J Oncol Sci 5 (2019) 100–104

Contents lists available at ScienceDirect

J Oncol Sci

journal homepage: www.journalofoncology.org

Original Article

The factors determining positive detection rate of 68Ga PSMA PET/CT in patients with early biochemical recurrence prostate cancer

Serdar Arici [a, *], Sevda Saglampinar Karyagar [b], Sener Cihan [a]

[a] Department of Medical Oncology, University of Health Sciences, Okmeydani Training and Research Hospital, 34384, Istanbul, Turkey
[b] Department of Nuclear Medicine, University of Health Sciences, Okmeydani Training and Research Hospital, 34384, Istanbul, Turkey

ARTICLE INFO

Article history:
Received 10 July 2019
Received in revised form
29 September 2019
Accepted 16 October 2019
Available online 24 October 2019

Keywords:
Biochemical recurrence
Prostat cancer
PSMA PET/C
Maximal androgen blokage

ABSTRACT

Aim: To examine predictive markers for high detection rates of 68Ga PSMA-PET/CT in biochemical recurrence (BR) prostate cancer (PCa) patients with low PSA levels.
Material and Method: This trial was planned as a retrospective single center study. Patients with BR prostat cancer were included. PSA levels of all patients were lower 2 μg/l.
Results: Totally thirty-two men patients with BR PCa were included in this study. 18 (56.3%) patients underwent radical prostatectomy and 14 (43.7%) patients curative intense radiotherapy. The number of patients received adjuvant maximal androgen blokage (MAB) treatment was 15 (46.9%). Median PSA levels was calculated 1.03 μg/l 17 (53.1%) of patients had <1 μg/l PSA levels and 7 (21.8%) of patients <0.5 μg/l. The patients number was 16 in unfavorable intermediate risk group (50.0%), 12 (37.5%) in high group and 4 (12.5%) in very high group. The median PSA doubling time was 6.2 months. The number of patients received adjuvant MAB treatment was 15 and in 14 (93.3%) of patients were found positive lesion in 68Ga PSMA-PET/CT. The number of patients with at least one lesion detected on 68Ga PSMA-PET/CT was 19 (59.4%). In univariate analysis to detect the factors affecting 68Ga PSMA-PET/CT positivity, there was only the presence of adjuvant MAB treatment as statistically significant importance ($p < 0.001$) and in multivariate analysis, the presence of adjuvant MAB treatment was found to be as statistically significant factor in terms of affecting 68Ga PSMA-PET/CT positivity ($p = 0.003$). The cut-off value was calculated as 1.12 μg/l in patients with no adjuvant MAB treatment (sensitivity 80% and specificity 83.3%).
Conclusion: Clinicians may perform 68Ga PSMA PET/CT in low PSA levels to detect lesions in biochemical recurrent prostate cancer patients who had received MAB treatment and in patients with higher PSA levels who had no received MAB treatment.

1. Introduction

Prostate cancer (PCa) is the most common malign tumor in men worldwide and the incidence of PCa is increasing in recent years.[1] Surgical and radiotherapy techniques were improved but still, biochemical recurrence (BR) is seen in 20%–30% of patients following radical prostatectomy (RP) or radiotherapy. In most cases, recurrence after initial therapy is diagnosed either by two consecutive PSA values of ≥0.2 μg/l after prostatectomy or external beam radiation therapy. A low tumor burden especially as the pelvic recurrence or extrapelvic oligo-metastases, were detected in patients with early stages of BR.[2–4] Early detection of recurrent disease is most important. If the tumor is eligible for surgery or external radiation therapy, patients may be cured or side effects of systemic therapy for the advanced-stage disease, can be delayed. Despite the significant advances that have taken place especially in the field of magnetic resonance imaging (MRI), conventional imaging modalities still have clear limitations in PCa recurrence assessment, especially in early stages of BR.[5]

^{68}Gallium-labelled prostate-specific membrane antigen ligand positron emission tomography-computed tomography (^{68}Ga PSMA-PET/CT) has demonstrated promise as a superior imaging technique with high sensitivity and specificity in detecting small regional and distant metastases. But, the detection rate of ^{68}Ga PSMA-PET/CT is lower in patients with low PSA levels than high levels.[6,7]

In low PSA levels, clinicians still have confusion as to which

* Corresponding author. Department of Medical Oncology, University of Health Sciences, Okmeydani Training and Research Hospital, 34384, Istanbul, Turkey.
E-mail address: serdararici@hotmail.com (S. Arici).
Peer review under responsibility of Turkish Society of Medical Oncology.

https://doi.org/10.1016/j.jons.2019.10.001

patient should be performed ^{68}Ga PSMA PET/CT and which should not. We aimed to examine predictive markers for high detection rates of ^{68}Ga PSMA-PET/CT in BR prostate cancer patients with low PSA levels.

2. Material and methods

2.1. Study population

This trial was planned as a retrospective single-center study. Medical informations were obtained from the archive files of patients who underwent ^{68}Ga PSMA-PET/CT between 2017 April-2019 May, for BR prostate cancer in Okmeydani Training and Research Hospital. Biochemical recurrence was defined as two consecutive PSA values of $\geq$0.2 μg/l after prostatectomy or <6 months doubling time of nadir PSA value for after radical radiotherapy. PSA levels of all patients who were included the study were lower 2 μg/l. Patients were grouped according to PSA levels < or $\geq$1 μg/l and National Comprehensive Cancer Network (NCCN) patients risk stratification scheme. Patients who started androgen blockage treatment within one year before PSMA PET/CT were excluded. Patients were under 18 age, with PSA higher 2 μg/l, and with no laboratory test results were excluded. PSA data added to analysis were obtained in ten days within before 68Ga PSMA-PET/CT.

2.2. Imaging methods

Whole body 68Ga-PSMA PET-CT imaging performed with the PET-CT scanner (Siemens Biograph 6, Chicago, IL, USA) consisting of full-ring HI-REZ LSO PET and 6-section CT scan at 60.minutes following the intravenous injection of 2 MBq/kg 68Ga PSMA I&T (Scintomics GRP, Germany) obtained from 68Ge/68Ga generator (iThemba LABS, South Africa). Images were evaluated visually by two nuclear medical experts who had knowledge about just the patients' primary diagnosis. 68Ga-PSMA I&T uptake, which is located outside the physiological activity regions and increased compared to background activity, was considered positive for recurrence. The SUVmax value of all 68Ga-PSMA I&T uptake foci was measured, but any SUVmax threshold value wasn't used as the criterion of positivity.

2.3. Statistical analysis

For statistical analysis, IBM Statistical Package for the Social Sciences 15.0 for Windows was used. Descriptive statistics were given as number and percent for categoric variables and as mean, standard deviation, minimum and maximum for numerical variables. Student's t-test was used when the numerical variables provided the normal distribution condition. The determinant factors were examined by Logistic Regression Analysis. Because of the low patients' number, variables that were calculated as $p < 0.25$ in univariate analysis were used for multivariate analysis. Statistical significance level was accepted as $p < 0.05$.

3. Results

Totally thirty-two men patients with BR PCa were included in this study. The median age at diagnosis and recurrence were calculated as 67.3 years and 72.5 years respectively. The median time to recurrence was calculated as 53.2 months. The number of patients with lower than 7 Gleason score was 7 (25%). For definitive treatment, 18 (56.3%) patients underwent radical prostatectomy and 14 (43.7%) patients curative intense radiotherapy. The number of patients received adjuvant maximal androgen blockage (MAB) treatment was 15 (46.9%). Median PSA level was calculated 1.03 μg/l 17 (53.1%) of patients had <1 μg/l PSA levels and 7 (21.8%) of patients <0.5 μg/l. The patients number was 16 in unfavorable intermediate risk group (50.0%), 12 (37.5%) in high group and 4 (12.5%) in very high group. The median PSA doubling time (dt) was 6.2 months. The number of patients with at least one lesion detected on ^{68}Ga PSMA-PET/CT was 19 (59.4%). The most common sites of ^{68}Ga PSMA positive lesion were prostatic bed and bone, respectively. Only local recurrence was detected in 11 patients (57.1% of PSMA positive patients). These patients were underwent salvage RT. Also, none-of PSMA positive patients required chemotherapy. The median number of lesions was calculated 1.83, in patients with positive ^{68}Ga PSMA-PET/CT. Median SUVmax was calculated 19.4 (Table-1).

For detecting the factors affecting 68Ga PSMA-PET/CT positivity, univariate analysis including age, recurrence duration, PSA, PSAdt, Gleason score, risk group, definitive treatment modality and adjuvant MAB treatment was done and there was only the presence of adjuvant MAB treatment as statistically significant importance ($p < 0.001$) (Table-2).

Variables that were calculated $p < 0.25$ in univariate analysis such as recurrence duration, PSA, RT for definitive treatment and adjuvant MAB treatment, were added to multivariate analysis and only, the presence of adjuvant MAB treatment was found to be statistically significant in terms of affecting 68Ga PSMA-PET/CT positivity (OR 41.875 95% CI 3.612–485.5 $p = 0.003$) (Table-3).

The number of patients received adjuvant MAB treatment was 15 and in 14 (93.3%) of patients were found a positive lesion in ^{68}Ga PSMA-PET/CT.

There was no any cut-off PSA value to determine the PSMA PET positivity in all patients but when patients were grouped according to adjuvant MAB treatment status, in patients with adjuvant MAB treatment, there was no a cut-off value but the cut-off value was calculated as 1.12 μg/l in patients with no adjuvant MAB treatment (sensitivity 80% and specificity 83.3%) (Fig. 1).

4. Discussion

This retrospective study was planned to determine the affecting factors on ^{68}Ga PSMA PET/CT positivity. In the literature, there are some studies focused on BR prostatic cancer and ^{68}Ga PSMA PET/CT and most of these studies are in recent five years. The first study was published in 2015, totally 319 patients who underwent 68Ga PSMA-PET/CT were included and in 82.8% of patients, at least one lesion had been detected as positive lesion. PSA level was found the most important factor in terms of detection rate of PCa but could not calculated any cut-off value.[8] In another study including 100 patients, 72% positive lesion was determined and median PSA level of all patients was calculated as 1.73 μg/l.[9] In a study including totally 107 Turkish patients, published in 2019, median PSA level was 1.22 μg/l and 100% detection rate was found in patients with PSA >3.5 μg/l but 43.8% in patients with PSA<0.2 μg/l.[10] In another study of totally 70 patients with PSA <2 μg/l, at least one positive lesion determined 44 of 70 (62.8%) patients.[11] In a meta-analysis including 29 studies reported that detection rate of ^{68}Ga PSMA PET/CT in patients with PSA<2 μg/l was 63% and 94% in patients with PSA> 2 μg/l.[12] In our study, PSA levels of all patients were under <2 μg/l and the median PSA level was calculated as 1.03 μg/l and positive detection rate was 59.4%.

Prostate-specific antigen was found the most important factor on ^{68}Ga PSMA PET/CT positivity in patients with higher PSA levels. Also, androgen deprivation treatment (ADT) was found an important factor in some trials. In a study a total of 319 patients discussed above, ADT was found statistically significant in terms of ^{68}Ga PSMA PET/CT positivity.[8] In contrast, in a study of 222 patients with

Table-1
Patients characteristics.

Age at diagnosis Med±SD (Min-Max)		67.3 ± 7.9 (54–86)
Age at BR Med±SD (Min-Max)		72.5 ± 7.4 (57–88)
Time to BR (month) Med±SD (Min-Max)		53.2 ± 41.6 (9–144)
Gleason score n (%)	3 + 3	8 (25.0)
	3 + 4	12 (37.5)
	4 + 3	2 (6.3)
	4 + 4	6 (18.8)
	4 + 5	4 (12.5)
Risk groups		
	Unfavorable intermediate	16 (50.0)
	High	12 (37.5)
	Very high	4 (12.5)
Definitive treatment n (%)	Radiotherapy	14 (43.8)
	Surgery	18 (56.3)
Adjuvant MAB n (%)	Yes	15 (46.9)
	No	17 (53.1)
PSA dt (month) Med±SD (Min-Max)		6.2 ± 3.5 (2–13)
PSA before PSMA PET Med±SD (Min-Max)		1.03 ± 0.76 (0.09–3.06)
	<1 μg/l	17 (53.1)
	≥1 μg/l	15 (46.9)
PSMA PET n (%)	Lesion positive	19 (59.4)
	Lesion negative	13 (40.6)
Lesion localisation n (%)	Local	11 (57.9)
	Bone	3 (15.8)
	Intraabdominal LN	1 (5.3)
	Local + Bone	4 (21.1)
Diagnosis correction n (%)	Biopsy	3 (16.7)
	PSA response to therapy	15 (83.3)
Lesion number Med±SD (Min-Max)		1.83 ± 1.86 (1–8)
Lesion SUVmax Med±SD (Min-Max)		19.4 ± 14.0 (3.6–54.5)

Abbreviations: Med: Median, SD: Standart deviation, BR: Biochemical recurrence, MAB: Maximal andogen blokage, dt: Doubling time, LN: Lymph node.

Table-2
Univariate analysis to detect the factors affecting the detection rate of ^{68}Ga PSMA PET/CT.

		PSMA PET				p
		Lesion positive		Lesion negative		
		Med±SD	Min-Max	Med±SD	Min-Max	
Age at diagnosis		67.3 ± 9.0	54-86 (65)	67.5 ± 6.1	61-82 (66)	0.945
Age at BR		73.1 ± 8.2	57-88 (73)	71.7 ± 6.3	63-85 (72)	0.604
Time to BR (month)		60.2 ± 44.5	13-144 (51)	43.0 ± 36.2	9-114 (29)	0.198
PSA dt (month)		6.4 ± 3.8	2-13 (4)	5.8 ± 3.1	3-12 (5)	0.696
PSA before PSMA PET (μg/l)		1.13 ± 0.76	0.09–2.70 (1.33)	0.88 ± 0.75	0.09–3.06 (0.71)	0.227
	<1	8	42.1	9	69.2	0.131
	≥1	11	57.9	4	30.8	
Gleason score	**3 + 3**	3	15.8	5	38.5	0.655
	3 + 4	7	36.8	5	38.5	
	4 + 3	2	10.5	0	0.0	
	4 + 4	4	21.1	2	15.4	
	4 + 5	3	15.8	1	7.7	
Risk groups	Unfavorable intermediate	10	52.7	6	46.1	0.547
	High	7	36.8	5	38.5	
	Very high	2	10.5	2	15.4	
Definitive treatment	**Radiotherapy**	10	52.6	4	30.8	0.221
	Surgery	9	47.4	9	69.2	
Adjuvant MAB	**Yes**	14	73.7	1	7.7	**< 0.001**
	No	5	26.3	12	92.3	

Abbreviations: Med: Median, SD: Standart deviation, BR: Biochemical recurrence, MAB: Maximal andogen blokage, dt: Doubling time.

Table-3
Multivariate logistic regression analysis to detect the factors affecting the detection rate of ^{68}Ga PSMA PET/CT.

		p	OR	95% CI	
Enter Method	**Time to BR**	0.222	1.016	0.991	1.042
	PSA before PSMA PET	0.390	1.835	0.459	7.326
	Definitive treatment (RT)	0.651	1.697	0.172	16.765
	Adjuvant MAB presence	**0.003**	41.875	3.612	485.5

Abbreviations: BR: Biochemical recurrence, RT: Radiotherapy, MAB: Maximal andogen blokage.

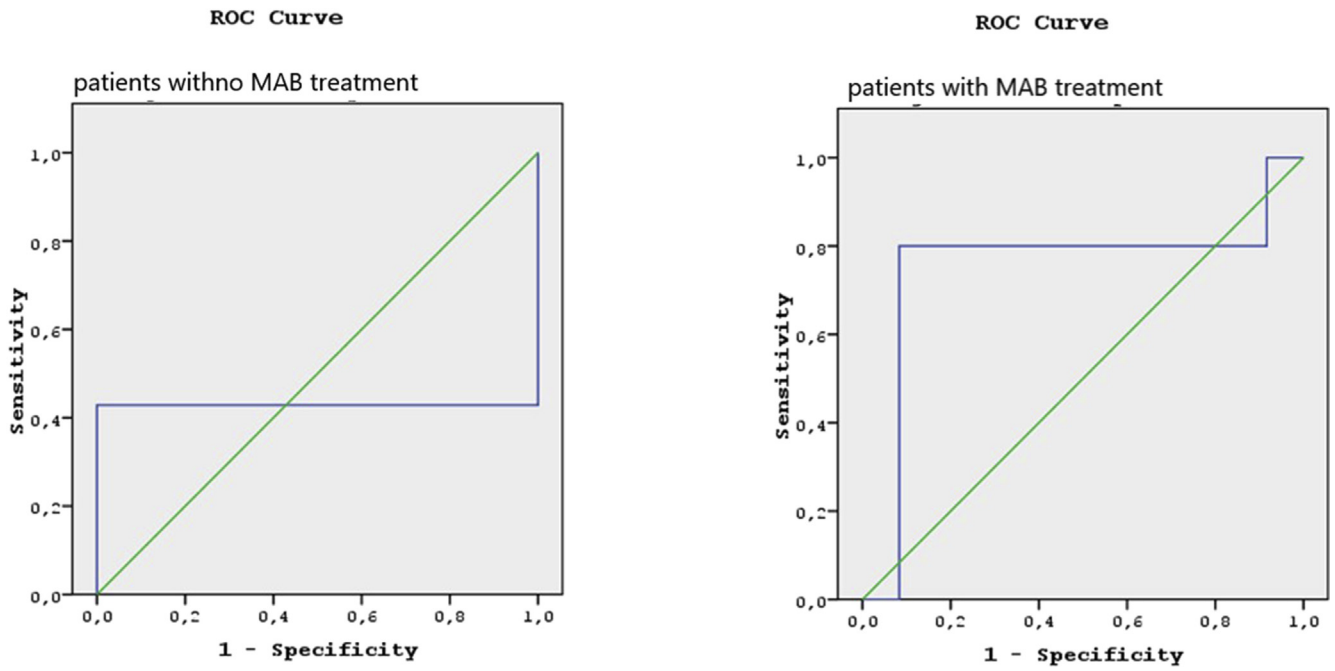

Fig. 1. PSA level and PSMA PET positivity.

median PSA levels 1.99 μg/l, lesions were detected in 95.7% (67/70) of patients with ADT and 87.1% (155/178) of patients without ADT and there was no found statistically significant importance of ADT on ^{68}Ga PSMA PET/CT positivity.[7]

Most of the studies examined PSA and ADT effects on ^{68}Ga PSMA PET/CT positivity were analyzed as discussed above, in patients with higher PSA levels. There are a few studies focused on affecting factors on ^{68}Ga PSMA PET/CT in patients with PSA level <2 μg/l, in the literature. In a study included 28 patients with median PSA 0.22 μg/l, the detection rate was found 60.7% like other studies but PSA levels were found similar between in patients with positive ^{68}Ga PSMA PET/CT and negative.[13] In our trial, PSA levels of most patients were under 1 μg/l and the median PSA level was calculated as 1.03 μg/l. PSA range was very narrow and we found that there was only adjuvant MAB treatment as a factor affecting ^{68}Ga PSMA PET/CT positivity in patients with this narrow PSA range. Also, we found that PSA value is important in determining which patients should be performed a PSMA PET in patients who had no received adjuvant MAB treatment.

There are a few limitations in this study. Firstly, we have planned this trial as a retrospective study. Secondly, we could separate the patients into two groups as PSA<1 μg/l vs >1 μg/l levels there were not sufficient patients for more grouping according to PSA levels. Also, we could not obtain the data of MAB treatment duration and which criteria was used to initiate MAB but there was no statistical difference between risk groups in terms of PSMA PET/CT positivity. The strength of our study was that the number of patients received adjuvant MAB treatment was similar in groups and this is the first study showed that the presence of MAB treatment maybe guides to perform ^{68}Ga PSMA PET/CT in patients lower PSA levels.

5. Conclusion

Clinicians may perform 68Ga PSMA PET/CT in low PSA levels to detect lesions in biochemical recurrent prostate cancer patients who had received MAB treatment and in patients with higher PSA levels who had no received MAB treatment.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

1. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. *CA A Cancer J Clin*. 2014;64:9–29. https://doi.org/10.3322/caac.21208.
2. Tosoian JJ, Gorin MA, Ross AE, et al. Oligometastatic prostate cancer: definitions, clinical outcomes, and treatment considerations. *Nat Rev Urol*. 2017;14:15–25. https://doi.org/10.1038/nrurol.2016.175.
3. Aus G, Abbou CC, Bolla M, et al. EAUguidelines on prostate cancer. *Eur Urol*. 2005;48:546–551. https://doi.org/10.1016/j.eururo.2005.06.001.
4. Tree AC, Khoo VS, Eeles RA, et al. Stereotactic body radiotherapy for oligometastases. *Lancet Oncol*. 2013;14:e28–e37. https://doi.org/10.1016/S1470-2045(12)70510-7.
5. Kosuri S, Akhtar NH, Smith M, et al. Review of salvage therapy for biochemically recurrent prostate cancer: the role of imaging and rationale for systemic salvage targeted anti-prostatespecific membrane antigen radioimmunotherapy. *Adv Urol*. 2012;2012:921674. https://doi.org/10.1155/2012/921674.
6. Rauscher I, Maurer T, Beer AJ, et al. Value of 68Ga-PSMA HBED-CC PET for the assessment of lymph node metastases in prostate cancer patients with biochemical recurrence: comparison with histopathology after salvage lymphadenectomy. *J Nucl Med*. 2016;57:1713–1719. https://doi.org/10.2967/jnumed.116.173492.
7. Eiber M, Maurer T, Souvatzoglou M, et al. Evaluation of hybrid 68Ga-PSMA ligand PET/CT in 248 patients with biochemical recurrence after radical prostatectomy. *J Nucl Med*. 2015;56:668–674. https://doi.org/10.2967/jnumed.115.154153.
8. 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;42:197–209. https://doi.org/10.1007/s00259-014-2949-6.
9. Brito AET, Mourato FA, de Oliveira RPM, et al. Evaluation of whole-body tumor burden with ^{68}Ga-PSMA PET/CT in the biochemical recurrence of prostate cancer. *Ann Nucl Med*. 2019;33:344–350. https://doi.org/10.1007/s12149-019-01342-z.
10. Yilmaz U, Komek H, Can C, et al. The role of (^{68}Ga)PSMA I&T in biochemical recurrence after radical prostatectomy: detection rate and the correlation between the level of PSA, Gleason score, and the SUV_{max}. *Ann Nucl Med*. 2019. https://doi.org/10.1007/s12149-019-01360-x ([Epub ahead of print]).
11. Hohberg M, Kobe C, Täger P, et al. Combined early and late [^{68}Ga]PSMA-HBED-

CC PET scans improve lesion detectability in biochemical recurrence of prostate cancer with low PSA levels. *Mol Imaging Biol*. 2019;21:558–566. https://doi.org/10.1007/s11307-018-1263-2.
12. Hope TA, Goodman JZ, Allen IE, et al. Metaanalysis of ^{68}Ga-PSMA-11 PET accuracy for the detection of prostate cancer validated by histopathology. *J Nucl Med*. 2019;60:786–793. https://doi.org/10.2967/jnumed.118.219501. Epub 2018 Dec 7.
13. Bashir U, Tree A, Mayer E, et al. Impact of Ga-68-PSMA PET/CT on management in prostate cancer patients with very early biochemical recurrence after radical prostatectomy. *Eur J Nucl Med Mol Imaging*. 2019;46:901–907. https://doi.org/10.1007/s00259-018-4249-z.