Research Article

Role of 68Ga-PSMA PET/CT in Patients with Recurrent Prostate Cancer and its Comparison with Serum PSA Levels and Gleason Scores

Syed Rashid-ul- Amin[1], Abdul Hai[1], Haider Ali [*, 1], Najeeb Niamatullah[2], Altaf Hashmi[3]

[1]*Department of Nuclear Medicine and Molecular Imaging, Sindh Institute of Urology and Transplantation (SIUT), Karachi, Pakistan.*

[2]*Department of Oncology, Sindh Institute of Urology and Transplantation (SIUT), Karachi, Pakistan.*

[3]*Department of Urology, Sindh Institute of Urology and Transplantation (SIUT), Karachi, Pakistan.*

Abstract: Background: Biochemical recurrence is seen in 27–53% of carcinoma prostate patients after treatment. GS (Gleason score) and baseline PSA level are a predictor of recurrence. Post- treatment persistent rising PSA levels represent the recurrence and PSMA labelled PET-CT is an important part of imaging workup in these patients.

Objective: To detect the relationship between PSA levels and Gleason score in patients investigated for Gallium-PSMA-11 fused molecular imaging in biochemical recurrent carcinoma prostate.

Material and Methods: This cross-sectional study was carried out at S.I.U.T Karachi. PSMA-PET/CT scans (September 2017-January 2022) of the patient who had a biochemical recurrence and not receiving any cancer-specific treatment at least 4 weeks prior scan were included. PSA level from lab reports and GS from the histopathological reports was recorded. Biochemical recurrence were defined as when PSA level > 0.4 ng/ml (post-prostatectomy) or >2.0 ng/ml higher than the nadir value after radiotherapy. PET/CT scans of 106 included patients were interpreted by the nuclear physician and radiologist team. SUVmax ≥ 2.5 was considered positive for recurrence. Local recurrences, lymph nodal, osseous, and visceral metastasis were documented. Statistical analysis was done by utilizing IBM SPSS software (version 22.0).

Results: In 88 of 106 patients (83%), Gallium-PSMA-11 PET/CT scan detected at least one lesion characteristic of recurrent PCa. The median PSA level was 12.1 (.01-892.0) ng/dl. In relating PSA value, it was noted that there was a significant difference between lesion positive and negative PSMA-11 labelled Ga-68 PET/CT scan but not statically significant for GS. Local recurrences were seen in 70 patients, whereas lymph node and osseous metastases were noted in 64 and 52 scans respectively. A PSA value of 0.68 ng/ml was determined by utilizing the ROC curve with an AUC of 0.924 (95% CI 0.86-0.98) and will likely predict the positive/negative PSMA-11 Gallium PET/CT scan.

Conclusion: Raised PSA level may predict the possibility of a positive Ga-PSMA-11 PET/CT scan but there was no relationship noted between GS and Ga-PSMA-11 PET/CT findings.

Keywords: PSMA-11 labelled Gallium PET/CT scan, Biochemical recurrent carcinoma prostate, Gleason score, PSA level, Non-metastatic prostate cancer, Metastases.

INTRODUCTION

Patients with non-metastatic prostate cancer are classified into low-, intermediate-, and high-risk groups based on baseline PSA (prostate-specific antigen) levels, Gleason score, and T stage. This risk stratification system predicts recurrence after local treatment, and the biochemical recurrence rate after five years was significantly higher in the high-risk category (>50%) than low-intermediate risk category (<50%) [1, 2]. Treatment options available for localized prostate cancer are active surveillance, radical prostatectomy, and/ or radiotherapy with/without hormonal therapy. In high-risk group, localized treatment (radical prostatectomy/ radiotherapy) with adjuvant hormonal therapy is recommended [3].

Serum PSA is an important biomarker in the primary diagnosis of prostate adenocarcinoma and is also helpful in the detection of recurrent disease [4]. After radical prostatectomy/radiotherapy, patients are followed on the PSA level and recurrence is suggested when its level is rising [5]. Serum PSA levels after radical prostatectomy should be undetectable (< 0.1 ng/mL), and levels > 0.1 ng/mL are markers of residual prostate cancer. However, after radiation therapy, PSA levels do not return to undetectable levels because there is residual normal prostate tissue [6]. Biochemical recurrence (BCR) occurs in 27–53% of patients after definitive local therapy [7]. It is defined as post-prostatectomy PSA level ≥ 0.4 ng/ml or an increase in PSA level >2 ng/ml higher than nadir value after radiotherapy [8, 9].

The sensitivity of rising PSA levels in detecting recurrence is high but it is not informative for the localization of recurrent sites which may both be local or distant and affect the management [10]. PET/CT (choline/PSMA-based) helps to identify metastases missed by routine imaging studies (CECT

*Address correspondence to this author at the Department of Nuclear Medicine and Molecular Imaging, Sindh Institute of Urology and Transplantation (SIUT), Karachi, Pakistan. Email: doctorhaiderali@gmail.com

and MDP-bone scan) leading to a change of treatment plan in up to 62% of patients [11]. In comparison with choline-based PET/CT Gallium-68 PSMA is an imaging modality that has shown better results even at a very low serum PSA level in recurrent carcinoma prostate [12].

Prostate-specific membrane antigen (PSMA) is a transmembrane protein whose gene resides on chromosome 11p. Apart from the prostate gland, it is also expressed in the normal salivary gland, ileum and kidney [13]. PSMA is over-expressed in malignant prostatic cells and research studies have demonstrated the detection capability of PSMA-11 labelled Gallium PET/CT is 96% in primary adenocarcinoma prostate and 71% in biochemical recurrence due to its overexpression in high grade metastatic, castration-resistant prostate cancer [14]. Till date a limited number of studies with variation in result on PSMA labeled 68Ga PET/CT in biochemical recurrent prostate adenocarcinoma were done with a small sample size, this needs validation. The study aimed was to detect the relationship between PSA levels and Gleason score in patients investigated for Gallium-PSMA-11 fused molecular imaging in biochemical recurrent carcinoma prostate.

MATERIALS AND METHODS

This analytical cross-sectional study was carried out at the molecular imaging section of the nuclear medicine department, S.I.U.T Karachi. After approval from the ethical review committee, (approval no: SIUT-ERC-2022/A-285) medical records of those patients who were scanned for PSMA-11 labelled Gallium PET/CT from September 2017-January 2022 were reviewed.

PSA levels and Gleason scores were recorded in data sheets from laboratory reports and histopathological reports respectively. Gleason score in histopathology report were calculated by adding up predominant and non-dominant cell patterns (1-5) in a biopsied tissue specimen. Inclusion criteria include histopathologically proven adenocarcinoma prostate, post-prostatectomy PSA level > 0.4 ng/ml or >2.0 ng/ml higher than nadir value after radiotherapy, not receiving any systemic therapy (chemo/ hormonal) at least 4-week prior scan. Known metastatic adenocarcinoma prostate patients, on systemic therapy (chemo/hormonal), Follow up patient with post prostatectomy PSA level < 0.4 ng/ml stable nadir PSA level after radiotherapy. Out of 495 patients who undergone for PSMA-11 Gallium PET/CT scans, 106 patients fulfilled these criteria. Eluted 68-Ga from 68Ge/68Ga generator was labelled with PSMA-11 (prostate specific antigen) in a semi-automated module with the help of good manufactured practice-grade cassettes and reagent kits (ABX GmbH).

Radiopharmaceutical 68Ga-PSMA was injected through intravenous route according to the patient body weight. 50-70min after injection, low dose plain computed tomogram was performed including head-thigh region with a slice thickness of 3mm, 120KeV, and 50-100mAs on a dedicated PET/CT scanner machine (Philips Gemini TF PET-CT 64-slice) followed by the three dimensional whole body PET scan with 2 minutes per bed position for (7-9 beds). An attenuation map is derived from the transmission images data for the attenuation correction of emission images. After the reconstruction of PET images using the iterative reconstruction PET images, CT images, and fused PET/CT images were viewed and reported using a Philips Fusion Viewer.

PET/CT scans of included patients, interpreted by radiologist and nuclear physician team. Maximum standard uptake value ≥ 2.5 were considered significant and interpreted as positive for recurrence. The lesions were documented as local recurrences, lymph node, osseous, and other visceral metastasis. Visual interpretation and SUVmax were the criteria used for the diagnosis.

STATISTICAL ANALYSIS

Data were analyzed by applying statistical methods utilizing IBM SPSS software (version 22.0). Mann Whitney U statistical test was used, to detect the statistical significant relationship between PSA levels and positive / negative PET/CT scan. Receiver operating characteristics (ROC) curves was used to compare the performance of PSMA-11 laballed PET/CT scan with triggered PSA levels by plotting sensitivity Vs 1-specificity. Similarly, Chi-square test was used to compare the findings of 68Ga PSMA-11 /PET-CT in relation of Gleason Scores. P-value < 0.05 were assumed as statistically significant.

RESULTS

In our study, all patients were male with a median age of 67 years (50-86 years), and 88 (83%) out of 106 patients had at least one lesion with high SUV max > 2.5 detected in PSMA laballed Gallium PET/CT scan in either local, lymph node or in bone. All the lesions with high SUV max >2.5 detected by PSMA-11 laballed Gallium PET/CT scan were considered as pathological. Local recurrence was the most common isolated recurrent site seen in 20 (22%) followed by isolated osseous metastasis seen in the 9 (10 %). Isolated lymph node recurrence was the least frequent site detected in only 5 (5.7%) patients. We have noted that if local recurrence is seen there is more chance of metastasis in lymph nodes/ and bone as evident in our result that in 50 (57%) patients, metastasis seen in lymph nodes and bone along with local recurrence (Table **1**).

We have interpreted the result of PSMA-11 Gallium-68 PET/CT scan in relation to total serum PSA level and it was noted that when PSA level is below 1.00 ng/ ml there were 7 (39%) out of 18 patients had recurrent positive PSMA-11 Gallium-68 PET-CT scan and 11 (61%) recurrence negative scan. As the PSA level is increased there is more chance of

Table 1. Location of Lesions in 68Ga-PSMA PET/CT.

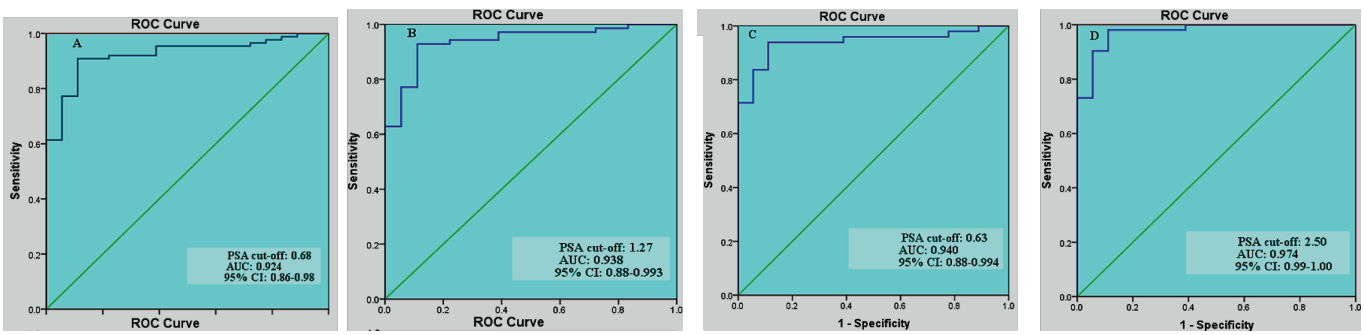
Region of Recurrence	No of Patients (%)
Isolated Local	20 (22.0)
Isolated Bone	09 (10.0)
Isolated lymph node	05 (5.7)
Local + Lymph node	11 (12.5)
Local + Bone	10 (11.4)
Lymph node + Bone	04 (4.5)
Local + Lymph node+ Bone	29 (34.0)
Total	88/106

Table 2. Result of Gallium-PSMA-11 PET/CT Scan in Relation to tPSA Level.

tPSA level < 1.00 ng/ml		**tPSA level 1.00-10.0 ng/ml**		**tPSA level >10.0-30.0 ng/ml**		**tPSA level > 30.0 ng/ml**	
PET/CT Positive scan	PET/CT Negative scan	PET/CT Positive scan	PET/CT Negative scan	PET/CT Positive scan	PET/CT Negative scan	PET/CT Positive scan	PET/CT Negative scan
07/18 (39%)	11/18 (61%)	24/30 (80%)	06/30 (20%)	25/26 (96%)	01/26 (4%)	32/32 100%	00/32 00%

Table 3. Serum PSA Cut-off Value in Local Recurrence, Lymph Node and Bone Metastases.

	N (Recurrence +)	PSA Cut Off Value (ng/ml)	Sensitivity	Specificity	Area Under Curve (AUC)	95% CI
Overall Study Cohortt	88	0.68	95.50%	72.10%	0.924	0.86-0.98
Local Recurrence	70	1.27	97.32%	83.30%	0.938	0.88-0.993
Lymph Node Metastases	49	0.63	98%	88%	0.94	0.88-0.944
Bony Metastases	52	2.5	94.60%	89.40%	0.974	0.99-1.00



(A) **(B)** **(C)** **(D)**

Fig.1. Optimal cut-off value of total serum PSA for distinguishing between positive and negative 68GaPSMA PET/CT images.
(A) Optimal cut-off value of total serum PSA for distinguishing between positive and negative 68GaPSMA PET/CT images.
(B) Optimal cut-off value of total serum PSA for distinguishing positive or negative local recurrence in patients with 68Ga- PSMA PET/CT images.
(C) Optimal cut-off value of total serum PSA for distinguishing positive or negative lymph node metastases in patients with 68Ga-PSMA PET/CT images.
(D) Optimal cut-off value of total serum PSA was determined for distinguishing positive or negative bony metastases in patients with 68Ga-PSMA PET/CT images.

recurrent positive PET-CT scans as shown in our result 32 patients had a PSA value of more than 30.0 ng/ml and all had recurrent positive PET-CT scans (Table **2**).

The median PSA value was calculated as 12.1 (IQR 39.42-3.38) ng/dl. In relating PSA value, the Mann-Whitney U test was used and it was noted that there was a significant difference between lesion positive (Z 5.56; p = 0.001), [PSA level; mean 71.4±163, median 17.4 (IQR 46.65-6.97ng/dl] and negative [mean 1.56±2.74, median 0.46 (IQR 1.55-0.19) ng/dl] PSMA-11 labelled Gallium PET/CT scan.

A PSA value of 0.68 ng/ml was determined by utilizing the receiver operating characteristic curve and with an AUC of 0.924 (95% CI 0.86-0.98 and this PSA cut-off value will likely predict the positive and negative PSMA-11 Gallium PET/CT scan as mentioned in Table **3** and Fig. **(1)**. Further, PSA cut off values were also calculated for each recurrent group (local recurrence, lymph nodes, and bone metastasis). We noted local recurrence in 70 patients, lymph nodes metastasis in 49 patients, and bone metastasis in 52 patients however no isolated visceral metastasis was detected in the current study.

68Ga-PSMA-11 PET/CT findings were also evaluated according to Gleason Scores. 9/13 (69%) patients with Gleason scores of 5-6 had positive PET-CT scans whereas 13/35 (37%) with Gleason scores of 7. We noted the highest percentage of positive scans 47/58 (81%) of Gleason score ≥ 8. However, in terms of the Gleason score no statistical significance was seen between positive and negative PSMA-11 labelled Gallium PET/CT scan ($\chi^2 = 1.086$; p = 0.581).

DISCUSSION

In the detection of recurrent focus in carcinoma prostate, choline-based hybrid imaging is commonly used but less sensitive and specific at serum PSA levels <1 ng/ml and low GS score ≤7. Gallium-PSMA-11 PET-CT, a targeted functional fused imaging modality likely provides the superior result for detecting recurrent PC [15]. The expected end result of this study was to elucidate the role of PSMA labelled Gallium PET-CT using serum PSA level and GS in the diagnosis of recurrent PC in patients who received different treatments at baseline. To date, the effectiveness of PSMA-11 labelled Gallium PET-CT has been explored by limited research studies in recurrent PC patients. Ceci *et al*. investigated the outcome of PSMA-11 labelled Gallium PET-CT in 70 patients who had recurrent PC after radical treatment [16]. They reported statistical significance in PET/CT positive vs negative scan in relation to PSA level [median PSA; 2.6 vs 0.7ng/ml, doubling time; median 4.74 vs 8.95 months]. Nevertheless, they also determined a PSA value of 0.83ng/ml with an AUC of 0.868, to predict positive and negative PET-CT scans. In addition, they reported a lesion detection rate of 93% for their study at a PSA cut-off value >2ng/ml. We found a serum PSA cut-off of 0.68 ng/dl in our study group to speculate a positive/negative PSMA-11 scan.

Eiber *et al*. noted the detection efficiency of PSMA-Gallium fused molecular imaging at 96.8% in recurrent prostatic carcinoma at PSA levels ≥2ng/ml [17]. Our results are also comparable with this study as we determined a 92% detection rate at PSA levels ≥1.00 ng/ml but it was lower at 39% for PSA levels <1.00 ng/ml. The resulting variation in low PSA levels (<1.00 ng/ml) may be due to the heterogeneity of treatment received in our study group while all patients in the Eiber *et al* study underwent radical prostatectomy only.

Yasmin *et al.* evaluated the relationship among PSA level, Gleason score, and Ga68-PSMA PET-CT scan findings in patients with recurrent PC [18]. They included 109 patients in their study and found statistical significance in positive and negative 68Ga-PSMA-11 molecular imaging /CT results in relation to serum PSA levels (median 9.14- versus 0.36ng/ml) and cut-off value was 0.67ng/ml with AUC 0.952 (95% CI 0.911-0.993). In our study, the cut-off value for serum PSA level is 0.68 ng/dl which is comparable to the result of Yasmin et al. We further calculated the PSA cut-off values for each recurrent group (local recurrence, lymph nodes, bone metastasis) which were 1.27, 0.63, and 2.50 respectively.

Afshar-Oremiehet *et al*. investigated 319 patients who were suspected of progressive disease in alternative imaging modalities such as CT / MRI and were scanned for 68Ga-PSMA-11 PET/CT having very low levels of serum PSA. They calculated the median for PSA values in 264 patients as 6.02ng/ml. Although the median calculated for the serum PSA levels in our study (12.1 ng/dl) is higher as compared to the above-mentioned studies but the optimal cut-off value and detection rate were comparable.

Current imaging methods are limited to assessing lymph node metastasis in recurrent diseases. Pelvic lymph node dissection followed by histopathology is an optimal method for the evaluation of nodal metastasis, but it has a limited role in recurrence setting [19, 20]. Though, Computed Tomography (CT) has low sensitivity (40%) and limited efficacy to detect nodal disease in prostate cancer but most frequently advised imaging modality in oncological practice for nodal staging [21, 22]. In this study, we detected lymph node metastases in 55 patients and the cut-off value limited to isolated nodal metastases in ROC analysis was 0.63ng/dl. Despite these findings, the diagnostic capability of PSMA-11 Ga-68 PET-CT has been challenged by Budaus *et al*. in searching for lymph node metastases in PC. In their study, the author compared 68Ga-PSMA PET/CT findings and histological workup after RP in high-risk PC. They observed patients with

nodal metastases and found that 33.3% were true positive while 66.7% were false negative [23]. They also determined the sensitivity and specificity of 68Ga-PSMA PET/CT in detecting nodal metastases and found sensitivity (33.3%) and specificity (100%). Furthermore, the median size of the lymph node was 13.6 vs 4.3 mm ($p < 0.05$) for 68Ga-PSMA PET/CT detected vs undetected lymph node metastases.

Although, after bone, pulmonary metastasis is the second most frequent site for metastasis in PC in our data we did not find lung metastasis even in a single patient. Visceral metastasis was found in only four patients. Meanwhile, isolated visceral metastasis was not seen in this study. All the lesions detected by PSMA-11 Ga-68 PET-CT scan in relation to visceral metastasis were considered pathological.

It is noted that PSMA expression is directly proportional to the metastatic state, tumor aggressiveness, and disease recurrence [24]. With recent advancements, Gleason Score has been chosen to be the most reliable histological tool to predict the prognosis of PC in patients who underwent radical treatment. Eiber *et al*. reported in their study that, 68Ga-PSMA PET/CT detection rate was 86.7% at GS ≤7 conversely it increased to 96.8% at GS >7. In contrast, Ceci *et al*. not found a significant association between GS and positive 68Ga-PSMA PET/CT results using multivariate analysis. Similarly, Yasmin *et al*. could not find a statistical difference between these parameters. Similarly, in these two studies, we noted no significant statistical difference with 68Ga-PSMA PET/CT positive results in relation to GS. These results may be due to the limited number of data and need to be investigated in a larger group of patients.

LIMITATION

We have some limitations in the current study. First, none of the lesions detected on PET/CT images were further evaluated by any type of surgery or biopsy so the histopathological evidence of the positive lesions could not be known. Second, this study has limited data specifically for isolated lymph nodes and bone metastases. A third, significant number of patients were from other hospitals for PSMA imaging so parameters such as PSA kinetics (PSA doubling time or PSA density) were difficult to measure due to the retrospective nature of the study. The strength of this study is that it was a single-centre study that specialized in Ga-68-PSMA PET-CT imaging in its area and has extensive experience in PET-CT imaging.

CONCLUSION

PSMA-11 Gallium PET/CT scan showed encouraging outcomes in biochemical recurrent carcinoma prostate imaging. Serum PSA level may predict the possibility of positive PSMA-11 Gallium fused PET/CT scan but there was no relationship noted between Gleason score and Ga-PSMA-11 PET/CT findings. This result also predicts that in near future PSMA targeted immunotherapy may be a potential role in prostate cancer management.

LIST OF ABBREVIATIONS

68-Ga: Gallium-68.
PSMA: Prostate specific membrane antigen.
PET: Positron emission tomography.
CT: Computed tomography.
PCa: Prostate carcinoma.
PSA: Prostate specific antigen.
GS: Gleason score.

AUTHORS' CONTRIBUTION

All authors' contributed equally.

CONFLICT OF INTEREST

Declared none.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] Rodrigues G, Warde P, Pickles T, *et al*. Pre-treatment risk stratification of prostate cancer patients: A critical review. Canadian Urol Assoc J 2012; 6(2): 121.

[2] Rebello RJ, Oing C, Knudsen KE, *et al*. Prostate cancer. Nat Rev Dis Primers 2021; 7(1): 9.

[3] Klotz L, Emberton M. Management of low risk prostate cancer-active surveillance and focal therapy. Nat Rev Clin Oncol 2014; 11(6): 324-34.

[4] Van Poppel H, Roobol MJ, Chapple CR *et al*. Prostate-specific antigen testing as part of a risk-adapted early detection strategy for prostate cancer: European Association of Urology Position and Recommendations for 2021. Eur Urol 2021; 80(6): 703-11.

[5] Freedland SJ, Presti Jr JC, Amling CL, *et al*. Time trends in biochemical recurrence after radical prostatectomy: Results of the SEARCH database. Urology 2003; 61(4): 736-41.

[6] Mottet N, van den Bergh RC, Briers E, *et al*. EAU-EANM-ESTRO-ESUR-SIOG guidelines on prostate cancer-2020 update. Part 1: Screening, diagnosis, and local treatment with curative intent. Eur Urol 2021; 79(2): 243-62.

[7] Artibani W, Porcaro AB, De Marco V, Cerruto MA, Siracusano S. Management of biochemical recurrence after primary curative treatment for prostate cancer: A review. Urol Int 2018; 100(3): 251-62.

[8] Brady L, Carlsson J, Baird AM, *et al*. Correlation of integrated ERG/PTEN assessment with biochemical recurrence in prostate cancer. Cancer Treat Res Commun 2021; 29: 100451.

[9] Van den Broeck T, van den Bergh RC, Briers E, *et al*. Biochemical recurrence in prostate cancer: the European Association of Urology prostate cancer guidelines panel recommendations. Eur Urol Focus 2020; 6(2): 231-4.

[10] Sachpekidis C, Eder M, Kopka K, *et al*. 68 Ga-PSMA-11 dynamic PET/CT imaging in biochemical relapse of prostate cancer. Eur J Nucl Med Mol Imaging 2016; 43(7): 1288-99.

[11] Roach PJ, Francis R, Emmet L, *et al.* The impact of (68) Ga-PSMA PET/CT on management intent in prostate cancer: Results of an Australian prospective multicenter study. J Nucl Med 2018; 59: 82-8.

[12] Afshar-Oromieh A, Avtzi E, Giesel FL, *et al*. The diagnostic value of PET/CT imaging with the 68 Ga-labelled PSMA ligand HBED-CC in the diagnosis of recurrent prostate cancer. Eur J Nucl Med Mol Imaging 2015; 42(2): 197-209.

[13] Van de Wiele C, Sathekge M, de Spiegeleer B, de Jonghe PJ, Beels L, Maes A. PSMA-targeting positron emission agents for imaging solid tumors other than non-prostate carcinoma: A systematic review. Int J Mol Sci 2019; 20(19): 4886.

[14] Barakat A, Yacoub B, El Homsi M, Aldine AS, El Hajj A, Haidar MB. Role of early pet/ct imaging with 68Ga-PSMA in Staging and Restaging of prostate cancer. Sci Rep 2020; 10(1): 1-6.

[15] Niziers V, Boissier R, Borchiellini D, *et al*. "Real-world" evaluation of 18F-Choline PET/CT practices in prostate cancer patients and impact on changes in therapeutic strategy. Urol Oncol 2020; 38(1): 2.e1-2.e9.

[16] Ceci F, Uprimny C, Nilica B, *et al*. 68 Ga-PSMA PET/CT for restaging recurrent prostate cancer: which factors are associated with PET/CT detection rate?. Eur J Nucl Med Mol Imaging 2015; 42(8): 1284-94.

[17] Eiber M, Maurer T, Souvatzoglou M, *et al.* Evaluation of Hybrid ^{68}Ga-PSMA ligand PET/CT in 248 patients with biochemical recurrence after radical prostatectomy. J Nucl Med 2015; 56(5): 668-74.

[18] Sanli Y, Kuyumcu S, Sanli O, *et al.* Relationships between serum PSA levels, Gleason scores and results of 68Ga-PSMA-PET/CT in patients with recurrent prostate cancer. Ann Nucl Med 2017; 31(9): 709-17.

[19] Giesel FL, Fiedler H, Stefanova M, *et al*. PSMA PET/CT with Glu-urea-Lys-(Ahx)-[68 Ga (HBED-CC)] versus 3D CT volumetric lymph node assessment in recurrent prostate cancer. Eur J Nucl Med Mol Imaging 2015; 42(12): 1794-800
.

[20] Heidenreich A, Bellmunt J, Bolla M, *et al*. EAU guidelines on prostate cancer. Part 1: Screening, diagnosis, and treatment of clinically localised disease. Eur Urol 2011; 59(1): 61-71.

[21] Perez-Lopez R, Tunariu N, Padhani AR, *et al*. Imaging diagnosis and follow-up of advanced prostate cancer: Clinical perspectives and state of the art. Radiology 2019; 292(2): 273-86.

[22] Hövels A, Heesakkers RA, Adang EM, *et al*. The diagnostic accuracy of CT and MRI in the staging of pelvic lymph nodes in patients with prostate cancer: A meta-analysis. Clin Radiol 2008; 63(4): 387-95.

[23] Tu X, Zhang C, Liu Z, *et al*. The role of 68Ga-PSMA positron emission tomography/computerized tomography for preoperative lymph node staging in intermediate/high risk patients with prostate cancer: A diagnostic meta-analysis. Front Oncol 2020; 10: 1365.

[24] Perner S, Hofer MD, Kim R, *et al*. Prostate-specific membrane antigen expression as a predictor of prostate cancer progression. Hum Pathol 2007; 38(5): 696-701.

Received: June 18, 2022 Revised: September 10, 2022 Accepted: September 12, 2022