas was thought to be a sign of local recurrence or bone metastases even if there is no morphological relationship. The highest uptake plane for prostate lesions was used to place volumes of interest, and maximum standardized uptake values (SUVmax) were evaluated and reported.

On CT, lesions that were morphologically evident and exhibited localized tracer uptake above the nearby background were known to be PSMA-positive lesions. Unless there were more than three visible prostate cancer lesions present in the individuals, in which case only three lesions were assessed. Since dominant lesions are typically chosen first, this selection strategy prevents SUVs from being overestimated. PSMA uptake was frequently observed but wasn't considered aberrant in the sacral, celiac, and stellate ganglia.

**Statistical analysis:**

By utilizing means or medians, absolute and relative frequencies, and standard deviations or ranges, descriptive statistics was employed to describe the research population.

The patients are placed into four groups according on their PSA values: G1 for PSA levels under 0.5 ng/ml, G2 for PSA levels between 0.5 and 1 ng/ml, G3 for PSA levels between 1:2 ng/ml, and G4 for PSA levels over 2 ng/ml.

It was determined that a significant difference existed when the P value was less than 0.05.

## Results:

Average age of the 83 individuals in the research, whose biochemical recurrence was evaluated and localized by 18F-PSMA PET/CT, was 67.23 years. The patients' ages varied from 47 to 86 years.

A lesion that could indicate recurrent prostate cancer was seen in at least 76 out of 83 individuals (91.6%). Therefore, 91.6% of the sensitivity was patient-based. In 7 cases (8.4%), the test came out negative.



In total, 124 lesions characteristic of recurrent prostate cancer were detected (**Table 1).**

Only a single lesion suggests of biochemical recurrence was discovered in 42 patients (50.6%), two lesions were detected 20 patients (24.1%), three lesions were in 12 patients (14.5%) and more than three lesions were detected in only 2 patients (2.4%).

Local recurrence was exclusively found in 21 individuals (25.3%) while exclusive lymph node metastasis was in 13 individuals (15.6%) and bone metastasis in 8 patients (9.6%). Exclusive visceral metastasis to the lung and liver were detected in two patients only (2.4%).

According to the patients' PSA values, there are four groups created. G1 with PSA values less than 0.5ng/ml, G2 with PSA level between 0.5:1 ng/ml, G3 with PSA level between 1:2 ng/ml and G4 with PSA level more than 2 ng/ml.

G1 included 10 patients and the PSMA scan was positive in four patients (40%). G2 included 12 patients and the PSMA scan was positive in 11 patients (91.6%) while G3 included 19 patients and the PSMA scan was positive in all of them (100%) and G4 included 42 patients and the PSMA scan was also positive in all of them (100%).

The highest standardized uptake values (SUVmax) were evaluated, and the local recurrence lesion's maximal SUV max was discovered at 60.3. Bony lesions had the highest mean and median SUV max values, which were 11.89 and 8.9, respectively. **(Table 2).**

The pathological results' median SUVmax values in patients with PSA levels in G1 was 2.6 (range 1.5-18.1), in G2 was 3.9 (range 1.5-30.1), in G3 was 6 (range 2.2-60.3) while in G4 was 7.9 (range 1.4-39) so that the median SUVmax values increases with higher PSA levels **(Table 3).**

**Table 1 Number and percentages of different sites of biochemical recurrence**

| Recurrent lesion | n | % |
|---|---|---|
| **Local recurrence** | 49 | 59.0 |
| **Lymph node metastasis** | 42 | 50.6 |
| **Bone metastasis** | 26 | 31.3 |
| **Lung metastasis** | 6 | 7.2 |
| **Liver metastasis** | 1 | 1.2 |

**Table 2 Average SUVmax of all lesions**

| | SUVmax of all lesions | SUVmax of local recurrence | SUVmax of lymph node lesions | SUVmax of bony lesions | SUVmax of lung lesions | SUVmax of liver lesions |
|---|---|---|---|---|---|---|
| **Mean (SD)** | 10.608(10.0) | 11.006(10.08) | 10.07(11.004) | 11.89(8.79) | 5.76 (4.35) | |
| **Median** | 6.65 | 8.4 | 4.7 | 8.9 | 4.6 | |
| **Minimum** | 1.3 | 1.5 | 1.5 | 1.5 | 1.3 | |
| **Maximum** | 60.3 | 60.3 | 45.8 | 38.1 | 11.4 | 9.9 |

**Table 3 Relation between SUV max values & PSA levels.**

| | G1 | G2 | G3 | G4 |
|---|---|---|---|---|
| **Mean (SD)** | 5.98(6.9) | 7.05(8.34) | 11.30(12.48) | 10.77(8.67) |
| **Median** | 2.6 | 3.9 | 6 | 7.9 |
| **Minimum** | 1.5 | 1.5 | 2.2 | 1.4 |
| **Maximum** | 18.1 | 30.1 | 60.3 | 39 |

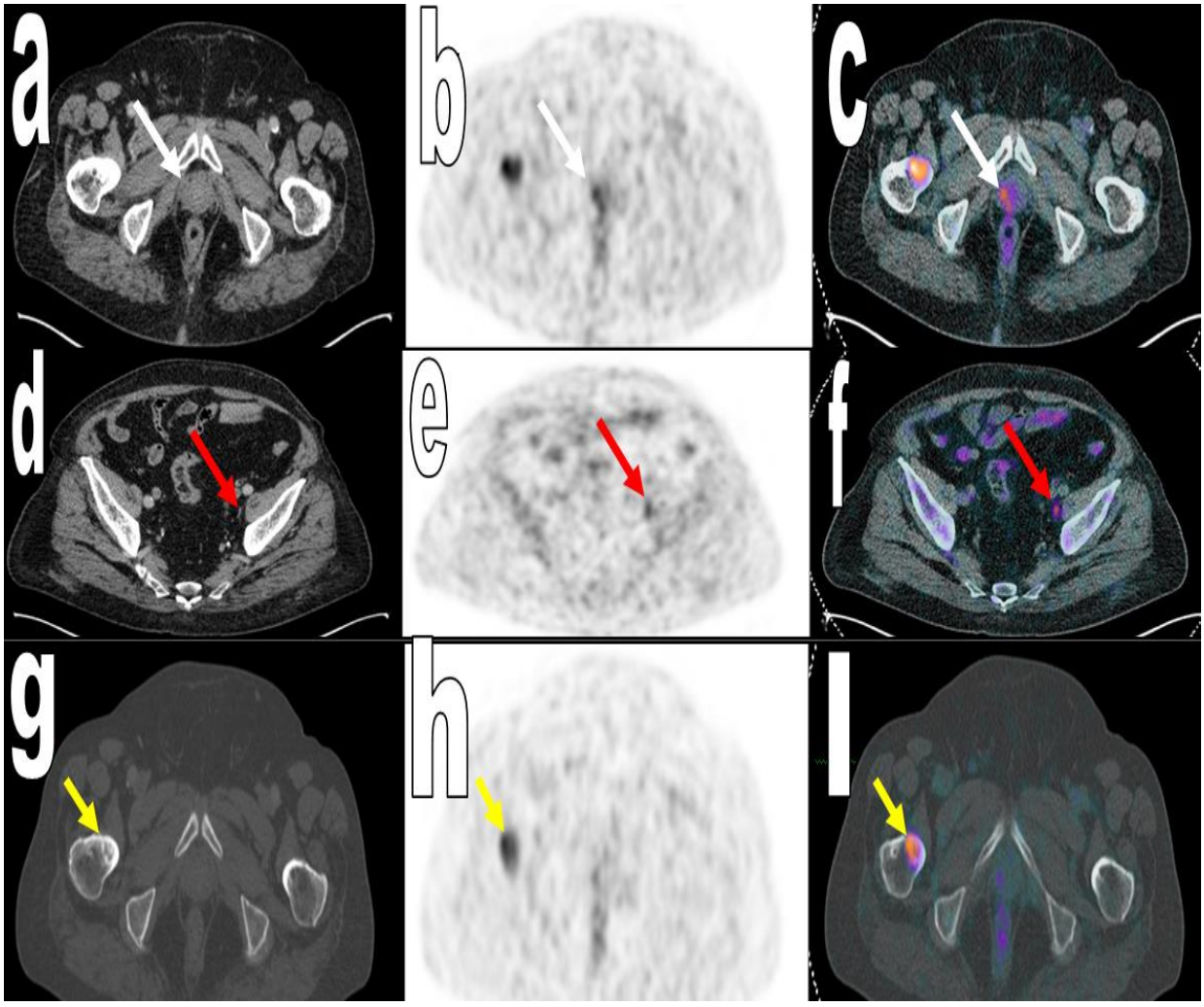
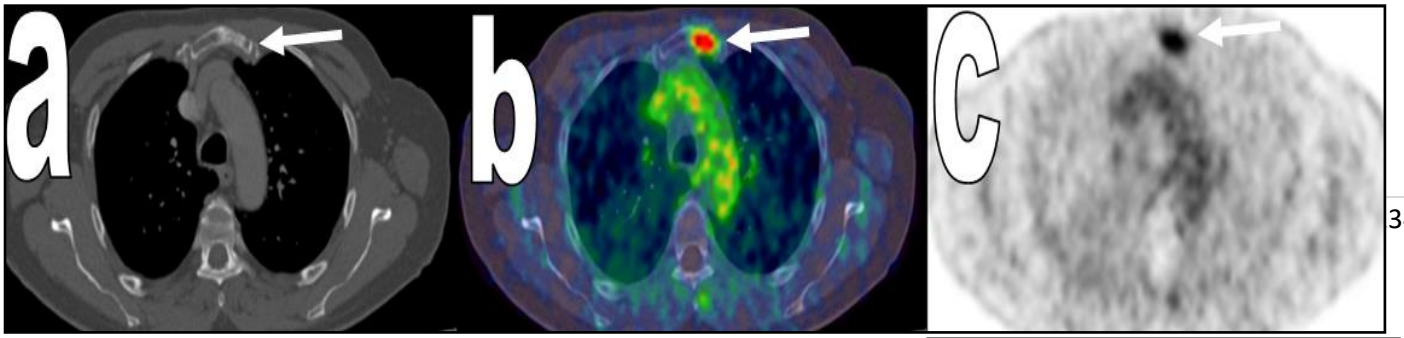



**Figure 1:** 78 year old patient with history of prostate cancer treated by radiation therapy 6 years ago, now elevated PSA level: 13.2 ng/ml. **Prostate:**(a) Axial CT, (b) axial PET and (c) fused PET/CT shows Increased PSMA uptake in the right peripheral zone of the mid gland with SUVmax 3.5 *(white arrows).* **Lymph node:** (d) Axial CT, (e) axial PET and (f) fused PET/CT Low grade PSMA uptake by small bilateral external iliac lymph nodes, SUVmax 3.3 on the left side *(Red arrows).***Bone:** (g) Axial CT bone window, (h) axial PET and (i) fused PET/CT increased PSMA uptake by sclerotic lesions in the right femoral neck, SUVmax 7.6 *(yellow arrows).*

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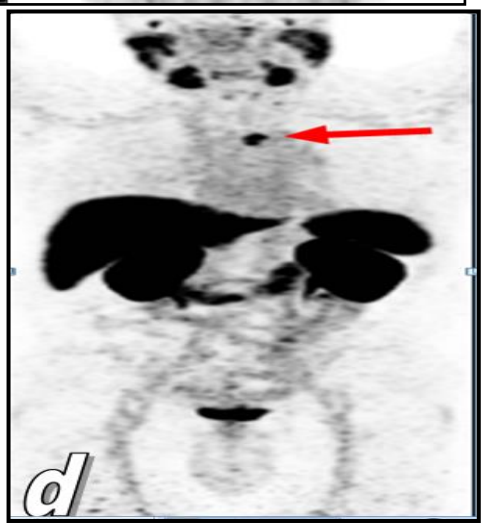
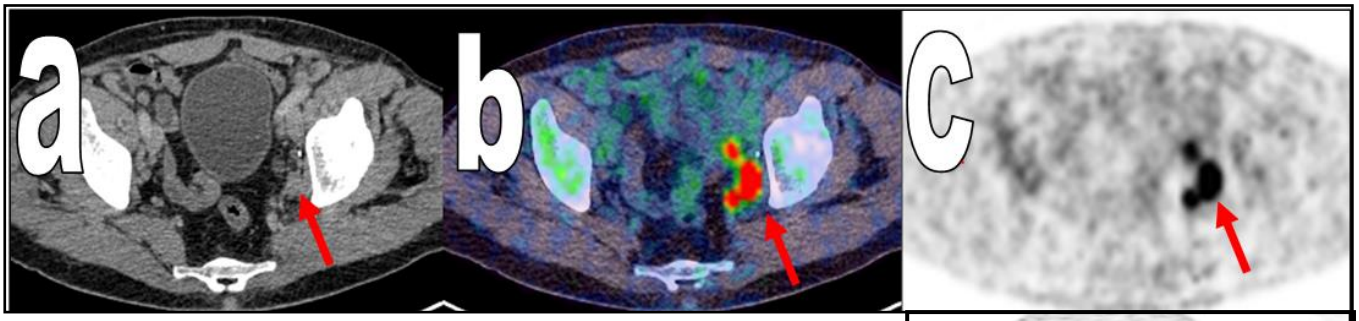



**Figure2:** 78 year old patient with history of prostatectomy for prostate cancer in 2007. PSA level: 2.3ng/ml. **Bone:** a) Axial CT, (b) fused PET/CT and (c) axial PET show increased PSMA uptake corresponding to sclerotic lesion in the manubrium sterni with SUVmax 6.6 (white arrows). (d) Maximum intensity projection image (MIP) shows increased PSMA uptake corresponding to sclerotic lesion in the manubrium sterni (Red arrow).



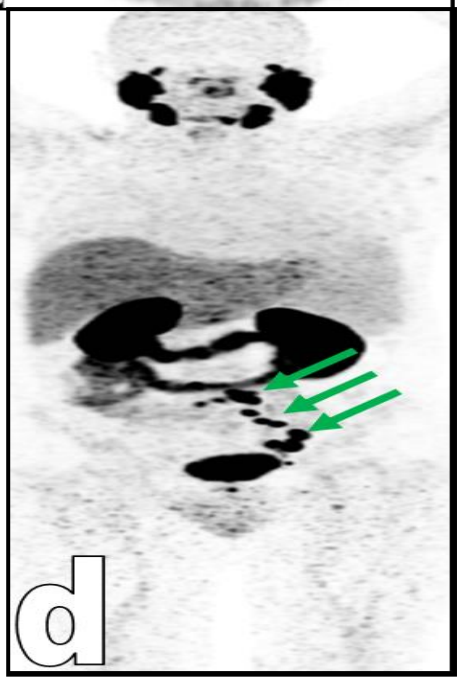




**Figure3:** 65 year old patient with history of prostate neoplasm underwent prostatectomy, now elevated PSA level 5.16 ng/ml. **Lymph node:** a) Axial CT, (b) fused PET/CT and (c) axial PET PSMA avid pathologically enlarged aortocaval, left para-aortic left common and internal iliac nodes, the most active is the left internal iliac having SUVmax 45.8 and measures 1.8 cm (Red arrows). (d) Maximum intensity projection image (MIP) shows PSMA avid pathologically enlarged aortocaval, left para-aortic left common and internal iliac nodes (Green arrows).

## Discussion

As of 2018, prostate cancer was the 2nd most frequent malignancy among males all over the world **(10).**

In the hopes of treating the disease, individuals with localized prostate cancer possess the choice of receiving radical therapy (prostatectomy, local treatment, or radiation therapy), however biochemical recurrence affects up to 32% of patients after 10 years. **(1).**

The goal of this research is defining imaging's function among people with prostate cancer who have biochemical recurrence using 18F-PSMA PET/CT.

There was at least one lesion that have been discovered on 18F PSMA-PET/CT in 76 out of 83 participants (91.6%). Consequently, the sensitivity based on patients was 91.6%.This appears to be compatible with recent published study by **Rahbar et al., 2018** where patient-based sensitivity was 95% **(11).**

**Kremer et al., (2018)** reported a rate of detection of 75% in a recent case series of 12 patients, which is lower than the detection rate found in the present investigation. The disparity might have resulted from the study's small sample volume of patients. In that research, only 62% of individuals with a PSA level under 2.0 ng/ml underwent imaging, but in our research, 100% of individuals with a PSA under 2.0 ng/ml underwent imaging **(12).**

This study's PET-positive rate was higher than a research done by **Afshar-Oromieh et al., 2017** that looked 68Ga-PSMA scan & performed on 1007 individuals who had biochemical recurrence (the biggest cohort studied to date). In our study, patient-based sensitivity was 91.6%; in contrast, it was 79.5%. The positron's lower energy (18F 633 keV vs. 68Ga 1,899 keV) and higher positron yield (18F 96.86% vs. 89.14%) of 18F may improve image quality and have a positive impact on diagnostic performance. Additionally, 68Ga's image spatial resolution is poorer than 18F's (2.4 vs. 1.4 mm) **(13).**

In our investigation, the detection rate in patients assigned to the (G1) with a PSA below 0.5 ng/ml was 40%. This seems to be somewhat consistent with findings from research by **Rousseau et al., 2019 and Giesel et al., 2018**, in which the detection rate was 60% and 61.5%, respectively, in individuals with PSA below 0.5 ng/ml **(14,9).**

This result, however, does not seem to be consistent with those from the **Rahbar et al., 2018** trial, where individuals with PSA value less than 0.5 ng/ml had a greater rate of detection (86%). This might be explained by the fact that our study's radiotracer injection and picture capture times were 60 min instead of the 120 min in **Rahbar et al., 2018.**'s study. According to **Rahbar et al., 2018,** 18F-PSMA had a greater lesion detection rate 120 minutes after injection compared to 60 minutes of imaging, and SUVmax had significantly increased **(11).**



The detection rate was 91.6% in (G2) with a PSA value 0.5: 1 ng/ml. The data from **Rousseau et al., 2019 and Giesel et al., 2018**, where the detection rates were 74.5% and 78.3% respectively, and **Rahbar et al., 2018,** where the detection rate was 88.9% appear to be consistent with this. **(14,9).**

The detection rate was 100% in our third group of individuals (G3) with PSA 1:2 ng/ml. This appears to be compatible with result form study done **by Rahbar et al., 2018** where the detection rate was 100% **(11)** and nearly compatible with **Giesel et al., 2018** results where the detection rate was 90.1% **(9).**

In the current study all individuals with PSA level above 2ng/ml were assigned as fourth group of patients (G4) and detection rate in this group was 100%. This appears to be compatible with **Rahbar et al., 2018** results where the detection rate was also 100% **(11)** and nearly compatible with **Giesel et al., 2018 and Rousseau et al., 2019** results where the detection rate was 94%. & 92.2 % respectively **(9,14).**

In our study, 59% of patients (49/83) had local recurrence, which is much higher than the findings of **Rahbar et al., 2018 (11)** where local relapse was 37% (37/100).

According to our findings, 18F-PSMA may be preferable to 68Ga-PSMA, particularly in individuals with low PSA levels. The higher detection rate could be attributed to a better ability to distinguish between ureter and urinary bladder activity and Lymph node metastases in the local area as well as local recurrence. As a result, the diagnosis of local recurrence is more secure. Local recurrence after radiotherapy, especially individuals with low PSA values may encourage a later secondary full remission. Therefore, a trustworthy imaging strategy to do in people with rising but still low PSA levels is crucial from a therapeutic standpoint.

The pathological results' median SUVmax values in individuals with PSA values below 0.5ng/ml was 2.6 (range 1.5-18.1), with PSA level between 0.5:1 ng/ml was 3.9 (range 1.5-30.1), PSA level between 1:2 ng/ml was 6 (range 2.2-60.3) while in PSA level higher than 2 ng/ml was 7.9 (range 1.4-39).

These results are lower than results of **Rahbar et al., 2018** that reported that clinical results' median SUVmax values in individuals with PSA levels below or equals 0.5 ng/ml was 10.25 (range 3.98–48.99), PSA value 0.51–1.0 ng/ml was 14.32 (range 4.36–38.61), PSA value 1.1–2.0ng/ml was 13.16 (range 3.14–136.18) and in PSA value above 2.0 ng/ml was 28.87 (range 5.03–248.27) **(11).**

This might be explained by the 120-minute difference between the injection of the radiotracer and the capture of the images in that investigation and the 60-minute difference in our study.

However, with increasing PSA levels in both investigations, the median SUV rose.

## Study limitations:

At 60 minutes after radiotracer injection, one picture is acquired, inability to correlate results with PSA doubling time or the Gleason score and lack of follow up studies are all considered as limitations of our study.

## Conclusions

Prostate cancer that returns can be found with 18F-PSMA-PET/CT. Although the detection rate is still higher than other approaches in individuals with PSA values as low as 0.5 ng/ml, the likelihood of a pathogenic 18F-PSMA PET/CT appears to be higher in individuals with higher PSA levels.

This study established that in prostate cancer with biochemical recurrence, the absence of urinary bladder activity visually enhances the evaluation of lesions near to the urinary system, including lymph nodes and local relapse.

## List of abbreviations

| | |
|---|---|
| **PSA** | Prostate specific antigen. |
| **PET/CT** | Positron emission tomography/ Computed Tomography. |
| **PSMA** | Prostatic specific membrane antigen. |
| **18F-PSMA** | Fluorine-18 prostatic specific membrane antigen. |
| **Ga68** | Gallium 68. |
| **IV** | Intravenous. |
| **SUV** | Standardized uptake value. |



**Consent for publication:** All patients included in this research were fully conscious and gave written informed consent to publish the data contained within this study.

**Availability of data and material:** All the datasets used and analyzed in this study are available with the corresponding author on reasonable request.

**Competing interests:** The authors declare that they have no competing interests

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**Authors contributions:**

- A.A.H and T.W.M.K put the idea of the study. Editor of the manuscript. Participated in the study design.
- M.A.S, M.F.O and N.D.E: participation in the study design and performed the statistical analysis.
- M.A.S: patients collection.

- All authors read and approved the final manuscript.

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