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RESEARCH ARTICLE

Application of [^{68}Ga]PSMA PET/CT in Diagnosis and Management of Prostate Cancer Patients

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Abstract

Purpose: The early and accurate diagnosis of locoregional recurrence or metastasis in prostate cancer (PC) has a significant impact on treatment options. Prostatic-specific membrane antigen (PSMA) positron emission tomography (PET)/x-ray computed tomograph (CT) imaging has recently been introduced as a novel procedure in managing PC. The aim of this study was to evaluate the efficacy of [^{68}Ga]PSMA PET/CT in managing PC patients and to compare the detection rate of PET/CT and bone scans (BSs) in detecting bone metastasis.

Procedures: We evaluated 415 patients with PC who underwent [^{68}Ga]PSMA PET/CT between March 2015 and September 2018. The patients were classified into three groups: staging, biomedical recurrence (BCR), and follow-up or monitoring, based on the intent to perform PET/CT.

Results: We evaluated 415 patients aged 41–99 (68.25 ± 9.59). Of these patients, 344 (82.9 %) had at least one localized lesion. The detection rates were 48.3 %, 52.6 %, 74.4 %, 79.6 %, and 93.9 % for a PSA value of < 0.2 ng/ml, ≥ 0.2–< 0.5 ng/ml, ≥ 0.5–< 1 ng/ml, ≥ 1–< 2 ng/ml, and ≥ 2 ng/ml, respectively ($p < 0.05$). The detection rates increased significantly with higher GSs; the rates were 68.3 % (28/41), 74.5 % (73/98), 93.9 % (46/49), and 91 % (61/67) for a GS of < 7, 7, 8, and > 8, respectively ($p < 0.05$). An ideal cut-off value of > 1.16 ng/ml was obtained for PSA value, which equates to specificity of 75 % and sensitivity of 77 %. In comparing BSs and PET/CT, a region-based analysis showed the superiority of PET/CT over BSs for all regions expect the skull ($p < 0.05$). PET/CT detected 258 suspicious regions, 255 of which were metastatic and three of which were equivocal. BSs detected only 223 suspicious regions, 203 of which were metastatic and 20 of which were equivocal.

Conclusions: [^{68}Ga]PSMA PET/CT showed a high detection rate for lesions in PC patients. PSA level, GS, and a PSA doubling time of less than 6 months were shown to be the affective variables. In addition, ^{68}Ga-PSMA PET/CT showed better performance in detecting bone lesions than BSs.

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Key words: PSMA, PET/CT, Bone scan, Prostate cancer, PSA, Gleason Score, Androgen deprivation therapy

Introduction

Prostate cancer (PC) is the most common malignancy and the fifth cause of cancer-related death in men [1]. PC is classified as localized, locally advanced (if beyond the prostate bed), or metastatic. Patients are classified as being at low, intermediate, or high risk of progression based on their clinical stage, prostate-specific antigen (PSA) levels, and Gleason Score (GS). Even with a low or undetectable PSA level, metastasis may occur [2]. Therefore, a sensitive imaging modality capable of diagnosing locoregional recurrence or metastasis when treatment modalities are effective is important.

Early and accurate diagnosis is necessary to determine the most effective patient-specific treatment plan to increase the expected five-year survival to 100 %. Current guidelines suggest anatomical imaging modalities, including x-ray computed tomography (CT), magnetic resonance imaging (MRI), and scintigraphy with Tc-99m-labeled bisphosphonate—such as a methylene diphosphonate bone scan to clarify the extent of primary or metastatic PC. However, their sensitivity in detecting the small amounts of PC, especially when there are low PSA values, is limited and thus they may underestimate the extent of disease [3]. The accurate determination of tumor sites is essential because this helps in deciding whether surgery, systematic treatment (such as androgen deprivation therapy (ADT) with or without chemotherapy), or targeted therapies such as radiotherapy are used [4].

In recent years, advances in PC-specific positron emission tomography (PET) have led to the development of new radiotracers to evaluate the extent of disease, such as [^{11}C]acetate [^{11}C]choline, [^{18}F]fluorocyclobutane-1-carboxylic acid (aka fluciclovine), and Ga-68 prostate-specific membrane antigen ([^{68}Ga]PSMA) [5].

Recently, prostate-specific membrane antigen (PSMA) has received increasing attention. A transmembrane antigen, PSMA is overexpressed in most prostatic adenocarcinomas, and its expression levels increase with increasing tumor dedifferentiation in hormone-refractory and metastatic PCs [6, 7]. Radio-labeled PSMA is increasingly used in evaluating PC. Gallium-68 labeled PSMA ([^{68}Ga]PSMA) PET/ CT was introduced for PC imaging a number of years ago [8], and several recent reports have indicated its promise in diagnosing PC, staging, follow-up, restaging in cases of biochemical recurrence (BCR), and assessing treatment response in patients with castration-resistant PC (mCRPC) [9–11]. The advantages of [^{68}Ga]PSMA imaging over [^{18}F]choline PET/CT [12] and Tc-99m-labeled bisphosphonates [13] have been demonstrated in the detection of PC and its metastases.

In PC, bone is the most common site for metastasis. The majority of bone metastases in PC are osteoblastic, but other kinds of bone metastases (such as osteolytic or mixed) can also occur. Traditionally, the widely available and cost-effective procedure of bone scintigraphy with Tc-99m-labeled phosphonates has been performed to evaluate bone metastasis for staging, follow-up, and treatment response assessment. However, its diagnostic utility—particularly in BCR—is limited [14]. It has also been shown that the sensitivity of bone scans (BSs) in cases of bone marrow involvement or early lesions with insufficient osteoblastic activity is limited [15]. Despite these limitations, BSs have been standard in evaluating bone metastases because of their wide availability, whole body coverage, and low cost [16].

In this study, we evaluated the diagnostic efficacy of [^{68}Ga]PSMA PET/CT in a large series of PC patients. Specifically, we aimed to evaluate the impact of the historical data of patients, including the GS, the PSA level and the PSA doubling time (PSAdt) on the detection rate of PET/CT. Finally, we compared the efficacy of PET/CT and BSs in detecting bone lesions.

Materials and Methods

Patients

In total, 415 patients who had undergone [^{68}Ga]PSMA PET/CT at the Nuclear Medicine Department of Razavi Hospital in Mashhad, Iran between March 2015 and September 2018 were retrospectively studied. In addition to demographic data, serum PSA, GS; PSAdt; and details of prior radiotherapy, chemotherapy, or ADT were examined from the medical records. The patients were classified into three groups—staging, BCR, and follow-up/monitoring. The characteristics of the patients are shown in Table 1. To compare BSs and PC PET/CT in the detection of bone involvement, patients with a delay of more than six months between their BS and PC PET/CT and those who had any changes in therapy between the two scans were excluded. All reported evaluations were performed based on the principles of the Helsinki Declaration and according to the national regulations. Retrospective analysis was performed according to ethical guidelines of the ethic commission of our university, and the requirement for separate informed consent for this analysis was waived.

[^{68}Ga]PSMA-11 PET/CT Scan

[^{68}Ga]PSMA-11 PET/CT was performed approximately 1 h after an intravenous injection of 185 MBq (2 MBq/Kg) of

Table 1 Characteristics of patients

Characteristic	All patients	PSMA-positive	PSMA-negative
Study	*N* = 415	*N* = 344	*N* = 71
Staging	45 (10.8)	40 (11.6)	5 (7)
Recurrence	194 (46.7)	153 (44.5)	41 (57.7)
Follow-up/monitoring	176 (42.4)	151 (43.9)	25 (35.2)
Age (years)	*N* = 396	*N* = 330	*N* = 66
Mean ± SD	68.25 ± 9.59	68.48 ± 9.58	67.11 ± 9.63
Range	41–99	41–99	48–92
PSA (ng/ml)	*N* = 374	*N* = 308	*N* = 66
Mean ± SD	67.96 ± 461.15	82.04 ± 507.197	2.22 ± 5.27
Range	0.002–5000	0.03–5000	0.002–33
PSA value (ng/ml), *n* (%)	*N* = 374	*N* = 308	*N* = 66
< 0.2	29 (7)	14 (4.5)	15 (21.4)
≥ 0.2 to < 0.5	38 (9.2)	20 (6.5)	18 (25.7)
≥ 0.5 to < 1	39 (9.4)	29 (9.4)	10 (14.3)
≥ 1 to < 2	54 (13)	43 (14)	11 (15.7)
≥ 2	214 (51.6)	202 (65.6)	12 (17.1)
PSA doubling time (months), *n* (%)	*N* = 140	*N* = 113	*N* = 28
< 6 months	87 (62.1)	76 (67.2)	12 (43)
≥ 6 months	53 (37.9)	37 (32.8)	16 (57)
Radical prostatectomy, *n* (%)	*N* = 415	*N* = 345	*N* = 70
Yes	255 (61.4)	203 (58.8)	52 (74.3)
No	160 (38.6)	142 (41.2)	18 (25.7)
Hormone therapy	*N* = 412	*N* = 342	*N* = 70
Yes	216 (52.5)	190 (55.6)	26 (37.1)
No	196 (47.5)	152 (44.4)	44 (62.9)
Chemotherapy/radiotherapy	*N* = 415	*N* = 345	*N* = 70
Radiotherapy	128 (30.8)	109 (31.6)	19 (27.1)
Chemotherapy	10 (2.4)	9 (2.6)	1 (1.4)
Both	29 (7)	28 (8.1)	1 (1.4)
None	248 (59.8)	199 (57.7)	49 (70)
Gleason Score	*N* = 255	*N* = 208	*N* = 47
Mean ± SD	7.6 ± 1.13	7.73 ± 1.12	7.06 ± 0.98
< 7	41 (16)	28 (13.5)	13 (27.7)
7	98 (38.5)	73 (35.1)	25 (53.2)
8	49 (19.2)	46 (22.1)	3 (6.4)
≥ 9	67 (26.3)	61 (29.3)	6 (12.8)

N, the number of patients

[68Ga]PSMA on a Biograph 6 Truepoint SIEMENS PET/CT scanner. For transmission scans, CT images were obtained using 4 mm slice thickness on a spiral six-slice scanner. 3D PET images were then obtained from the base of the skull to the mid-thigh (unless there was a suspicious history of the possibility of involvement beyond the aforementioned boundaries) for 6–8 bed positions at 3 min per position. The iterative method using ordered-subset expectation maximization (OSEM) with two iterations and eight subsets, and 5 mm Gaussian filter size was used for reconstruction of the PET images.

Images Analysis

The [68Ga]PSMA PET/CT images were reviewed by two nuclear medicine physicians. [68Ga]PSMA uptake was considered physiological in the following tissues: liver, lacrimal and salivary glands, kidneys, small intestine, spleen, and colon. Focal tracer uptake that was higher than the adjacent background and that was not associated with the mentioned physiological tracer uptake was considered as indicative of PC. PET-positive lesions were classified as local metastases (prostate/prostate bed metastases, and/or pararectal lymph nodes (LNs) and/or iliac LNs) or distant metastases (LNs above the iliac bifurcation and/or retroperitoneal LNs and/or bone lesions and/or other visceral lesions).

Bone Scan Analysis

The skeletal system was classified into eight regions—skull, sternum, ribs, vertebrae, clavicle, pelvis, scapulae, and upper and lower limbs. BSs and [68Ga]PSMA PET/CT images were reviewed by two nuclear medicine physicians. A three-point visual scale—negative (normal or benign), equivocal, and positive—was determined to classify bone metastasis at each region.

The final diagnosis was according to the blending of correlative imaging, histopathologic examinations, and also clinical follow-up.

Statistical Analysis

PSA values were classified as < 0.2 ng/ml, 0.2–< 0.5 ng/ml, 0.5–< 1 ng/ml, 1–< 2 ng/ml, and ≥ 2 ng/ml; GSs were classified as < 7, 7, 8, and > 8; and PSAdt was classified as < 6 months and ≥ 6 months. The detection rate of [^{68}Ga]PSMA PET/CT and BSs was defined as the ratio between the numbers of cases with a positive scan to the whole number of patients. Continuous variables were presented as mean ± SD, and categorical variables were presented as number and percentages. Wilcoxon rank and chi-squares tests were used to compare continuous and categorical variables, respectively. A multivariable logistic model was used to evaluate the relationship between the results of [^{68}Ga]PSMA PET/CT and BSs and demographic and clinical features. Receiver operating characteristic (ROC) curve analysis was used to determine the cut-off value, area under the curve (AUC), and 95 % confidence interval (CI). A p value < 0.05 was considered statistically significant. Data analysis was performed using SPSS (Windows software version 20, SPSS Inc.).

Results

Patients

We evaluated 415 patients with PC who had undergone [^{68}Ga]PSMA PET/CT. They ranged in age from 41–99, with a mean age of 68.25 ± 9.59. No adverse or detectable pharmacological effects were observed in patients following the injection of a radiotracer. PSA values were 0.002–5000 ng/ml with a mean of 67.96 ± 461.155 ng/ml. GSs ranged from 6–10 with a mean of 7.6 ± 1.13. Of the 415 patients evaluated, 255 (61.4 %) had radical prostatectomy, 216 had hormone therapy (ADT), 128 had radiotherapy, 10 had chemotherapy, and 29 had both chemotherapy and radiotherapy. Of the 415 patients, 45 (10.8 %) presented for staging, 194 (46.7 %) presented for recurrence, and 176 (42.5 %) presented for follow-up/monitoring; there were no statistical differences between mean PSA values and GSs in these groups (p > 0.05). The patient characteristics are shown in Table 1.

Detection Efficacy of [^{68}Ga]PSMA

Of the 415 patients, 344 (82.9 %) were shown to have at least one localized region classified as suspicious for PC. There were no significant statistical differences among the three groups. The detection efficacy of PET/CT was 89 % (40/45), 79 % (153/194), and 86 % (151/176) for the staging, BCR, and follow-up groups, respectively (p > 0.05).

We found a direct relationship between PSA values and the detection rate (p < 0.05) (Fig. 1). The detection efficacy of [^{68}Ga]PSMA PET/CT was 48.3 % (14/29) for a PSA value < 0.2 ng/ml; 52.6 % (20/38) for a PSA value ≥ 0.2–< 0.5 ng/ml; 74.4 % (29/39) for a PSA value ≥ 0.5–< 1 ng/ml; 79.6 % (43/54) for a PSA value ≥ 1–< 2 ng/ml; and 93.9 % for a PSA value ≥ 2 ng/ml (p < 0.05). In patients with a positive [^{68}Ga]PSMA PET/CT, the PSA values were significantly higher than in patients with a negative PET/CT (82.30 ± 508 ng/ml vs. 2.24 ± 5.23 ng/ml, p = 0.03).

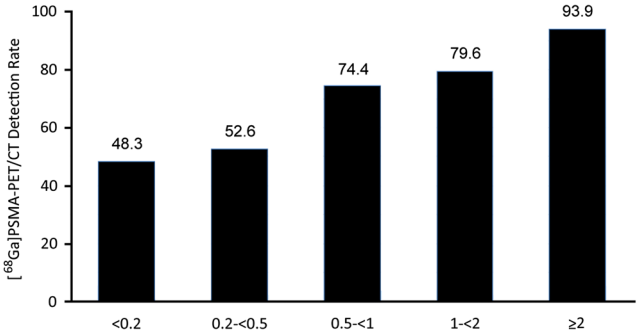

Fig. 1. Detection rate (%) of [^{68}Ga]PSMA in relation to PSA values (ng/ml).

The detection efficacy of [^{68}Ga]PSMA PET/CT was 68.3 % (28/41), 74.5 % (73/98), 93.9 % (46/49), and 91 % (61/67) for a GS of < 7, 7, 8, and > 8 respectively, indicating a significant association between a positive [^{68}Ga]PSMA PET/CT and the GS (p < 0.05) (Fig. 2). In addition, the mean GS was significantly higher for patients with a positive [^{68}Ga]PSMA PET/CT than for patients with a negative [^{68}Ga]PSMA PET/CT (7.73 ± 1.12 vs. 7.06 ± 0.98, p = 0.001).

There was a trend towards a higher detection rate in patients with radiotherapy/chemotherapy (87 % vs. 79.8 %) (p < 0.05). The detection rate of PET/CT was lower for patients with a history of RP (88.1 % vs. 79.6 %, p < 0.05). The detection rate of PET/CT was significantly higher for patients with a PSAdt of less than 6 months than for patients with a PSAdt of more than 6 months (86.4 % vs. 69.8 %, p < 0.05).

The PSA value was relatively lower in patients with a prior history of ADT (48.9 ± 363.98 vs. 61.37 ± 407.18 ng/ml) (p = 0.51) and was significantly lower in patients with a prior history of RP (46.37 ± 348.91 vs. 107.99 ± 617.30, p = 0.047). There was a significant direct relation-

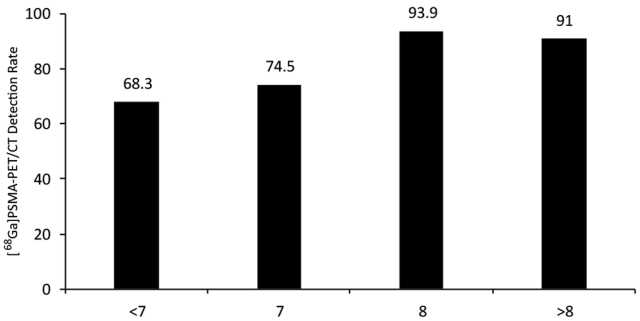

Fig. 2. [^{68}Ga]PSMA detection rate (%) in relation to Gleason score (GS).

ship between the number of lesions and PSA value (2.52 ± 3.73 for a PSA value < 0.2 ng/ml; 1.68 ± 3.00 for a PSA value ≥ 0.2–< 0.5 ng/ml; 2.28 ± 3.5 for a PSA value ≥ 0.5–< 1 ng/ml; 2.09 ± 2.81 for a PSA value ≥ 1–< 2 ng/ml; and 5.73 ± 4.59 for a PSA value ≥ 2 ng/ml, $p < 0.0001$) and GS (3.27 ± 4.50, 2.59 ± 3.57, 5.31 ± 4.57, 5.33 ± 4.64 for a GS of < 7, 7, 8, and > 8, respectively, $p < 0.0001$). The mean number of lesions in patients with a PSAdt of less than 6 months was significantly higher than that of patients with a PSAdt of more than 6 months (5.8 ± 4.74 vs. 2.21 ± 3.35, $p < 0.0001$) (Fig. 3). In addition, the mean number of lesions in patients with a prior history of RP was significantly lower than that in patients without such a history (4.93 ± 3.81 vs. 3.81 ± 4.33, $p = 0.022$).

In the evaluation of lesion detection results, 71 patients (17.1 %) had a normal [68Ga]PSMA PET/CT scan, 100 (24.1 %) showed only local uptake (prostate/prostate bed), and 244 (58.8) showed at least one extraprostatic lesion. In 230 (55 %) patients, at least one distant lesion was seen. Table 2 describes the lesion detection results. The number and location of lesions is given in Tables 3 and 4.

ROC Analysis

We analyzed the PSA value data to determine the cut-off value using the receiver operating characteristic (ROC) curve. An ideal cut-off value of > 1.16 was obtained using ROC analyses (AUC = 0.805; 95 % CI 0.749–0.861; $p < 0.0001$). The application of this cut-off is related to a specificity of 75 % and a sensitivity of 77 % (Fig. 4).

Comparison of [68Ga]PSMA PET/CT and BS

Of the 415 patients, 227 underwent a BS to determine bone involvement before PET/CT. PET/CT detected 258 suspicious regions, 255 of which were metastatic and 3 of which were equivocal (Table 3). BSs detected 223 suspicious regions, 203 of which were metastatic and 20 of which were equivocal. As seen in Table 3, PET/CT showed significantly better performance in detecting lesions in all regions except the skull and vertebrae compared with BSs ($p < 0.05$). BSs showed significantly more lesions in the skull than PET/CT ($p < 0.05$). The two types of scans showed relatively equivocal results for the vertebrae, although BSs detected 11 equivocal lesions.

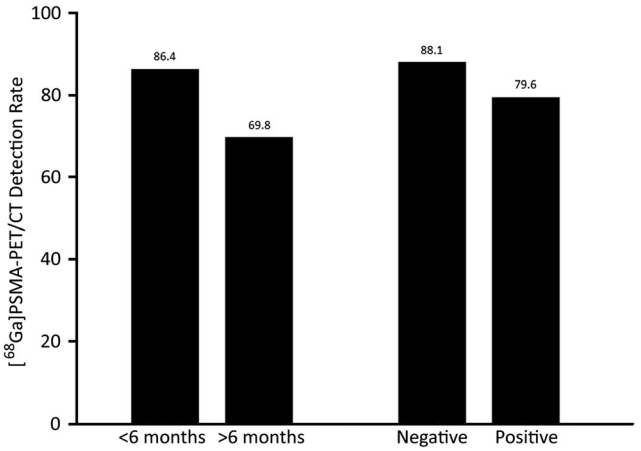

Fig. 3. Detection rate (%) of [68Ga]PSMA in relation to PSAdt and radical prostatectomy.

Table 2 Location of detected sites in [68Ga]PSMA PET/CT

Site	Number (%) of patients with suspicious site
Pelvic LNs	71 (17.1)
Local	19 (4.6)
Pelvic LNs + distant LNs	101 (24.3)
Local + pelvic LNs	19 (4.6)
Pelvic LNs + bone	14 (3.4)
Distant LNs	11 (2.7)
Bone	42 (10.1)
Local + bone	42 (10.1)
Distant LNs + bone	20 (4.8)
Local + pelvic LNs + distant LNs	7 (1.7)
Pelvic LNs + distant LNs + bone	12 (2.9)
Lung ± liver	3 (0.7)
Local + distant LNs	5 (1.2)
Local + pelvic LNs + distant LNs + bone	11 (2.7)
Local + pelvic LNs + bone	12 (2.9)
Bone + local + distant LNs	11 (2.7)
Normal	71 (17.1)

LN, lymph node

Discussion

In the last years, several studies evaluated the valuable role of [68Ga]PSMA PET-CT on management of PC patients around the world; however, there are only a few studies with limited number of patients on this topic in middle east population, thus we decided to perform this study with acceptable number of evaluated patients.

In PC patients, the early, localized and accurate detection of cancer-related involvement can impact and lead to changes in treatment decisions as local cancer is usually treated locally and metastatic cancer requires additional

Table 3 The number and location of detected legions in [68Ga]PSMA PET/CT and bone scan (BS)

	PET/CT number of lesions		BS number of lesions	
	Positive	Equivocal	Positive	Equivocal
Skull	10	0	14	0
Vertebrae	68	0	67	11
Ribs	50	0	35	1
Sternum	10	0	6	0
Clavicle	7	0	5	1
Pelvic	74	3	57	4
Upper limbs-scapula	18	0	6	3
Lower limbs	18	0	13	0
Total	255	3	203	20

Analysis was done in all cases whom had either 68Ga-PSMA PET/CT or bone scan

Table 4 Classification of the patients based on number of detected lesions on [68Ga]PSMA PET/CT

Number of lesions	Number (%) of patients with suspicious site
Normal	71 (17.1)
1	118 (28.4)
2	39 (9.4)
3	32 (7.7)
4	23 (5.5)
5	9 (2.2)
6	3 (0.7)
7	1 (0.2)
8	1 (0.2)
> 8	118 (28.4)

systematic therapy such as chemotherapy or radionuclide therapy. Traditionally, The European Association of Urology guidelines for the detection and evaluation of any local or metastatic disease have suggested the use of CT, MRI, and BSs (if PSA levels are > 10 ng/ml) [2]. However, these modalities have low specificity and give limited information about soft tissue metastasis [17]. For example, although MRI plays an increasing role in management of PC patients, in several studies, the superiority of 68Ga-PSMA PET-CT in PC patients has been proved [18–20]. Sawicki et al. [18] compared detection rate of whole body MRI and [68Ga]PSMA PET-CT on BCR patients after prostatectomy. They reported that [68Ga]PSMA PET-CT significantly out-performed whole body MRI in the detection of BCR in PC patients.

In patients with PSA values less than 7 ng/ml, BSs are reported to have low efficacy and CT has shown low sensitivity in detecting local and LN involvement [21]. Because the conventional imaging procedures, including

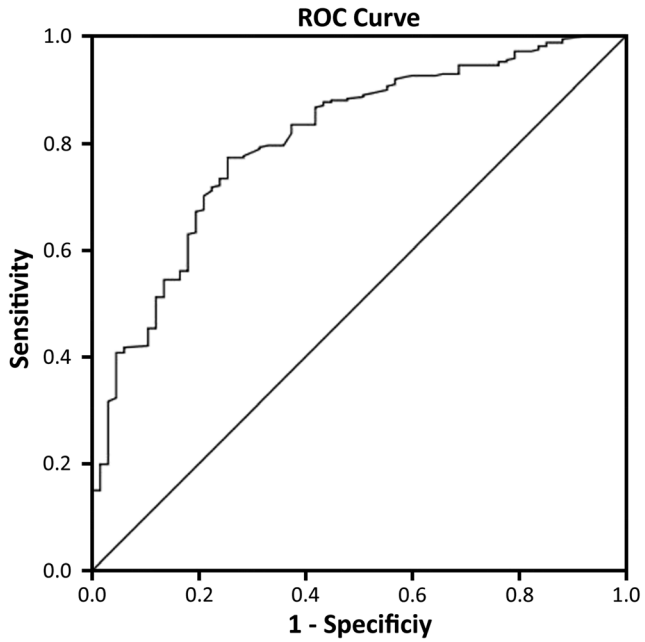

Fig. 4. ROC curve for PSA value (cut-off value of > 1.16 ng/ml, AUC = 0.805; 95 % CI 0.749–0.861; $p < 0.0001$).

MRI, CT, BSs, and other forms of PET have low sensitivity for the early detection of involved regions [11, 22], the aim of this study was to assess the detection efficacy of [68Ga]PSMA PET/CT in PC patients and to compare that with the efficacy of traditional BSs in detecting bone involvement. Several studies have shown [68Ga]PSMA to have high diagnostic efficacy [5, 9, 12, 13, 22].

The early detection of PC-related involvement is both very important and effective in determining the best treatment plan. In our study, we evaluated [68Ga]PSMA PET/CT in 415 PC patients, and overall [68Ga]PSMA PET/CT showed a high detection rate of 82.9 % (344/415), 88.9 % (40/45), 78.9 % (153/194), and 85.8 % (151/176) in staging, BCR, and follow-up patients, respectively. Our results correlate with those of previous studies in terms of the overall detection efficacy of [68Ga]PSMA PET/CT [5, 19]. The efficacy in our study ranged from 82.2–90.7 %, thus proving the capability of this modality to detect PC-related involvement. Hamed et al. [5] reported an overall detection rate of 87.8 %, which was relatively higher than the current study. However, in the largest study that included 1007 patients, Afshar-Oromieh et al. [22] obtained a detection rate of 79.5 %, which was relatively lower than our study. There was no significant difference in detection rate within three groups; therefore, it could be concluded that 68Ga-PSMA PET-CT is helpful for management of all PC patients.

According to our results, the detection rate of [68Ga]PSMA PET/CT increased with increasing PSA values; it was 48.3 % (14/29) for a PSA value < 0.2 ng/ml; 52.6 % (20/38) for a PSA value ≥ 0.2–< 0.5 ng/ml; 74.4 % (29/39) for a PSA value ≥ 0.5–< 1 ng/ml; 79.6 % (43/54) for a PSA value ≥ 1–< 2 ng/ml; and 93.9 % for a PSA value ≥ 2 ng/ml. These findings correlate with those of previous studies [5, 11]. Our study revealed a direct relationship between GS and the detection efficacy of PET/CT. The detection efficacy of PET/CT was 68.3 % (28/41), 74.5 % (73/98), 93.9 % (46/49), and 91 % (61/67) for GSs of < 7, 7, 8, and > 8, respectively. This is in agreement with Eiber et al. [10], who reported a significant direct relationship between higher GSs and a positive [68Ga]PSMA PET/CT. However, this contrasts with the results of Hamed et al. [5] and Afshar-Oromieh et al. [22], who found no significant relationship between GSs and a positive [68Ga]PSMA PET/CT. Overall, it can be concluded that increases in PSA value and GSs indicate the progression of the disease. Therefore, due to the high detection rate of [68Ga]PSMA PET/CT, even with low GSs and PSA values, it can be used as a standard modality to evaluate PC patients.

In our study, the detection rate was significantly higher in patients with a PSAdt of less than 6 months than in patients with a PSAdt of more than 6 months. Our results correlate with those of Ceci et al. [23], who reported positive PSMA PET in 93 % of patients with a PSAdt of < 6.5 months compared with 34.8 % in patients with a PSAdt of > 6.5 months. However, other studies have found no significant relationship between PSAdt and pathological [68Ga]PSMA PET/CT [9, 10, 22].

Our results indicate that 100 patients (24.1 %) showed only local uptake (prostate/prostate bed) and 244 (58.8) showed at least one extraprostatic lesion, which correlates with the findings of Einspieler et al. [24] (59.8 %) and is almost in line with the results of Hamed et al. [5] (69.1 %). Therefore, because [^{68}Ga]PSMA can detect extraprostatic metastases early and because the management of patients strongly depends on the site and extent of involvement, it could be a valuable and important modality in managing PC patients in helping to determine appropriate therapy and in avoiding futile treatment [5].

In our study, an ideal cut-off value of > 1.16 ng/ml for PSA value was obtained to detect PC-related involvement which is higher than the 0.67 ng/ml obtained by Sanli et al. [25]. In our study, 20 % (9/45) of staging patients had no or minimal uptake in the prostate gland, despite proven PC. This is relatively equivocal equivalent to the results of a previous study [26]. This result might be due to the neuroendocrine differentiation of PC, which may be the main cause of false negatives in PC diagnosis and which limits the detection efficacy of [^{68}Ga]PSMA [27].

In comparing [^{68}Ga]PSMA PET/CT and BSs, the superiority of PET/CT in all regions except the skull and vertebrae was revealed. Our results correlate with those of Pyka et al. [28], who concluded [^{68}Ga]PSMA PET is better than BSs in detecting bone lesions in PC patients. Therefore, it can be concluded that if [^{68}Ga]PSMA has been obtained, generally a BS is not needed and it can become a "one-stop-shop" in PC evaluation. In addition, the number of equivocal lesions appearing on BSs was significantly higher compared with [^{68}Ga]PSMA PET/CT, which can result in limiting additional studies to clarify unclear BS findings. A lower number of detected lesions in the skull in [^{68}Ga]PSMA PET/CT compared with BSs relates to the area covered by PET, which does not routinely include the cranium.

It should be mentioned that, although PSA cut-off is a worthwhile item of PSMA PET/CT indication, patients with low PSA values should be imaged with PSMA PET/CT because at that stage of disease changes in management are more drastic.

The main drawbacks of this study include its retrospective design, single-center site, and the inability to generalize our values. In our study, the time interval between scans and therapy was not considered. In addition, our patients had different types of therapy (including focal and systematic) and wide variation in PSA values. It must also be mentioned that the classification of some cases into the staging, recurrence, and follow-up/monitoring groups was challenging. Cost-effectiveness analysis was not conducted. However, although [^{68}Ga]PSMA PET/CT is relatively expensive compared with other imaging modalities, it can detect any prostate-related involvement and therefore can have a positive impact on patient management and can guide clinicians in making appropriate treatment plans, thus reducing patient costs.

Conclusion

This study demonstrates the promising detection rate of [^{68}Ga]PSMA PET/CT for PC patients, even those with low PSA values. It also shows the superiority of [^{68}Ga]PSMA PET/CT in detecting bone involvement compared with BSs. Because PSMA is heavily expressed in PC, even in the early stages, it can be used as a standard tool in PC work ups.

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Compliance with Ethical Standards

Conflict of Interest

The authors declare that they have no conflict of interest.

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent

For this type of study, formal consent is not required.

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