



# The Diagnostic Power of the Gallium-68 Prostate-specific Membrane Antigen Positron Emission Tomography-Computed Tomography in Biochemical Recurrence After Primary Curative Treatment in Patients with Prostate Cancer: A Single-center Experience

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## Abstract

**Objective:** Our study aimed to investigate the efficacy of Gallium-68 (<sup>68</sup>Ga) prostate-specific membrane antigen (PSMA) positron emission tomography-computed tomography (PET-CT) in terms of focus detection in the presence of biochemical recurrence (BCR) after primary curative treatment in patients with prostate cancer (PCa).

**Methods:** This study included 34 PCa patients who underwent <sup>68</sup>Ga-PSMA PET-CT for BCR following radical prostatectomy (RP) or primary curative radiotherapy (RT), between August 2017-December 2018 at Okmeydanı Training and Research Hospital, Clinic of Nuclear Medicine.

**Results:** Thirteen patients (38.2%) had RP and 21 (61.8%) had RT. PSMA-positive lesion was detected in 21 (61.7%) of 34 patients. PSMA positive lesion was present in six of 13 patients (46.1%) in the RP group and 15 of the 21 patients (71.4%) in the RT group. There was a PSMA-positive lesion in five out of 13 patients with serum prostate-specific antigen (PSA) values of 0.01-1 ng/mL, in five of eight patients with serum PSA values of 1-2 ng/mL, in four of five patients with serum PSA values of 2-5 ng/mL, and in seven of eight patients with serum PSA values of >5 ng/mL. PSA levels of PSMA-positive patients were found to be significantly higher than those of PSMA-negative, whereas PSA-positive and negative patients did not differ significantly in terms of PSA doubling time, time to BCR, and Gleason score.

**Conclusion:** <sup>68</sup>Ga-PSMA PET-CT is an effective method in the diagnosis of BCR after primary curative treatment in PCa patients.

**Keywords:** Gallium-68 prostate-specific membrane antigen positron emission tomography-computed tomography, biochemical recurrence, curative radiotherapy, radical prostatectomy

## INTRODUCTION

Prostate cancer (PCa) is the most common cancer in men and is responsible for 1/3 of cancer-related deaths. In PCa patients, biochemical recurrence (BCR) occurs in 25% of patients after radical prostatectomy (RP) or primary curative radiotherapy (RT) (1,2). Prostate-specific membrane antigen (PSMA) is a cell surface protein that is 100-1.000 fold increased expression in PCa cells compared to benign prostate tissues (3,4). Gallium-68 (<sup>68</sup>Ga)-labeled PSMA ligands bind to the extracellular part of PSMA and internalize to PCa cells (3,4). PSMA is a preferable and suitable target for imaging with these features. <sup>68</sup>Ga-PSMA positron emission tomography-computed tomography (PET-CT) imaging has been increasingly used in recent years in PCa patients for

staging purposes and the purpose of focus detection in the presence of BCR (5-8). The aim of this study was to determine the efficacy of <sup>68</sup>Ga-PSMA PET-CT for the detection of recurrence focus in the presence of BCR after RP or primary curative RT treatments in PCa patients, and to investigate the correlation between PSMA positive focus detection and serum prostate-specific antigen (PSA) value, PSA doubling time (PSAdt), time to BCR, Gleason score.

## METHODS

This study included 34 PCa patients who underwent <sup>68</sup>Ga-PSMA PET-CT for BCR following RP or primary curative RT between August 2017-December 2018 at Okmeydanı Training and



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Research Hospital, Clinic of Nuclear Medicine. The following were defined as BCR criterion:  $>0.2$  ng/mL PSA value at post-RP follow-up, PSA levels that were increased 2 ng/mL compared to the rare value in the patient at post-RT follow-up, or, increasing PSA value in a patient who had achieved rare value in three consecutive PSA measurements. In patients with BCR, the diagnostic power of  $^{68}\text{Ga}$ -PSMA PET-CT imaging in the detection of recurrence focus and the relationship between imaging findings and serum PSA value, PSA<sub>dt</sub>, time to BCR, and Gleason score were investigated. Whole-body  $^{68}\text{Ga}$ -PSMA PET-CT imaging was performed with PET-CT scanner (Siemens Biograph 6, Chicago, IL, USA) consisting of full-ring HI-REZ lutetium oxyorthosilicate PET and 6-section CT scan at 60th minutes following the intravenous injection of 2 MBq/kg  $^{68}\text{Ga}$  PSMA I&T (Scintomics GRP, Germany) obtained from Germanium-68/ $^{68}\text{Ga}$  generator (iThemba LABS, South Africa). Images were evaluated visually by two nuclear medical experts who knew just the patients' primary diagnosis.  $^{68}\text{Ga}$ -PSMA I&T uptake, which is located outside the physiological activity regions and increased compared to background activity, was considered positive for recurrence. The standardized uptake value maximum (SUV<sub>max</sub>) value of all  $^{68}\text{Ga}$ -PSMA I&T uptake foci was measured, but any SUV<sub>max</sub> threshold value was not used as the criterion of positivity. Ethics committee approval was obtained from Okmeydanı Training and Research Hospital Ethics Committee with the 1181 decision number and on 03.05.2019 date, for this clinical study, which was designed retrospectively.

### Statistical Analysis

For statistical analysis, IBM SPSS Statistics 22 (IBM SPSS, Turkey) program was used. In the evaluation of the study data, the conformity of the parameters to the normal distribution was evaluated by Shapiro-Wilks test, and it was found that the parameters did not show normal distribution. In addition to descriptive statistical methods (mean, standard deviation, frequency), Mann-Whitney U test was used for the comparison of quantitative data between two groups. Significance was evaluated as  $p < 0.05$ .

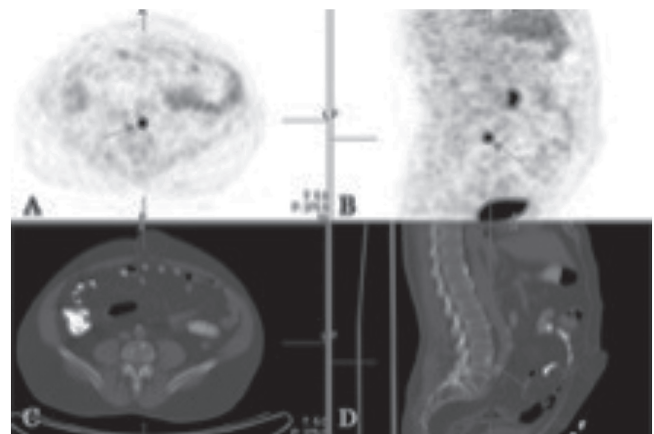
### RESULTS

Thirty-four male patients were included in the study. The mean age was  $70.76 \pm 6.94$  years (range, 56-84). Thirteen patients (38.2%) had RP, and 21 (61.8%) had RT as primary treatment. While  $^{68}\text{Ga}$ -PSMA PET-CT was applied with the diagnosis of BCR in patients, the mean serum PSA level was  $6.33 \pm 11.06$  ng/mL (median 1.23; range=0.01-40.19) and the mean PSA<sub>dt</sub> was  $9.97 \pm 6.77$  (median 8; range=1-31) months. The mean time to BCR was  $71.03 \pm 52.05$  months (median 52; range=9-179). Gleason score was 3+3 in

nine patients, 3+4 in nine patients, 4+3 in three patients, 4+4 in eight patients, and 4+5 in five patients. The PSMA-positive lesion was detected in 21 (61.7%) of the 34 patients: In six of the 13 patients (46.1%) in the RP group and 15 of the 21 patients (71.4%) in the RT group. The pathologies detected with  $^{68}\text{Ga}$ -PSMA PET-CT were local recurrence in 12 patients, local recurrence plus pelvic metastatic lymph node in one patient, local recurrence plus bone metastasis in two patients, pelvic metastatic lymph node alone in two patients and bone metastasis alone in four patients. The mean SUV<sub>max</sub> value was 18.37 (range=3.6-56.43) in local recurrent lesions, 6.58 (range=3.38-13.51) in metastatic lymph nodes, and 10.52 (range=3.69-43.14) in bone metastases (Figure 1). There was a PSMA-positive lesion in five out of 13 patients with serum PSA values of 0.01-1 ng/mL, in five of eight patients with serum PSA values of 1-2 ng/mL, in four of five patients with serum PSA values of 2-5 ng/mL, and in seven of eight patients with serum PSA values of  $>5$  ng/mL. PSA levels were found to be significantly higher in patients who had a positive lesion in  $^{68}\text{Ga}$ -PSMA PET-CT compared to patients with no lesion ( $p=0.008$ ). Between the patients with and without a positive focus in  $^{68}\text{Ga}$ -PSMA PET-CT, no statistically significant difference was found in terms of PSA<sub>dt</sub>, time to BCR, and Gleason score ( $p > 0.05$ ) (Table 1).  $^{68}\text{Ga}$ -PSMA PET-CT imaging was found to provide a potential change in the treatment plan through detection of the metastatic lesion without local recurrence, in addition to the detection of local recurrence in nine patients.

### DISCUSSION

In PCa patients, RP or primary curative RT is the primary



**Figure 1.** A 62-year-old man with prostate cancer, Gleason score 4+4, who underwent radio therapy June 2017. Gallium-68 prostate-specific membrane antigen positron emission tomography-computed tomography ( $^{68}\text{Ga}$ -PSMA PET/CT) was performed for a persistently raised prostate-specific antigen level (0.47 ng/mL). (A) Axial, (B) Sagittal  $^{68}\text{Ga}$  PSMA PET and (C) Axial, (D) Sagittal CT images showed  $^{68}\text{Ga}$  PSMA-positive sclerotic lesion at the lumbar 4<sup>th</sup> vertebra corpus (black arrow)

**Table 1. Relationship between Gallium-68 prostate-specific membrane antigen positron emission tomography-computed tomography findings and serum prostate-specific antigen, time to biochemical recurrence, and prostate-specific antigen doubling time**

	PSMA positive	PSMA negative	Totally	p
Serum PSA	8.41±12.5 (2.39)	2.97±7.47 (0.89)	6.33±11.06 (1.23)	0.008*
BCR time	80.67±54.22 (58)	55.46±46.1 (29)	71.03±52.05 (52)	0.070
PSA <sub>dt</sub>	10.2±7.34 (8)	9.62±6.05 (8)	9.97±6.77 (8)	0.986

PSA<sub>dt</sub>: Prostate-specific antigen doubling time, PSMA: Prostate-specific membrane antigen, BCR: Biochemical recurrence

treatment option in the presence of localized disease. BCR is seen in 20-30% of patients after RP, and 60% after curative RT in 10-15 years follow-up (5,9). Although adjuvant RT is the first and most important treatment option in patients with BCR, the efficacy of this treatment is related to the detection of the recurrent disease as early as possible and is limited to the prostate region (6). In a meta-analysis of Tan et al. (10) which included 5113 patients with BCR who underwent <sup>68</sup>Ga-PSMA PET-CT to detect the recurrence focus, <sup>68</sup>Ga-PSMA PET-CT scan was reported to have a 70% focus detection rate, and, for the serum PSA values of <0.5 ng/mL, 0.5-0.9 ng/mL, 1-1.9 ng/mL and ≥2 ng/mL, these rates were reported as 44.9%, 61.3%, 78.2%, and 93.9%, respectively. In our study, at least one PSMA-positive lesion was detected in 21 of the 34 patients (61.7%) as the BCR focus, and this rate was 46.1% in the RP group and 71.4% in the RT group. The pathologies detected with <sup>68</sup>Ga-PSMA PET-CT were local recurrence in 12 patients, local recurrence plus pelvic metastatic lymph node in one patient, local recurrence plus bone metastasis in two patients, pelvic metastatic lymph node alone in two patients and bone metastasis alone in four patients. In the study of Vinsensia et al. (11) as BCR focus, 30.4% local recurrence and pelvic metastatic lymph nodes, 42.1% bone metastasis, 13.7% retroperitoneal metastatic lymph nodes and 13.7% distant metastasis were detected. Accurate and early detection of local recurrence and possible metastatic focus in the presence of BCR is essential for appropriate treatment planning (12,13). In our study, there was a PSMA-positive lesion in five out of 13 patients with serum PSA values of 0.01-1 ng/L in five of eight patients with serum PSA values of 1-2 ng/mL, in four of five patients with serum PSA values of 2-5 ng/mL, and in seven of eight patients with serum PSA values of >5 ng/mL. In a prospective study that included 314 cases, Caroli et al. (14) reported that PSMA-positive focus detection rate was found to be 94.8% among patients with BCR who had a serum PSA value of ≥2 ng/mL. In a study conducted

with patients with serum PSA values <5 ng/mL, Kabasakal et al. (15) detected a PSMA positive focus in 58% of patients by <sup>68</sup>Ga-PSMA PET-CT imaging, and, this rate was reported to be 31% in patients with serum PSA <0.2 ng/mL and 54% in patients with 0.2-2 ng/mL. In patients with BCR, the major effective factor for detecting the focus with imaging methods is serum PSA, and as the PSA increases, the focus detection rate increases (10,16). In a study by Sanli et al. (17) on the <sup>68</sup>Ga-PSMA PET-CT imaging performed due to BCR, at least one focus was detected in 83.4% of the patients. Furthermore, there was a significant difference between the PSA positive and negative patients in terms of serum PSA levels, but no significant relationship was found in terms of the Gleason score. In our study, we showed that PSA levels were significantly higher in patients who had PSMA-positive lesion in <sup>68</sup>Ga-PSMA PET-CT compared to patients without a PSMA-positive lesion, but there was no statistically significant difference in terms of Gleason score, time to BCR and PSA<sub>dt</sub>. In a meta-analysis examining 37 investigations conducted by Eissa et al. (18) the rate of focus detection was found to be 47-96.6% with <sup>68</sup>Ga-PSMA PET-CT imaging in patients with BCR. Moreover, this rate was 11.1% to 75% in patients who had <0.5 ng/mL serum PSA value. In this study, it was also reported that there was a significant relationship between high serum PSA values and PSMA positive focus detection, and <sup>68</sup>Ga-PSMA PET-CT imaging provided a change in treatment in 28.6-87.1% of the patients (18). In a study of 70 cases, conducted by Ceci et al. (5) a significant relationship was found between positive focus detection in <sup>68</sup>Ga-PSMA PET-CT imaging and the PSA<sub>dt</sub>. Also, It was reported that PSMA positive focus detection rate was 85% among patients with PSA<sub>dt</sub> <6.5 months and serum PSA value <2 ng/mL (5). However, in the study of Afaq et al. (16) no significant relationship was found between PSA<sub>dt</sub> and PSMA positive focus detection. The treatment plan change provided by <sup>68</sup>Ga-PSMA PET-CT imaging in BCR patients has been reported in the literature in 39-76%. Significant treatment changes have been in the form of RT area-dose change for pelvic lymph node metastasis in patients scheduled rescue RT and the transition to systemic therapy in patients who were detected distant metastases (9,19-21). In our study, <sup>68</sup>Ga-PSMA PET-CT imaging was found to provide a potential change in the treatment plan through detection of the metastatic lesion without local recurrence, in addition to the detection of local recurrence in nine patients.

## CONCLUSION

<sup>68</sup>Ga-PSMA PET-CT imaging is an effective method for detecting BCR after primary curative treatment in PCa patients and provides optimal treatment planning. In our study, there was

a significant relationship between high PSA level and PSMA positive focus detection rate, while there was no significant difference between PSA positive and negative patients in terms of PSA<sub>dt</sub>, time to BCR, and Gleason score.

## Ethics

**Ethics Committee Approval:** Ethics committee approved.

(İstanbul Okmeydanı Training and Research Hospital, decision number 1181/date 03.05.2019).

**Informed Consent:** Obtained from all patients.

**Peer-review:** Externally peer-reviewed.

## Authorship Contributions

Surgical and Medical Practices: S.T.D., Concept: S.S.K., Design: S.S.K., Data Collection or Processing: S.S.K., S.T.D., Analysis or Interpretation: S.S.K., Literature Search: S.S.K., Writing: S.S.K.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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