EVALUATION OF HYBRID PET/CT IMAGING WITH THE ^{68}GA-LABELLED PSMA LIGAND IN PATIENTS WITH PROSTATE CANCER AND BIOCHEMICAL PROGRESSION IN THE LOW-RANGE VALUES OF PSA AFTER RADICAL PROSTATECTOMY

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ABSTRACT

INTRODUCTION: Currently ^{68}Ga-PSMA PET/CT is making a significant shift in the diagnosis, staging and re-staging of prostate cancer (PC) patients. Many questions have been raised concerning the indications and the sensitivity of the method. Most of them are related to the PSA values in biochemical progression, specifically in the low PSA values of up to 2.00 ng/mL.

AIM: The aim of this study was to analyze the influence of PSA values in biochemical progression on ^{68}Ga-PSMA PET/CT sensitivity, detection rate and the association with regional or metastatic lesions incidence in patients after radical prostatectomy (RP) with a focus on the impact of the lower ranges of the PSA values.

MATERIAL AND METHODS: We performed a retrospective analysis in 144 consecutive patients with radical prostatectomy (RP) who underwent ^{68}Ga-PSMA PET/CT from July 2019 to February 2020. The patients were divided into six groups according to the PSA value: 1) ≤0.040 ng/mL; 2) 0.041–0.160 ng/mL; 3) 0.161–0.500 ng/mL; 4) 0.501–1.0 ng/mL; 5) 1.001–2.00 ng/mL; 6) >2.00 ng/mL.

RESULTS AND DISCUSSION: The mean age of the patients was 67.3 (7) years and the mean PSA level was 11.0 (52.28) ng/mL. A total of 62 patients (43.1%) showed at least one positive lesion. ^{68}Ga-PSMA PET/CT detection rate varied into the different groups between 12.0% and 94.0%. There was a significant relationship between the PSA level and the ability of ^{68}Ga-PSMA PET/CT to detect the lesions. Local recurrence was determined in patients with higher PSA values. Regional metastatic lymph nodes incidence in the 6 groups was between 17.0% and 50.0%. Bone metastases were most commonly diagnosed in patients with low PSA levels. Distant lymph nodes involvement in the studied groups ranged between 0.0% and 75.0%. Distant metastases were detected most commonly in patients with low levels of PSA. The PSA-based assessment of the overall sensitivity and specificity of ^{68}Ga-PSMA PET/CT was 58.0% and 87.0%, respectively. Sensitivity of 15.0% was found in the group with the lowest mean PSA levels.

CONCLUSION: Tumor detection rate is positively associated with PSA levels. Biochemical progression after RP is more commonly related to distant metastases, specifically bone metastases in patients with lower levels of PSA.

Keywords: *68Ga-PSMA PET/CT, prostate cancer, PSA levels, biochemical progression*

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INTRODUCTION

Prostate cancer (PC) is one of the most common malignant diseases in males worldwide (1). Radical prostatectomy (RP) and radiation therapy are well known treatments of localized PC (2). After RP, concentrations of PSA typically decrease below the detection threshold (3). However, post-prostatectomy biochemical failure (namely biochemical persistence and biochemical recurrence (BCR)) is a considerable issue; with 20% to 30% males encountering PSA elevation after RP (4,5). Biochemical recurrence is defined as an elevation in PSA values to above 0.2 μg/L after radical surgery (3). The accurate and early identification of the PC relapse is of paramount importance. Conventional imaging techniques used to diagnose PC (MRI, bone scan, CT, and choline-PET/CT) exhibit considerable limitations. They are all commonly negative at low PSA levels, with most recommendations not suggesting any of these methods at PSA<2 ng/mL (6). These restrictions have contributed to the development of imaging methods with better utility, especially at an earlier stage of the PC, presented by lower PSA values. PSMA is a transmembrane glycoprotein with significantly increased expression in PC cells, showing a major extracellular domain which can be targeted by ligands for imaging and therapy reasons (7,8). PSMA expression is commonly robust in highly aggressive tumor, metastatic PC and relapse, while being slightly or not expressed in uninvolved prostate tissue (9). Its transmembrane localization and incursion after ligand connection make it a beneficial and optimal target for imaging. The first radiopharmaceutical presented to the market, labelled with ^{68}Ga (PSMA-11 or PSMA-HBED-CC), very fast became the primary radiotracer for PSMA- PET imaging (10). ^{68}Ga-PSMA PET/CT have been confirmed to ensure a surpassing diagnostic performance over other radiopharmaceuticals and imaging techniques in biochemical failure of PC, especially at low PSA values (6, 11,12). A lot of issues arose regarding the indications and the sensitivity of the modality. Most of them are relevant to the PSA levels in biochemical progression, and particularly to the low PSA- up to 2.00 ng/mL. The important question whether the rise in the PSA levels is indicative of local recurrent PC or metastatic disease is yet to be answered.

AIM

The purpose of this study was to assay the impact of PSA level in biochemical progression on ^{68}Ga-PSMA PET/CT detection rate, sensitivity and the relation with regional or distant metastatic involvement in males following RP in the low ranges of PSA levels.

MATERIALS AND METHODS

Patients

This single-center research was based on data extracted from the electronic medical records of males with PC referred for ^{68}Ga-PSMA PET/CT between July 2019 and February 2020. We accomplished a retrospective assessment of data from 144 consecutive males with RP as a primary therapy. The inclusion criteria were biochemical progression in two consecutive PSA measurements <0.2 ng/mL and BCR in patients after RP. All 70 patients with two consecutive PSA measurements <0.2 ng/mL were included in the study, despite the fact that they did not belong to the BCR definition. We defined them as a special and clinically important cohort with biochemical progression in the low range values of PSA. All 74 patients with BCR were also included. Biochemical recurrence was defined as an increase of serum PSA levels after first treatment of at least 0.2 ng/mL in two consecutive tests.

The males were divided into six groups pursuant to the PSA level: group 1) PSA≤0.040 ng/mL; group 2) PSA 0.041–0.160 ng/mL; group 3) PSA 0.161–0.500 ng/mL; group 4) with PSA 0.501–1.0 ng/mL; group 5) PSA 1.001–2.00 ng/mL; and 6) PSA>2.00 ng/mL. All of the listed above results—biochemical values and previous history, were found from patients' data. All males gave a written informed consent to PET imaging.

Radiopharmaceutical

^{68}Ga-PSMA was produced at the nuclear pharmacy of the Nuclear Medicine Clinic in St. Marina University Hospital, Varna, Bulgaria. ^{68}Ge/^{68}Ga generator iThemba LABS (50 mCi) Automated Synthesis–SCINTOMICS GRP 4V was used to derive the positron emitting ^{68}Ga from an origin of decaying Ge-68. The quality inspection was completed by HPLC system, UV and gamma detector for TLC (thin-layer chromatography). ^{68}Ga-PSMA-HBED-

CC (^{68}Ga-PSMA-11) was synthesized employing a procedure identical to that represented by Eder et al. (13), transferred to an automated cassette-established synthesis module [ABX Advanced Biochemical Compounds], founded on acetone-free cation exchange post-processing.

^{68}Ga-PSMA-11 PET/CT Image Acquisition

All males' ^{68}Ga-PSMA PET/CT scans were examined at St. Marina University Hospital, Varna. ^{68}Ga-PSMA PET/CT imaging was conducted in accordance with current guidelines (14). Images were obtained on Philips Gemini TF PET/CT hybrid technique (2009) following intravenous bolus administration of ^{68}Ga-PSMA-11–ligand compound at a mean dose of 2 MBq (0.054 mCi) per kg body weight. Males received 20 mg of furosemide at the time of tracer application if there was no contraindication in order to reduce bladder activity. The males were enquired to void their bladder directly prior to the PET/CT imaging. The PSMA PET/CT was validated for appropriate quantification and quality of the images obtained. Daily quality inspection approaches were completed. An attenuation-corrected whole-body scan in 3D mode (emission duration 3 min per bed position with an axial field of view of 18 cm per bed position) beginning 60 min following tracer administration was obtained. A low-dose CT scan (120 keV, 50–130 mAs) was performed immediately after the PET imaging (for attenuation correction). Images were additionally altered for random and scatter concurrence events.

^{68}Ga-PSMA-11 PET/CT Image Interpretation

All available PSMA PET/CT images were assessed and interpreted through visual inspection by proficient nuclear medicine physicians pursuant to procedure guidelines and current approaches (14,15). Any area of focal tracer accumulation higher than the adjacent surround level without correlation with physiologic PSMA expression or well-known pitfalls (16) was determined indicative of cancer. The physicians established each location of non-physiological PSMA expression into 1 of 3 types: 1) negative for PC, 2) equivocal—lesions that cannot be categorical characterized as benign or cancerous, 3) positive—lesions defined as PC (14). Consequently, assessment was accomplished founded on a patient level. In the evaluation of detection rates, equivocal results were regarded positive.

The following regions were systematically analyzed for recurrence and PSMA-positive lesions were defined as: local relapse (prostate bed recurrence/seminal vesicle remnants); regional metastatic lymph nodes (LN) (beneath the bifurcation of the common iliac arteries) involve pelvic LN: obturator, external and internal iliac, pararectal, sacral; distant metastatic LN involve the subsequent: common iliac, paraaortic, retroperitoneal, deep and superficial inguinal, scalene, cervical, chest and other); distant metastases as a whole include: distant LN, bone and visceral lesions. Differentiation between inflammatory and malignant LN (reactive and/or granuloma) was defined on measure of tracer accumulation (commonly mild and low PSMA uptake for inflammatory process), and localization (usually distant LN, such as axillary, hilar stations or inguinal for inflammatory nodes). When contradictory reports were encountered, they were considered and resolved by the reviewing physicians.

Statistical Analysis

Descriptive statistical analyses were performed and quantitative data were presented as means and standard deviation or median and IQR and qualitative variables as proportions. Overall detection rate of ^{68}Ga-PSMA PET/CT and the positivity (incidence) rate of local recurrence, regional metastatic LN, bone metastases and distant metastases were estimated for the whole sample and separately for the 6 studied groups. PSA-based analysis of sensitivity and specificity of ^{68}Ga-PSMA PET/CT were estimated for the whole cohort as well as in the different PSA groups. Continuous variables were compared between two groups using the two-sample t test and among three and more groups using one-way analysis of variance. The chi-squared test was used for testing association between two categorical variables. Level of significance alpha of 0.05 was used. Statistical analyses were performed using IBM SPSS ver. 19 (IBM Corporation, United States).

RESULTS AND DISCUSSION

The The mean age of the males was 67.3 (7) years. Patients had a median level of PSA 0.233 ng/mL, (0.02–497) ng/mL (Table 1). More than half of the males with previous RP showed PSA levels ≤0.5

ng/mL (Fig. 1). The mean uptake period was 60 (7) min. The main parameters were the association of positive ^{68}Ga-PSMA PET/CT scans with PSA levels in biochemical progression in the studied groups, as well as the association with regional or metastatic sites of PC lesions.

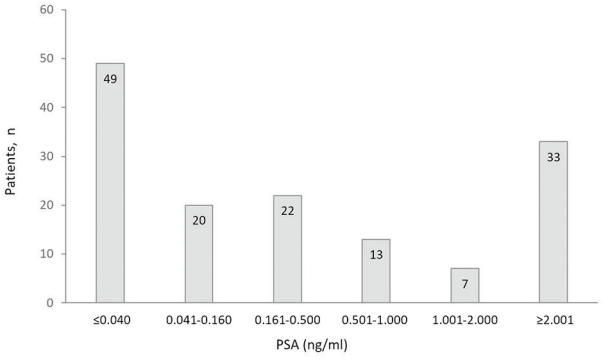


Fig. 1. Distribution of the patients according to the PSA values (PSA groups)

Table 1. Characteristics of patients, regions and frequency of recurrent PC detected with ^{68}Ga-PSMA-ligand PET/CT

Characteristics	Parameters
Number of patients	144
Age (y) (144)	
- Median	68
- Range	47-87
Mean ± SD	67.3 ±7
PSA (ng/ml) (144)	
- Median	0.233
- Range	0.02-497
Mean ± SD	11.03±52.28
Total/PET/CT positive patients N(%)	62 (43.1)
Tumor location N (%)	
Local recurrence	19 (13.2)
Lymph node metastases	
- local/regional	15 (10.4)
- distant	18 (12.5)
Bone metastases	39 (27.1)
Distant metastases as a whole	47 (32.6)

PSA (prostate-specific antigen); SD (standard deviation); N (number of patients)

Table 2. Location of PC recurrence in relation to PSA value

PSA-groups (PSA ng/ml)	Local recurrence, n(%)	Regional metastatic LN, n(%)	Distant metastatic LN, n(%)	Bone metastases, n(%)	Distant metastases as a whole, n(%)	Positivity rate, n(%)
Group 1 (≤0.040)	0 (0.0)	1 (17.0)	2 (33.3)	5 (83.3)	6 (100.0)	6 (12.0)
Group 2 (0.041- 0.160)	0 (0.0)	0 (0.0)	1 (33.3)	3 (100.0)	3 (100.0)	3 (15.8)
Group 3 (0.161-0.500)	3 (27.3)	3 (27.3)	0 (0.0)	8 (72.7)	8 (72.7)	11 (50.0)
Group 4 (0.501-1.000)	3 (42.9)	1 (14.3)	3 (42.9)	2 (28.6)	4 (57.1)	7 (53.8)
Group 5 (1.001-2.000)	1 (25.0)	2 (50.0)	3 (75.0)	1 (25.0)	3 (75.0)	4 (57.1)
Group 6 (≥2.001)	12 (38.7)	8 (25.8)	9 (29.0)	20 (64.5)	23 (74.2)	31 (94.0)
p value	p <0.001	p=0.012	p =0.001	p< 0.001	p<0.001	p<0.001

PSA (prostate-specific antigen); n (number of patients)

Table 3. Performance of ^{68}Ga-PSMA PET/CT according to PSA value

PSA-groups (PSA ng/ml)	N (%)	Detection rate, n (%)	Sensitivity (%)
	144.	62 (43.1)	58.0
Group 1 (≤0.040)	50 (34.7)	6 (12.0)	-
Group 2 (0.041- 0.160)	19 (13.2)	3 (15.8)	15.0
Group 3 (0.161-0.500)	22 (15.3)	11 (50.0)	50.0
Group 4 (0.501-1.000)	13 (9.0)	7 (53.8)	53.0
Group 5 (1.001-2.000)	7 (4.9)	4 (57.1)	57.0
Group 6 (≥2.001)	33 (22.9)	31 (94.0)	93.0

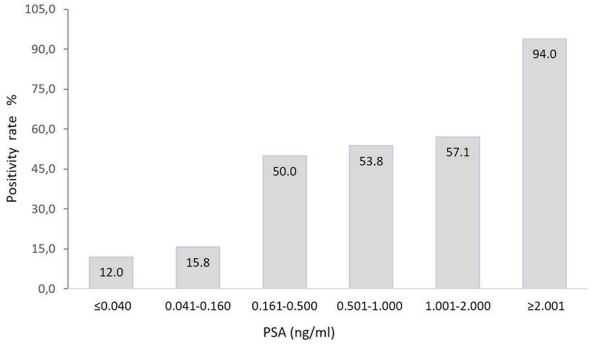


Fig. 2. Detection rate according to the PSA value (p<0.001)

Detection Efficacy and PSA Values

Sixty-two (43.1%) of all 144 males in the cohort presented at least one positive lesion or suspect for malignancy, as demonstrated by ^{68}Ga-PSMA PET/CT. ^{68}Ga-PSMA PET/CT was rated as negative in 82 males.

Local relapse was evident in 19 (30.0%) of the patients with a positive ^{68}Ga-PSMA-11 PET/CT. Fifteen (24.0%) of the patients with a positive PET/CT showed metastases at regional LN and 18 (29.0%) showed metastases at distant LN. Bone metastases were discovered in 39 (62.0%) of the patients with a positive PET/CT. Distant metastases as a whole were found in 47 (75.0%) of the positive patients (Table 1).

The detection rate of ^{68}Ga-PSMA PET/CT in the different groups increased with the increase of the PSA levels. There was a significant relationship between the PSA level and the ability of ^{68}Ga-PSMA PET/CT to the lesions (Table 2, 3; Fig. 2).

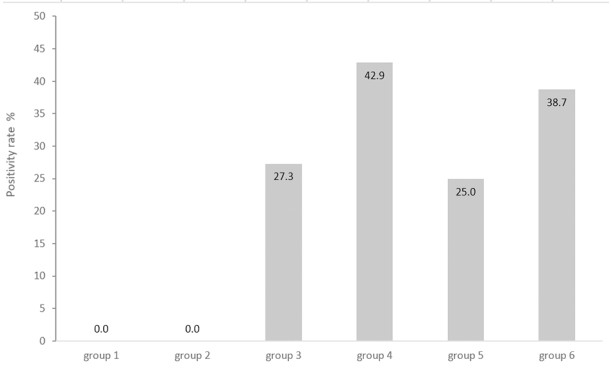


Fig. 3. Distribution of the local recurrence in the groups (p<0.001)

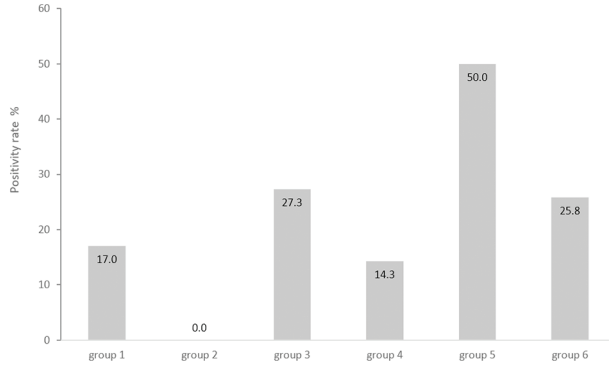


Fig. 4. Distribution of the regional metastatic LN in the groups (p=0.012)

Local relapse was established in males with higher PSA values (>0.16 ng/mL). The results are presented in Supplementary Table 2, Fig.3.

Regional metastatic lymph nodes incidence in the 6 groups was between 17.0% and 50.0%. The results are shown in Table 2, Fig. 4.

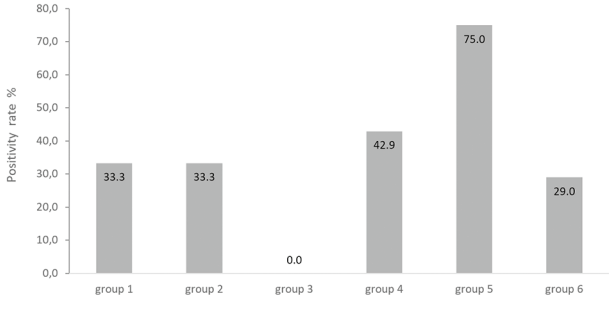


Fig. 5. Distribution of the distant metastatic LN in the groups (p=0.001)

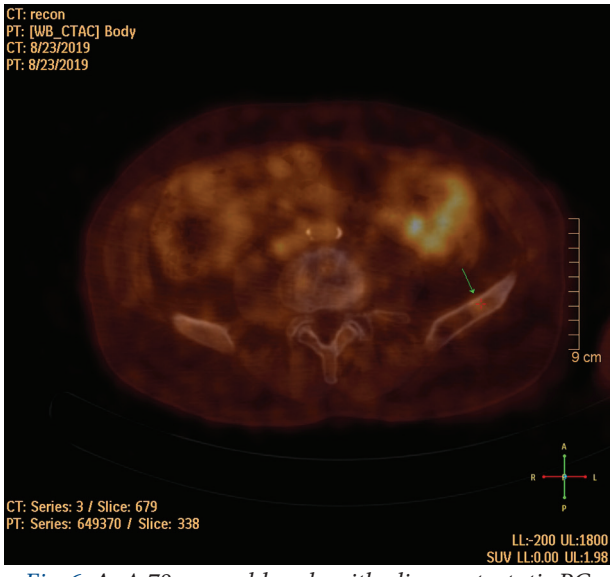


Fig. 6. ***A****. A 78-year-old male with oligo-metastatic PC after radical prostatectomy (RP) and salvage radiotherapy (SRT) for BCR, currently on androgen-deprivation therapy (ADT) with actual PSA level of 0.010 ng/mL, Gleason score 6 (3+3). The patient presented with bone metastases on ^{68}Ga-PSMA PET/CT study. ^{68}Ga-PSMA PET/CT-fused image demonstrating mildly sclerotic lesion with moderately increased PSMA activity in the wing of the left iliac bone.*

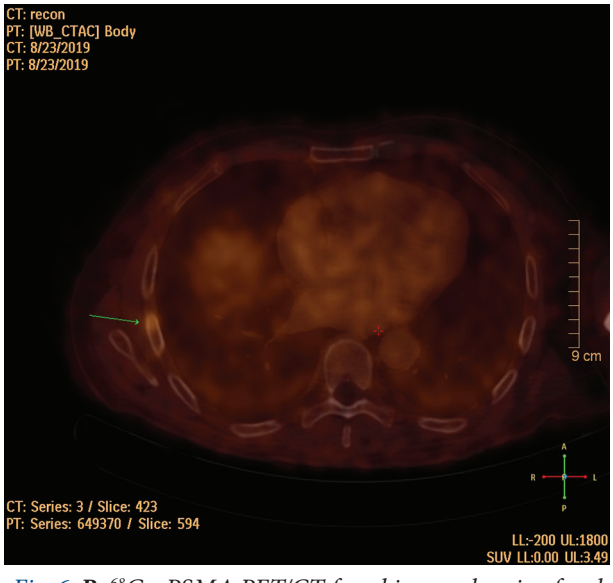


Fig. 6. ***B.*** *^{68}Ga-PSMA PET/CT-fused image showing focal increased tracer uptake in the right sixth rib with no corresponding lesions or abnormalities on CT scan.*

Distant metastases, which occurred after RP, included: involvement of a distant LN and organs, typically bone or LN, by PC. Distant LN involvement in the studied groups ranged between 0.0% and 75.0% (Table 2, Fig. 5).

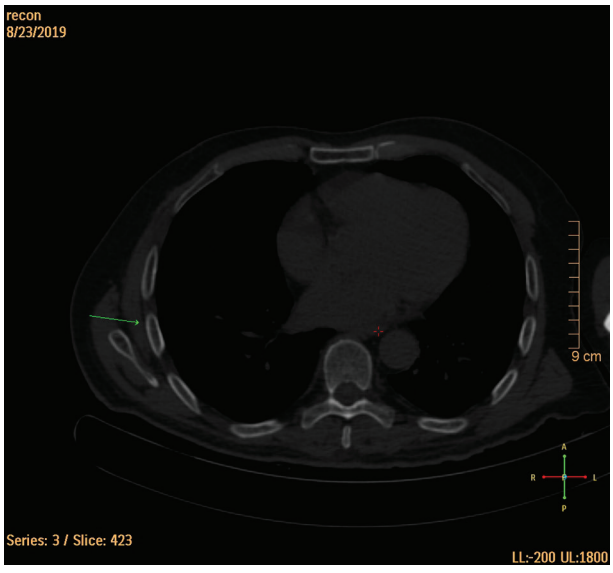


Fig. 6. ***C.*** *CT scan with no corresponding lesions.*

Bone involvement was most predominantly diagnosed in males with low PSA values, comprising five males in the first group (Figure 6 A-F; Fig. 7 A, B). The results are shown in Table 2, Fig. 8.

Distant metastatic disease as a whole was detected most typically in males with low values of PSA (Table 2, Fig. 9). The graph in supplementary Fig.10 shows the relationship between location of PC recurrence and PSA values in the six groups.

A PSA-stratified evaluation of overall specificity and sensitivity established levels of 87.0% and 58.0% accordingly.

We calculated the sensitivity of PSMA-PET into the studied groups. A sensitivity of only 15.0% was established at lower PSA values (group 2). In the other groups, the test performed better. The results are presented in Supplementary Table 3, Fig. 11.

In addition, overall, 71 males without prostatectomy underwent PSMA-PET in our Nuclear Medicine Department during the same period and higher PSA levels were more commonly found: 57 (80.3%) of the patients had values higher than 2.0 ng/mL.

DISCUSSION

PSMA is characterized as an excellent biological target for exceptional quality PET/CT examination of PC. ^{68}Ga-PSMA PET/CT is an better method,

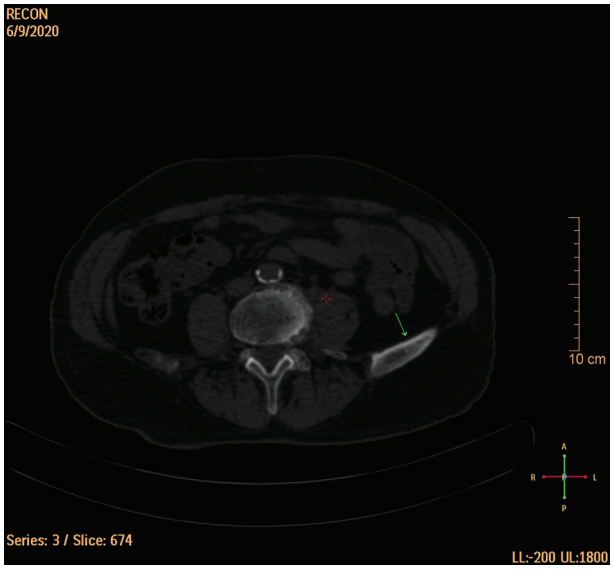


Fig. 6. ***D.*** *The follow-up low-dose CT image 12 months later showed sclerotic lesions of the left iliac bone with no significant change.*

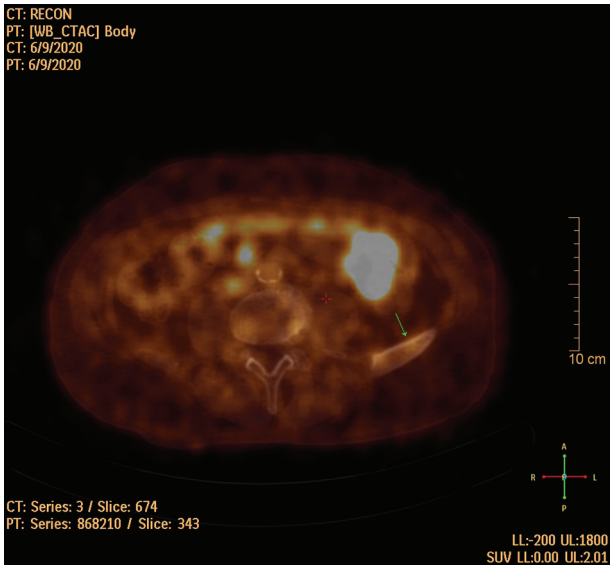


Fig. 6. ***E.*** *The follow-up ^{68}Ga-PSMA PET/CT (12 months later) demonstrated increased PSMA activity in the wing of the left iliac bone with no significant change.*

compared to conventional imaging, for determining locations of PC BCR at low PSA levels (17,18) with quite high detection rates at low PSA values less than 0.5 ng/mL (varying from 11.1% to 75.0%), thus permitting the choice of the best therapeutic strategy as early as possible (12). ^{68}Ga-PSMA PET/CT is highly specific (6) and sensitive for diagnosing regional as well as distant metastatic disease (18,19). The utilization of PSMA-PET disclosed desirable specificity and

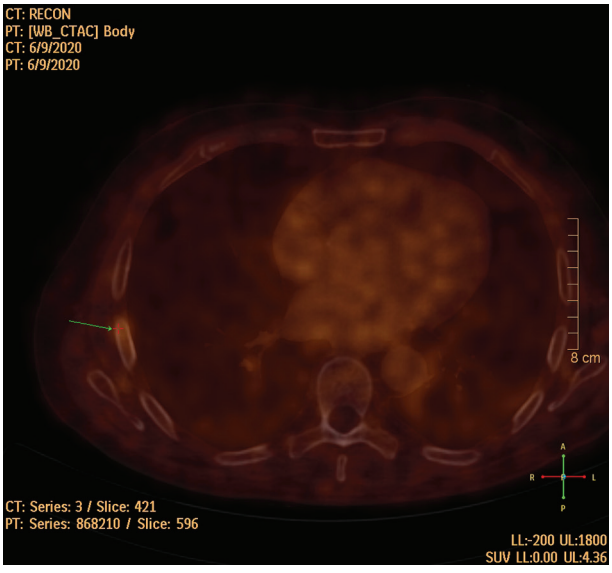


Fig. 6. ***F.*** *The follow-up ^{68}Ga-PSMA PET/CT-fused image showed increased tracer uptake in the right sixth rib with no significant change. The follow-up ^{68}Ga-PSMA PET/CT examination was considered as stable disease (SD).*

sensitivity performance in comparison to the fluciclovine or choline PET/CT imaging modalities (12).

PSMA-PET shows a superior detection rate in the lower diapason of PSA values in the course of PC relapse versus fluciclovine or choline PET/CT (6,17,18). In previous research, ^{68}Ga-PSMA PET/CT established malignant lesions in 44% of males with negative choline-PET results (6). Furthermore, this technique provided significant changes in the therapeutic management of 28.6–87.1% of patients (12). The potential to exactly confine the site of PC relapse is of great importance for referring males to optimal "imaging-guided" treatment approach (i.e., metastases-directed therapy, salvage radiation therapy, androgen deprivation therapy (ADT) or combination treatment approaches) (20,21).

Biochemical recurrence for PC after RP is a great clinical issue, and consequently, imaging modalities for early revelation and location of relapse are determinant. In our study, the method was capable of discovering a PC relapse in 10 males with PSA value below 0.2 ng/mL (of 62 males with identified lesions) (16.1%). The recurrence of PC, determined by PSMA-PET, in our research was 43.1% of all males. This was vastly lower than shown in previous studies data, in which detection rates of 53.3%; 62.0% to 85.5% were reported for restaging PSMA-PET after

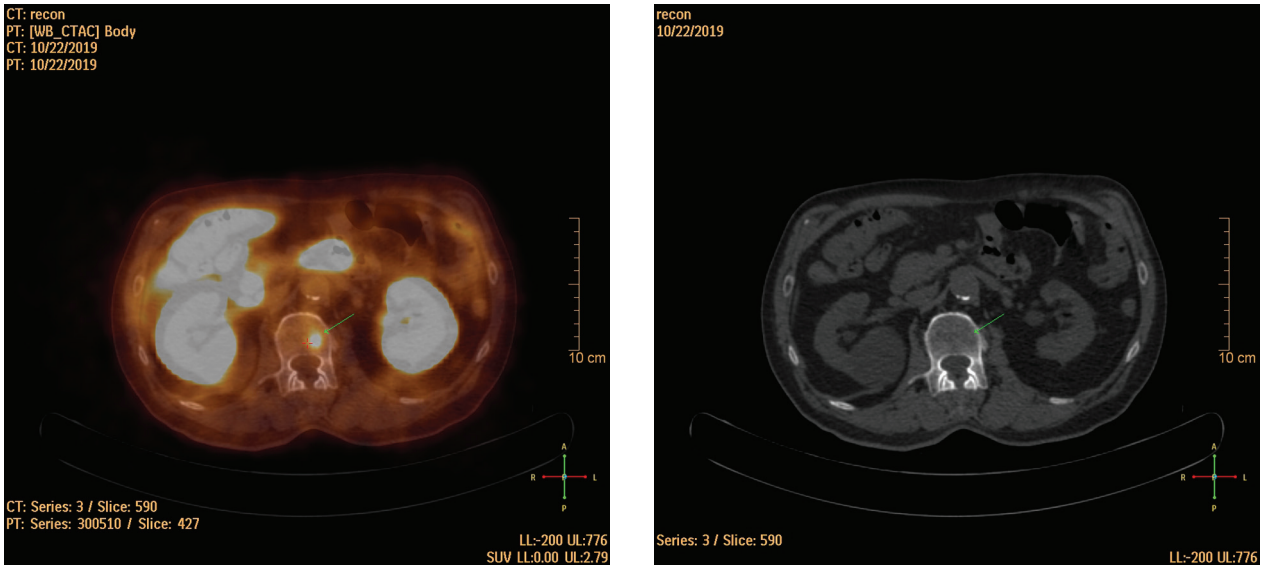


Fig. 7. ***A.*** *A case of 74 year-old male diagnosed with oligo-metastatic disease after RP with actual PSA level of 0.035 ng/mL; Gleason score 7 (4+3). ^{68}Ga-PSMA PET/CT-fused image revealed focal intense PSMA uptake of the L1 vertebral body, with no corresponding lesions or abnormalities on CT scan and was considered as bone marrow metastatic involvement.*

B. *No corresponding cortical lesion at low-dose CT image.*

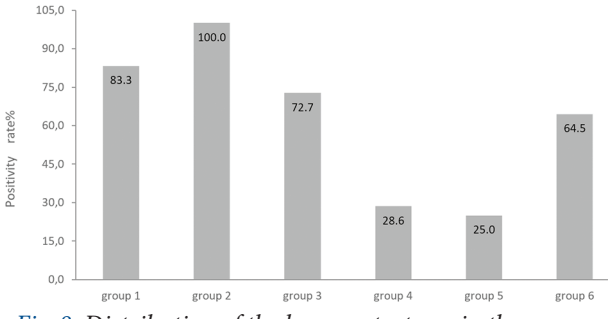


Fig. 8. Distribution of the bone metastases in the groups (p<0.001)

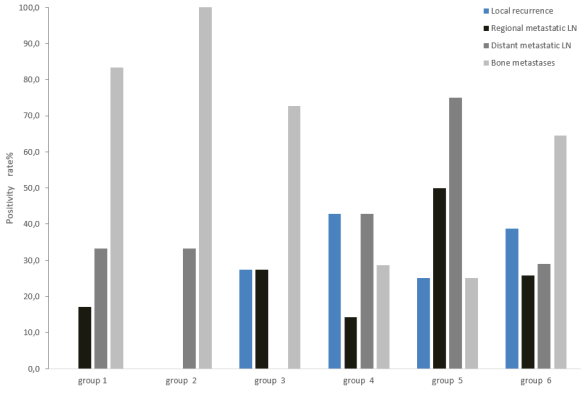


Fig. 10. The relationship between PSA levels and location of PC recurrence

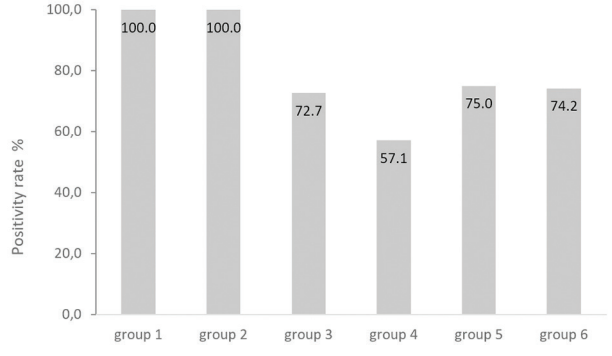


Fig. 9. Distribution of the distant metastases as a whole in the groups (p<0.001)

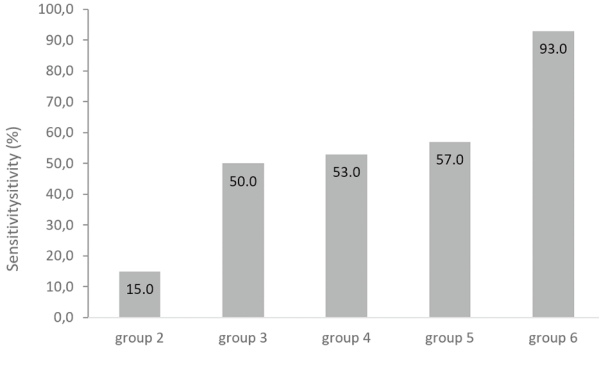


Fig. 11. A PSA-based analysis of sensitivity in the different groups

RP (22,23,24). The low overall detection rate may be interpreted by the low PSA levels in the majority of males (90 of 144 patients had PSA < 0.5 ng/mL during the PSMA-PET scanning). Our data presented a detection rate of 50.0% in males with PSA value (>0.16–0.50 ng/mL), corresponding to the detection rate shown by previous researches (19,25). Afshar-Oromieh et al. (19) presented a detection rate of 46.0% in patients with PSA levels ≤0.5 ng/mL. The research by Ceci et al. (25) revealed a detection rate of 48.0% for males with PSA values of 0.83 ng/mL or less. Farolfi et al. (10) presented 34.4% overall detection rate in males with PSA≤0.5 ng/mL. These latest data were considerably lower than the present findings. These latter results were considerably lower than the present findings. Our data presented a detection rates of 53.8%, 57.1%, and 94.0% for group 4, group 5, and group 6, respectively. There was a significant relationship between the PSA value and the capability of ^{68}Ga-PSMA PET/CT to detect the relapse of PC ($p<0.001$). These results (for males with PSA value higher than 0.5 ng/mL) support the data reported in previous recent study (26).

The population we studied was stratified into six groups according to the PSA value, as described above. Bone metastases, as well as distant metastatic disease as a whole, were the most common finding in males with low PSA values (these patients had high-risk PC). Results in literature suggest metastatic incidence in higher values of PSA (27, 28). These results might be explained with more aggressive recurrent tumors and altered lymphatic drainage after total pelvic lymphadenectomy. Our results showed that biochemical progression after RP was more typically presented with distant metastatic involvement, especially bone metastatic lesions in males with lower PSA values, even less than 0.04 ng/mL. The clinical use of BCR as a substitute end point for intervention to alter the subsequent PC management has been questionable in this context, which is fully concordant with observations in other studies (29, 30).

In our study, the sensitivity increased with higher PSA values from 15.0% at lower PSA values (>0.04–0.16 ng/mL) to 93.0% for PSA>2.0 ng/mL, with the results corresponding to the data reported in previous recent studies (31,32). Dietlein et al. (31) reported a PSA-stratified sensitivity of 66.0% for PSA levels of 0.5–3.5 μg/L; PSMA PET/CT modality achieved a sensitivity of 89.0% in males following prostatectomy with PSA>3.5μg/L. Comparable data are presented by Bluemel et al. (32) reporting a sensitivity of 85.0% for PSMA PET/CT in males with BCR after RP. The study by Perera et al. (6) found an 86.0% specificity and sensitivity for both, although the test was patient-based.

Despite the considerable advantages, there is an important goal for supplementary studies in ^{68}Ga-PSMA PET/CT for biochemical progression after RP, especially in the low-range values of PSA. There is a requirement for more reliable PSA-based specificity and sensitivity rate evidence.

CONCLUSION

The present research establishes that ^{68}Ga-PSMA PET/CT is a superb method for diagnosing relapsed PC and metastatic involvement with high sensitivity rate even at lower PSA values, which can impact subsequent therapeutic approach. Establishing the presence of the tumor is positively associated with the PSA value. Biochemical progression after RP, in the lower values of PSA (even less than 0.04 ng/mL), is predominantly associated with distant metastatic involvement. Our study implies that ^{68}Ga-PSMA PET/CT can be used in males with very low increasing PSA values (< 0.2 ng/mL). The high sensitivity of the method is a premise for a future change in the definition of BCR towards lower range values of PSA.

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