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Original Scientific Paper

INDICATIONS AND RESULTS FOR GA-68 PSMA PET/CT IN PATIENTS WITH BIOCHEMICAL RELAPSE OF PROSTATE CANCER

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SUMMARY – In order to evaluate the diagnostic performance of ^{68}Ga-PSMA PET-CT, we retrospectively analysed 100 patients with biochemically confirmed recurrence (BCR) of prostate cancer (PC). We compared positivity rates of PSMA PET scans with well-established disease indicators such as serum PSA levels, initial PSA (iPSA), PSAdt (PSA doubling time), elapsed time from prostatectomy, and Gleason score (GS). Of the 100 studies, 56 (56%) had lesions with pathological ^{68}Ga-PSMA uptake. Positivity rate of PSMA PET studies was 50% (28/56) for PSA levels of 0.2-0.5 ng/mL, 47.83% (11/23) for PSA 0.51-1 ng/mL, 71.43% (10/14) for PSA 1.01-2 ng/mL, and 100% (7/7) for patients with PSA above 2.01 ng/mL. PSMA-PET/CT study positivity correlated with higher Gleason score (3+4 – 31.82%, 4+3 – 63.16%, 8 – 60%, and 9 – 85.71%). Local recurrence was found in 19.43% and lymph node metastases in 75% of studies with pathological tracer uptake, while bone metastases were found in 25% of PSMA-PET/CT positive studies. Regarding PSAdt, the PSMA-PET/CT positivity rate was 66.67% (20/30) in cases with short PSAdt of less than 6 months, 57.14% (12/21) for PSAdt >6≤12 months, whereas only 23.53% (4/17) were positive in a group with very long PSAdt of >12 months. We have demonstrated that PSAdt may be considered the main positivity predictor of disease recurrence. Shorter PSAdt, even with low values of serum PSA, was linked with a higher positivity rate, while longer PSAdt was most often linked with negative scans. ^{68}Ga-PSMA PET/CT is a sensitive PET method for the detection and localization of lesions in early biochemical recurrence of disease, even in cases with very low PSA serum values.

Key words: *^{68}Ga-PSMA PET/CT; prostate cancer; biochemical recurrence; prostate-specific-antigen; PSA kinetics; PSA doubling time*

Introduction

According to GLOBOCAN 2018 estimates, prostate cancer is the second most common malignancy in the male population worldwide, accounting for around 7% of all cancers in men, and the fifth cause of death from malignancies[1,2]. Increased life expectancy and easy-to-access screening methods are responsible for the current trend of increasing incidence. A large number of patients are diagnosed with local disease at an early tumor stage, for which the primary therapeutic approach is radical prostatectomy (RP) or radiation therapy[3].

Following RP, PSA typically reaches a nadir that is undetectable within weeks of surgery[4].

Biochemical recurrence (BCR) is a clinical state characterized by rising PSA serum levels to >0.2 ng/

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mL after radical prostatectomy or an increase of more than 2 ng/mL above the PSA nadir (lowest PSA value following radiation therapy), with or without clinical and radiographic signs of metastases. Elapsed time to biochemical recurrence can vary from 20 to 38 months[5]. After radiotherapy, most patients experience a biochemical recurrence in the first three years, but longer follow-ups are recommended because in some cases recurrence can be observed after as much as fifteen years[6]. Patients can have variable clinical courses, from indolent disease to rapid progression, with metastases in the lymph nodes and bones[7]. Early localization of the disease is key to starting or modifying treatment. Standard imaging methods (bone scan, CT, MRI scan) are not very sensitive, especially in patients with BCR who have low PSA levels. Conventional imaging techniques face significant restrictions as they fail to detect lymph nodal lesions smaller than 8 mm, since they cannot differentiate infiltrated from non-metastatic lymph nodes[8].

Molecular hybrid imaging, such as choline PET/CT scans, can diagnose and localize cancer recurrence in patients with BCR, but with lower sensitivity (detection rates for PSA levels less than 1 ng/mL are 36%)[9]. Prostate specific membrane antigen (PSMA) is a transmembrane protein primarily present in all prostatic tissues. PSMA is a transmembrane protein (glutamate carboxypeptidase II) and is overexpressed in different kinds of malignancies, but most notably in prostate cancer cells – especially in the higher PC grade group, recurrent PC, and metastatic cancer[10]. In benign prostate tissue, it is expressed only weakly or not at all. PSMA is a great target for specific molecular imaging, providing us with a method that has superior detection rates in patients with BCR with still low PSA values[11,12]. Therefore, a number of PET agents have been designed and developed to attach to the PSMA molecule, including the most extensively studied molecule – ^{68}Ga-PSMA.

Patients and methods

Patient characteristics

In our retrospective study, we analysed 100 patients who underwent ^{68}Ga-PSMA PET-CT scans between April 2021 and January 2022 at the Department of Nuclear Medicine, University Hospital Centre Zagreb. We evaluated patients who had undergone primary definitive treatment and who had BCR of PC. The inclusion criteria for the performance of a ^{68}Ga-PSMA-11 PET/CT scan were: (a) histopathologically proven primary PC; (b) treatment with RP or RT (with or without ADT); and (c) proven BC. **Table 1** summarizes the clinical and pathological characteristics of our patients. At the time of the scan, the median PSA value was 0.46 (range 0.2-17.4). The current 2016 World Health Organization (WHO) classification of prostate cancer uses a five-grade group system, which is easier to apply and has a much better correlation to the prognosis and therapeutic needs of patients[13]. A Gleason score 3+4 was identified in 22 patients, 38 patients had GS 4+3, 15 patients had GS 8, and 12 patients had GS 9. The primary treatment for most patients was radical prostatectomy (92%). 54 patients received treatment with radiotherapy, while 23 patients had systemic androgen deprivation therapy (ADT) in their medical history.

Table 1. Patient characteristics

Characteristics (n)	Parameters (n)
Number of patients	100
Age (y) mean, (range)	68.25±7.55; (49-84)
Initial PSA median (range)	9.33 (3.9-187) ng/mL
Gleason score	
7 (3+4)	22
7 (4+3)	38
8	15
9	12
PSA mean	0.8 ng/mL
PSA median	0.46 ng/mL
PSA range	0.2-17.4 ng/mL
PSAdt mean	8.5 months
PSAdt median	6 months
Prior treatment of PC	
Surgery	86
Surgery + radiotherapy	54
Radiotherapy only	5
ADT	23
Dose administered	mean 207.4 MBq, range 130-280 MBq

PSA = prostate specific antigen; PSAdt = PSA doubling time; ADT = androgen deprivation therapy; PC = prostate cancer

^{68}Ga-PSMA PET/CT

^{68}Ga was produced from a ^{68}Ge/^{68}Ga radionuclide generator and complexed with PSMA molecules at our radiopharmaceutical laboratory. Patients were administered a synthesized ^{68}Ga-PSMA complex solution as an intravenous bolus injection (mean 207.4 MBq, range 130-280 MBq). At 45 to 90 minutes after injection, standard image acquisition was performed. Low-dose CT images were obtained for both attenuation correction and localization of lesions from the base of the skull to the proximal parts of the thigh.

Results

Out of 100 patients included in our study, 56% showed one or more lesions PET positive for PC recurrence, whereas 44% had negative PSMA PET/CT results, with no detectable disease. A significant increase in the positivity rate was observed with rising PSA levels. Pathological uptake of ^{68}Ga-PSMA was found in all cases with PSA serum levels above 2.01 ng/mL and in 71% of cases with PSA values of 1.01-2.00 ng/mL. A lower but still clinically relevant positivity rate of 49% was observed in patients with PSA levels between 0.2-1.0 ng/mL (50% (28/56) for PSA levels of 0.2-0.5 ng/mL, 47.83% (11/23) for PSA 0.51-1.0 ng/mL) (**Figure 1**). We thus demonstrated that PSA was higher in PET-positive vs. PET-negative scans. Patients with pathological radiotracer uptake had a mean PSA of 1.27 ng/mL ± 1.36, a range 0.20-5.65 ng/mL, and a median of 0.495 ng/mL, while mean PSA in negative studies was 0.51 ng/mL ± 0.256, range 0.22-1.22 ng/mL, and median of 0.47 ng/mL.

The highest observed positivity rate was in WHO grade group 5 (Gleason score 9-10) – 66.67% (8/12) and in grade group 4 (Gleason score 8) – 53% (8/15). In patients with grade 3 (Gleason score of 4+3=7), 63.16% of studies had pathological uptake, while 31.82 % had positive scans in grade group 2 (Gleason score 3+4=7).

PSA	Number of patients	Positivity rate	
ng/mL			%
0.2-0.5	56	28	50.00%
0.5-1.0	23	11	47.83%
1.0-2.0	14	10	71.43%
2.0-5.0	4	4	100.00%
>5.0	3	3	100.00%

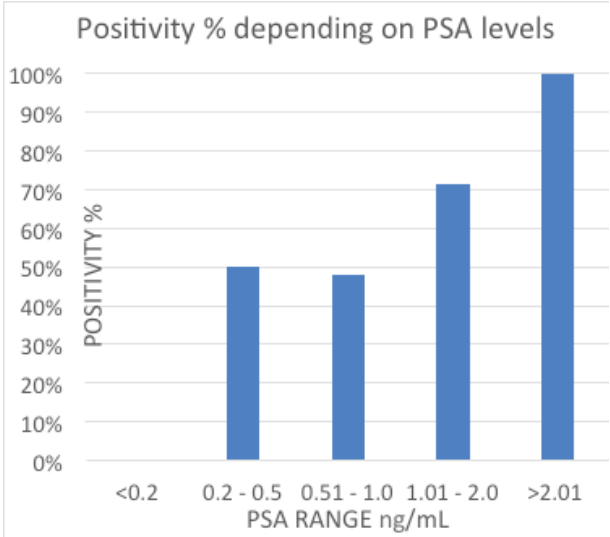

Figure 1. Percentage of positive 68Ga-PSMA PET/CT depending on PSA levels.

Regarding the doubling time of PSA (PSAdt), out of 68 patients, PSMA-PET/CT positivity rate was 66.67% (20/30) in patients with PSAdt ≤6 months, 57.14% (12/21) for PSAdt >6≤12 months, whereas only four patients were positive 23.53% (4/17) in the group with very long PSAdt of >12 months (**Figure 2**).

PET-positive lesions within the prostate bed were found in 16% (9/56) and suspicious pelvic lymph nodes and/or distant lymph node metastases were identified in 73% (41/56) of the studies. ^{68}Ga-PSMA positive bone metastases were diagnosed in 30% (17/56) of the studies. Visceral PET-positive lesions in the lungs

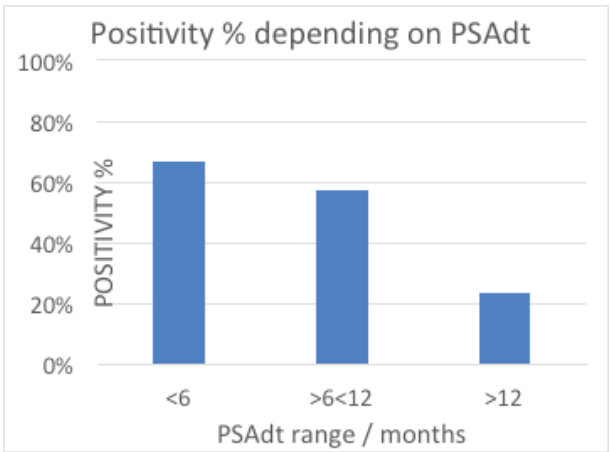

Figure 2. Percentage of positive 68Ga-PSMA PET/CT depending on PSAdt.

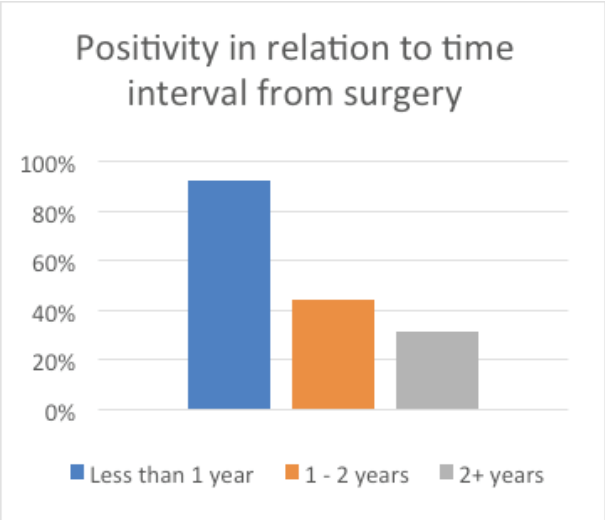

Figure 3. Percentage of PET positive studies in relation to time elapsed from prostatectomy. Patients who had ADT included or were treated with RT after surgery were excluded.

were found in one patient. Patients with bone metastases showed approximately the same PSA values as patients with metastases in the lymph nodes (median of 0.53 ng/mL vs. 0.45 ng/mL). Higher levels of PSA values were observed in patients with local recurrence of the disease (median of 0.84 ng/mL) (**Figures 4-7**).

Out of all patients, androgen deprivation therapy was reported in 23% of the patients. 78% (18/23) of patients that were AT-treated showed a positive ^{68}Ga-PSMA PET-CT.

In the group of patients who were treated only with radical prostatectomy, we observed that patients who had the procedure within a year of a PET scan had a higher percentage of PET-positive scans – 93% (13/14). If the PET/CT scan was done in the period between one and two years after surgery, lesions with pathological uptake were found in 44% (4/9) of cases. Meanwhile, only 32% (6/19) of studies were PET positive if more than 2 years had passed between the scan and prostatectomy (**Figure 3**).

Regarding initial PSA (iPSA), pathological uptake was observed in 42% of studies with iPSA below 10 ng/mL, 57.9% of studies were PET-positive in the group with iPSA of 10-20 ng/mL, and 83.3% of the studies were positive if iPSA was higher than 20 ng/mL.

Clinically significantly, in the group with PSA levels of 0.2-0.5 ng/mL where we diagnosed pathological uptake in 50% of patients, median PSA was 0.3 ng/mL in both positive and negative studies. Interestingly, the main difference in those groups (negative vs. positive) was in PSAdt time (median of 12 vs 5.5 months).

Discussion

Our results and the positivity rates we have identify suggest the important clinical utility of ^{68}Ga-PSMA-

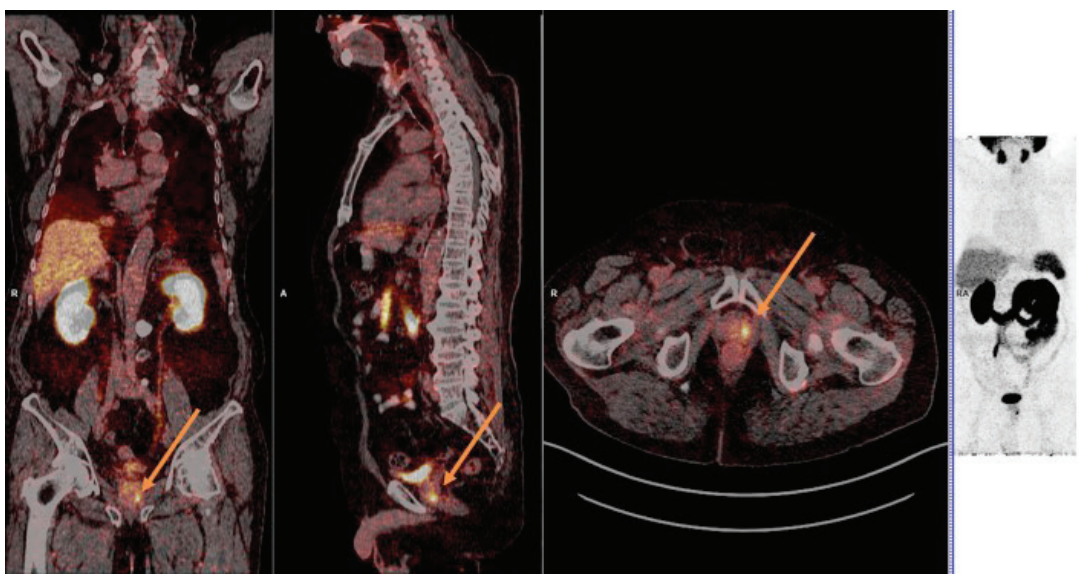

Figure 4. Local prostate recurrence in a patient treated with radiotherapy (PSA 2.30 ng/mL, PSAdt less than 6 months). SUVmax 19.

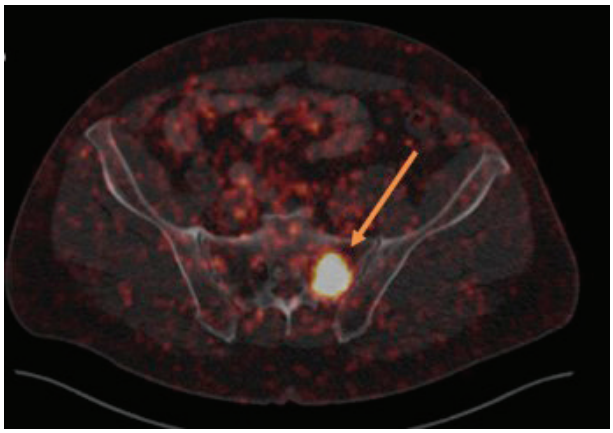

Figure 5. Bone metastasis in the sacrum in a patient with PSA 0.56 ng/mL. The patient had a radical prostatectomy and PSAdt of only 2 months. SUVmax 39.6.

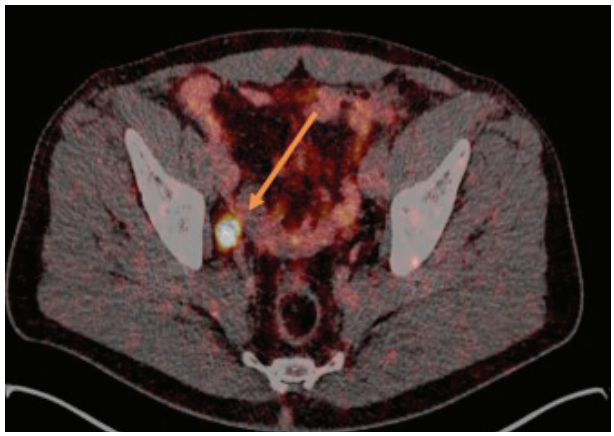

Figure 6. Lymph node metastasis behind external iliac vessels in a patient with PSA 0.21 ng/mL. The patient had a radical prostatectomy 4 years before BCR and PSAdt of only 2 months. SUVmax 45.

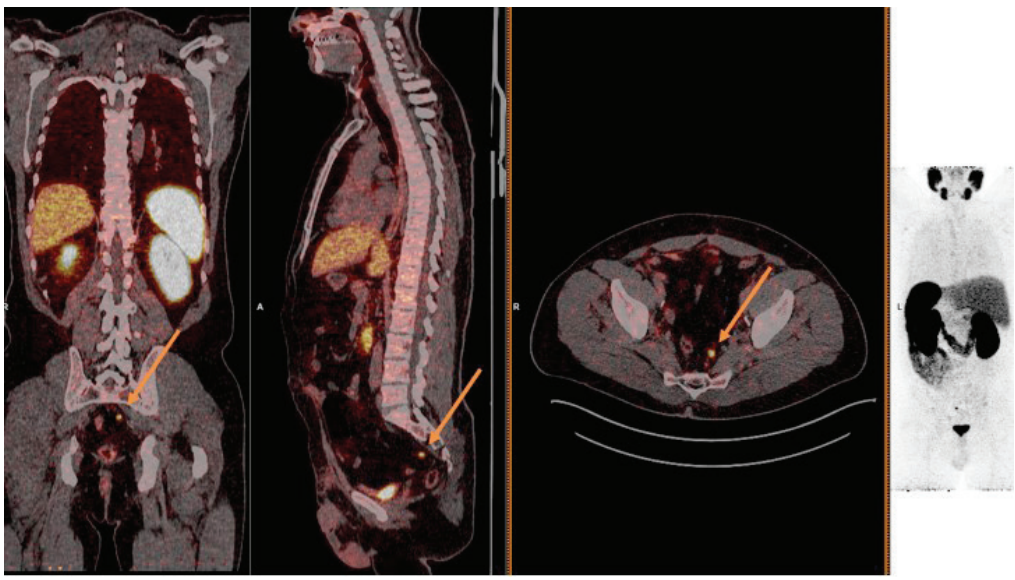

Figure 7. Presacral lymph node metastasis in a patient with PSA 0.22 ng/mL. The patient had radical prostatectomy 9 years before BCR and PSAdt of only 4 months. SUVmax 35.

PET/CT in patients with biochemical recurrence of prostate cancer. Our study showed high sensitivity even with very low PSA levels, and it was possible to localize lesions in non-enlarged lymph nodes. We were also able to detect pathological uptake in bone metastases without lesions visible on CT. The sensitivity of our PSMA study was similar to that reported in earlier studies.

In recent years, ^{68}Ga-PSMA/PET CT has become a powerful diagnostic imaging modality with high sensitivity and specificity in patients with confirmed biochemical recurrence of PC, even with very low PSA values[12,14]. A recent meta-analysis of 37 articles assessing the diagnostic accuracy of ^{68}Ga-PSMA PET in patients with BCR showed that the overall positivity was 45% for PSA values of 0.2-0.5 ng/mL and 95% for PSA values >2 ng/mL[14]. Our study found results comparable to this meta-analysis (50% for PSA levels of 0.2-0.5 ng/mL and 100% for PSA levels >2 ng/mL).

^{68}Ga-PSMA has been shown to have better detection rates than ^{18}F-choline tracers in of recurrent PCa[15,16]. The observed positivity rates in our study were correlated with higher PSA levels and Gleason score.

Androgen deprivation therapy is known to affect and reduce metabolism in prostate cancer cells, but our findings have shown a high percentage of positive ^{68}Ga-PSMA PET studies even in patients with ADT in their therapy. Patients with short PSA doubling time had a very high positivity rate (93% with PSAdt under a year), making PSAdt one of the main PET positivity predictors of disease recurrence in our study.

Conclusion

^{68}Ga-PSMA PET/CT is a very sensitive method for the detection and localization of tumor activity in patients with biochemical recurrence of prostate cancer.

When the ^{68}Ga-PSMA PET/CT scan was performed in patients who were treated with radical prostatectomy alone (and had confirmed BCR after surgery), the chance for a positive scan was very high in the first year after the surgery. A longer period from surgery was linked with a lower positivity rate. We have shown that PSAdt may be considered the main positivity predictor of disease recurrence. Shorter PSAdt, even with low PSA, was associated with a higher positivity rate, while longer PSAdt was most often linked with negative scans.

Early prostate cancer recurrence, even in patients with very low PSA serum levels, can be detected with ^{68}Ga-PSMA PET/CT, providing us with a very useful imaging modality and enabling modification and individualization of the therapy for each patient.

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Sažetak

INDIKACIJE I REZULTATI GA-68 PSMA PET/CT-A U PACIJENATA S BIOKEMIJSKIM POVRATOM RAKA PROSTATE

I. Rogić, A.T. Golubić, M. Dobrenić, M. Žuvić, T. Šmitran, N. Jukić i *D. Huić*

Cilj ove studije bio je procijeniti efikasnost ^{68}Ga-PSMA PET/CT pretrage u pacijenata koji su imali biokemijski verificirani relaps karcinoma prostate i usporediti rezultate pretrage s vrijednostima PSA, inicijalnim PSA (iPSA), PSAdt (vrijeme udvostručenja), GS (Gleason zbroj) i vremenom od radikalne prostatektomije. Lezije s patološkim nakupljanjem ^{68}Ga-PSMA pronađene su u 56% studija. U grupi pacijenata s PSA 0.2-0.5 ng/ml patološke lezije nađene su u 50% (28/56) studija, u 48% u grupi s PSA 0.51-1 ng/ml, u 71% u grupi s PSA 1.01-2 ng/ml i 100% (7/7) u pacijentima s PSA većim od 2.01 ng/ml. Rezultati PSMA-PET/CT korelirali su s višim Gleason zbrojem - Gleason zbroj 3 + 4 - 31.82%, 4 + 3 - 63.16%, 8 - 60%, and 9 - 85.71% studija imali su lezije s patološkim nakupljanjem PSMA. Lokalni recidiv bolesti nalazio se u 19% pozitivnih studija, limfni čvorovi su bili zahvaćeni u 75%, dok su metastaze u kostima nađene u 25% pozitivnih studija.

PSAdt je bitan prediktor rezultata PSMA-PET/CT-a. U pacijenata s kratkim vremenom udvostručenja PSA (manje od 6 mjeseci) PET pozitivno je bilo 67% studija, dok u pacijenata s duljim vremenom udvostručenja primijetili smo više negativnih nalaza.

^{68}Ga-PSMA PET/CT je kvalitetna, visoko specifična i senzitivna hibridna metoda koja omogućava pacijentima s biokemijskim relapsom bolesti ranu lokalizaciju lezija, modifikaciju i individualni pristup terapiji.

Ključne riječi: *Ga-68 PSMA; PET/CT; karcinom prostate; biokemijski relaps; PSA kinetika; Gleason grupa; udvostručenje PSA; hibridno oslikavanje.*