Factors affecting overall survival and progression-free survival in patients with metastatic castration resistant prostate cancer received ^{177}Lu PSMA I&T therapy

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Abstract

Objective: Lutetium-177 (^{177}Lu) prostate specific membrane antigen (PSMA) radionuclide therapy (RNT) is an effective and safe treatment option in patients with metastatic castration resistant prostate cancer (mCRPC). The first aim of this study was to determine RNT response rate. The second and main aim of this study is measure overall and progression-free survival (OS and PFS) and to determine the factors have effect on OS and PFS. **Materials and Methods:** Patients with mCRPC had ^{177}Lu PSMA RNT every 6-8 weeks. Therapy response of each cycle determined wit PSA after 6-8 weeks. Overall survival and PFS were measured, then effects of age, Gleason grade, local recurrence, extraabdominopelvic located lymph node metastasis, visceral metastasis, prostate specific antigen (PSA) changing after the first RNT, pretreatment PSA, hemoglobin (Hb), alkaline phosphatase (ALP) and lactate dehydrogenase (LDH) values on survivals were determined. **Results:** Forty-five patients were treated with total of 164 cycles of RNT. Fifteen patients (33%) had PSA decline of ≥50%, 23 patients (51%) showed any PSA decline and 20 patients (44%) showed PSA increase of ≥25%. Median OS and PFS were 17,1 months and 7,4 months. Patients had any or ≥50% PSA response after the first cycle, lower initial ALP (<120U/L) had longer OS and PFS. Patients had normal Hb showed longer OS and patients had lower initial PSA (<51ng/mL) had longer PFS. Patients had PSA progression of ≥25% had shorter OS and PFS. **Conclusion:** Prostate specific antigen response after the first cycle, lower initial ALP is related to longer OS and PFS. Normal pretreatment Hb is a predictor of longer OS and lower initial PSA is related to longer PFS. Prostate specific antigen progression after the first cycle causes shorter OS and PFS.

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Introduction

Prostate cancer is the second most diagnosed malignancy and the fifth most cause of cancer related death in men [1]. Survival is high in localized disease [2].

Antiandrogen therapy supplies high treatment success in the early stages of disease but resistance of antiandrogen drugs and metastases is seen during the course of disease [3]. In this situation; abiraterone, enzalutamide, docetaxel, cabazitaxel, sipuleucel-T and radium-223 prolongs overall survival [4-9]. Lutetium-177 (^{177}Lu) prostate specific membrane antigen (PSMA) radionuclide therapy (RNT) is one of the options if progression occurs despite these treatments.

Prostate specific membrane antigen (PSMA) called glutamate carboxypeptidase 2 is a type 2 membrane glycoprotein [10-11]. It is overexpressed on the prostate cancer cell surfaces [12]. There are many studies about efficiency and safety of ^{177}Lu PSMA RNT on metastatic castration resistant prostate cancer (mCRPC) in the literature [13-22].

The aim of this study to determine efficiency and factors affecting overall survival (OS) and progression-free survival (PFS), to identify patients who may benefit better from RNT.

Subject, Material and Methods

Patient population

In this analysis, 45 patients who had mCRPC treated with ^{177}Lu PSMA between October

2015 and October 2018 were included. All patients had been treated with at least one line of chemotherapy (docetaxel and/or cabazitaxel) and at least one line of antiandrogen drug (abiraterone and/or enzalutamide) and progressed by biochemically or radiologically. Treatment decision was taken by multidisciplinary tumor board. All patients received detailed information about treatment process and all possible adverse events and gave their written inform consent before treatment. Local ethics committee approved this study.

Patient preparation

All patients underwent gallium-68 (^{68}Ga) PSMA positron emission tomography/computed tomography (PET/CT) prior to treatment to demonstrate PSMA uptake of malign foci. Blood count, renal and liver laboratory parameters, electrolytes, prostate specific antigen (PSA), lactate dehydrogenase (LDH) and alkaline phosphatase (ALP) tests were performed for possible toxicities before treatment.

Preparation and administration of ^{177}Lu PSMA

Lutetium-177 PSMA I&T was been synthesized in our department with previously described methods [23]. All patients were administered intravenous granisetron in 100cc of % 0,9 NaCl for premedication of nausea and vomiting. An our later, 7,4GBq fix dose of ^{177}Lu PSMA was infused to patients intravenously over 30 minutes. All patients were observed by hospitalized for 24 hours and ^{177}Lu PSMA whole body anterior-posterio planar scintigraphic views were made to confirm uptake of radiopharmaceutical by tumor foci at 24th hour.

Evaluation of safety

Clinical examination, control of the blood count, renal and liver laboratory parameters, and electrolytes, PSA, LDH and ALP were made 2 weeks after treatment and repeated monthly. If there were no renal, liver and bone morrow toxicities and no withdraw by patient consent, ^{177}Lu PSMA RNT was repeated every 6-8 weeks.

Evaluation of response and survival

According to the Prostate Cancer Working Group-3 (PCWG-3) criteria, PSA decline ≥50% was evaluated as biochemical response, PSA increase ≥25% was evaluated as biochemical progression and any other PSA changing out of these was evaluated as stable disease [3].

Overall survival was the primary clinical endpoint. Overall survival was defined as the time between first RNT and death. Progression-free survival was defined as the time between first RNT and biochemically or radiologically progression.

Effects of age at the first RNT, ISUP (International Society of Urological Pathology) Gleason grade [24], local recurrence, extraabdominopelvic located lymph node metastasis and visceral metastasis according to ^{68}Ga PSMA PET/CT, PSA changing after the first RNT, pretreatment PSA, hemoglobin (Hb), ALP and LDH values on OS and PFS were evaluated. For cut-off values of laboratory tests, upper limits of tests were selected for ALP (120U/L) and LDH (220U/L); lower limit of test were selected for Hb (13g/dL). Further, another value of 10,8 g/dL for Hb, 51ng/mL for PSA were determined as cut-off value according to therapy responses and pretreatment values.

Statistics

SPSS statistic 24 (IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp.) was used for statistical analysis. Descriptive statistics reported as median (minimum-maximum) because all values of independent variables were out of normality distribution. Kaplan-Meier analysis, log-rank test and Cox regression analysis were used to determine effects of multiple parameters on OS and PFS. Results of regression analysis were presented as Hazard ratio (HR) with corresponding 95% confidence intervals (95% CI). P values considered statistically significant if it is <0,05.

Results

Forty-five patients were treated with total of 164 cycles of RNT. Median number of cycle was 3 (1-8). Treatment doses were standard as 7,4 GBq for all patients and all cycles. Median follow-up time after the last cycle was 6 months (1-32 months). Only 10 patents were alive during this analyses. Detailed patients and lesions characteristics are presented in Table 1 and Table 2.

Table 1. *Detailed patient characteristics n:45.*

Parameters	Median	Minimum-maximum
Age	64	49-88
Gleason score	8	6-10
Gleason grade	4	1-5
PSA (ng/mL)	58	0,51-1594
LDH (U/L)	239	145-3256
ALP (U/L)	139	48-3424
Hb (g/dL)	10,9	7,4-14,2
Number of cycles	n	
1	4	
2	8	
3	13	
4	7	
5	6	
6	1	
7	3	
8	3	

Table 2. *Detailed lesions characteristics.*

	n	(%)
Local recurrence	26	(58)
Localization of metastasis		
Bone	39	(87)
Lymph node	30	(67)
Lung	4	(9)
Liver	5	(11)
Surrenal	4	(9)
Other	3	(7)
Extraabdominopelvic lymph node metastasis	21	(47)

Response after the first and last cycle

Fourteen patients (31%) showed PSA decline of ≥50% after the first cycle. Of these responders, 9 (64%) showed PSA decline of ≥50% after the last cycle. Twenty-four patients (53%) showed any PSA decline after the first cycle, 12 of them (50%) showed PSA decline of ≥50% after the last cycle. Seventeen patients showed PSA increase of ≥25% after the first cycle, only 3 of them (18%) showed PSA response or PSA stayed stable of these patients. Treatment responses after the first and last cycles are presented in Table 3.

Regarding to pretreatment and after the last cycle PSA, 15 patients (33%) had PSA decline of ≥50%, 23 patients (51%) showed any PSA decline and 20 patients (44%) showed PSA incerase of ≥25%.

Survival analyses

Median OS and PFS were 17,1 months and 7,4 months for all patients.

Patients who responded treatment with PSA decrease of ≥50% after the first cycle had significantly longer OS (21,8 months, 95% CI 17,6-25,9) than not responded with PSA decrease of ≥50% after the first cycle (13,7 months, 95% CI 8,9-18,6; P=0,025; Figure 1A). Also, responders with PSA decrease of ≥50% after the first cycle had significantly longer PFS (11,7 months, 95% CI 8,9-14,5) than the others (5,6 months, 95% CI 4,1-7,1; P=0,001; Figure 1B).

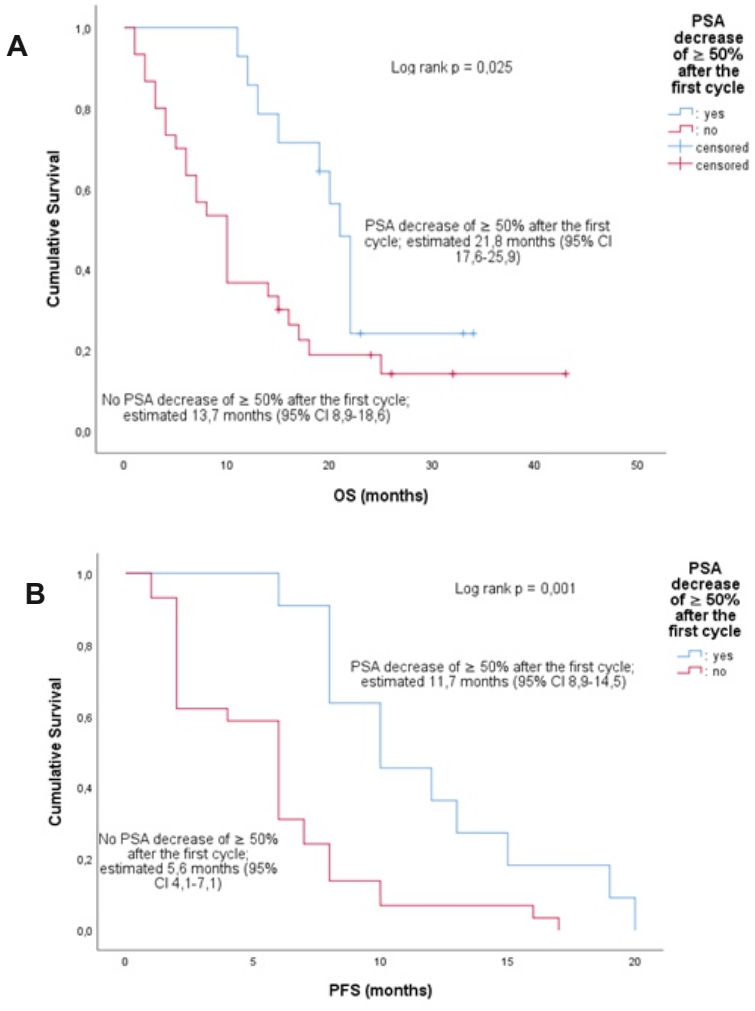

Figure 1. Kaplan-Meier plots of PSA decline of ≥50% after the first cycle and A) overall survival, B) progression-free survival.

Kaplan-Meier survival analysis showed significantly longer OS of 19,1 months (95% CI 15,3-22,8) in patients who showed any PSA decline after the first cycle than not responders (13,8 months; 95% CI 7,2-20,4; P=0,048; Figure 2A). Also, responders with any PSA decrease after the first cycle had significantly longer PFS (10,6 months, 95% CI 8,7-12,4) than the others (4,0 months, 95% CI 2,8-5,2; P=0,000; Figure 2B).

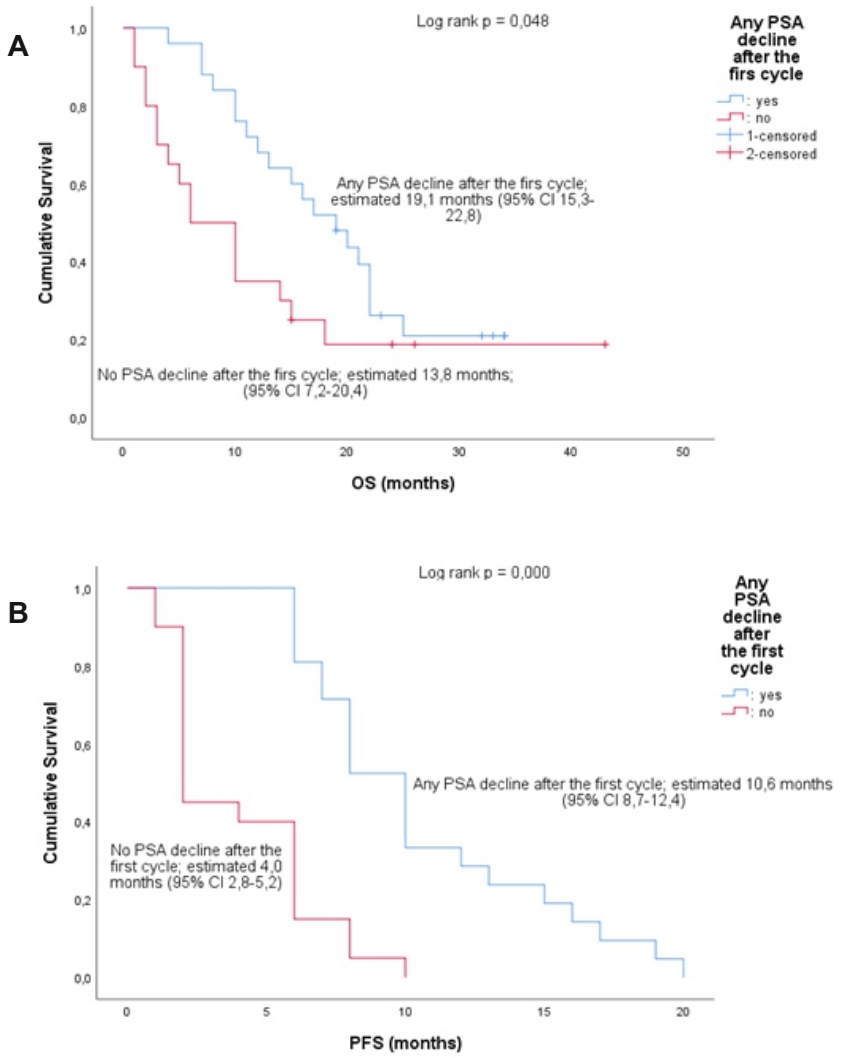

Figure 2. Kaplan-Meier plots of any PSA decline after the first cycle and A) overall survival, B) progression-free survival.

Patients who had PSA increase of ≥25% after the first cycle had significantly shorter OS (8,7 months, 95% CI 22,2-15,1; Figure 3A) and significantly shorter PFS (2,3 months, 95% CI 1,3-3,3; Figure 3B) than patients who did not have PSA increase of ≥25% after the first cycle (Median OS: 18,8 months, 95% CI 15,3-22,2 and median PFS: 9,4 months, 95% CI 7,9-11,0; P values=0,001 and 0,000, respectively).

Patients whose pretreatment ALP <120U/L had longer OS (23,7 months, 95% CI 17,4-30,1; Figure 4A) and longer PFS (9,8 months, 95% CI 7,3-12,5; Figure 4B) than patients whose pretreatment ALP ≥120U/L (Median OS: 11,7 months, 95% CI 8,2-15,2 and median PFS: 5,8 months, 95% CI 4,3-7,3; P values=0,008 and 0,009, respectively).

Pretreatment normal Hb values were related to significantly longer OS. Patients who had Hb≥13g/dL had significantly longer OS of 32,7 months (95% CI 23,8-41,6) than pretreatment anemic patients (Median OS: 13,8 months, 95% CI 10,6-16,9; P=0,011; Figure 5A). Median PFS in anemic patients (Median PFS: 6,7 months, 95% CI 5,3-8,2) was shorter than patients had normal pretreatment Hb values (Median PFS: 12,3 months, 95% CI 7,8-16,8), but difference was not statistically significant (P=0,054). Also patients whose Hb ≥ 10,8 had significantly longer OS (21,9 months, 95% CI 16,5-27,3) than Hb<10,8g/dL (11,1 months, 95% CI 6,9-15,3; P=0,014; Figure 5B).

There was no significant difference on OS between patients whose pretreatment PSA<51ng/mL (19,3 months, 95% CI 12,3-26,2) and ≥51ng/mL (15,6 months, 95% CI 11,5-19,7; P=0,634). But PFS were significantly longer for patients whose pretreatment PSA<51ng/mL (Median PFS: 8,7 months, 95% CI 6,4-10,9) than whose pretreatment PSA ≥51ng/ mL (Median PFS 5,6 months, 95% CI 4,2-7,1; P=0,022; Figure 6).

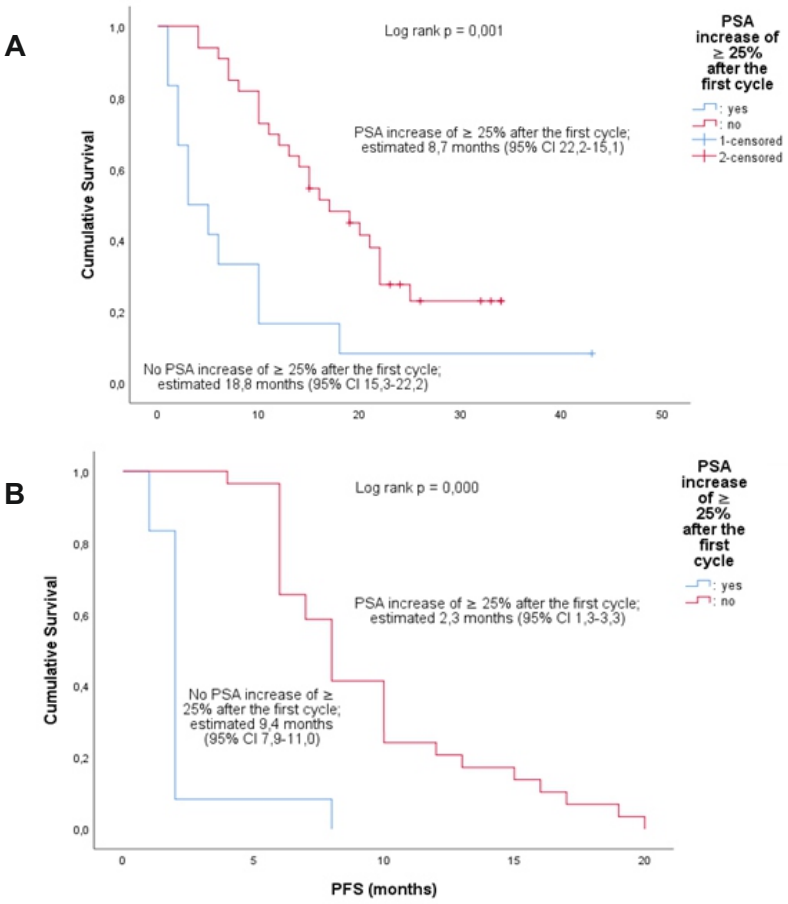

Figure 3. Kaplan-Meier plots of PSA increase of ≥50% after the first cycle and A) overall survival, B) progression-free survival.

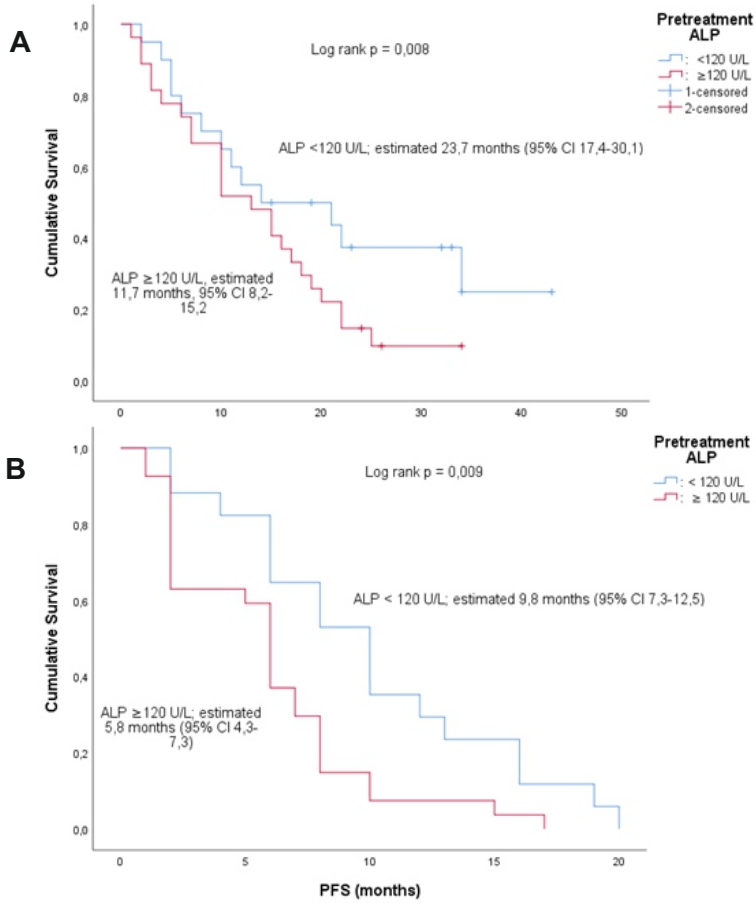

Figure 4. Kaplan-Meier plots of pretreatment ALP and A) overall survival, B) progression-free survival.

There were no effects of age, pretreatment LDH, local recurrence, extraabdominopelvic located lymph node metastasis and visceral metastasis according to ^{68}Ga PSMA PET/CT on OS and PFS (Table 4).

In multivariate analyse, normal Hb values was found as an independence factor for a longer OS (Hazard ratio: 4,810, 95% CI 1,080-21,428; P=0,039) (Table 5).

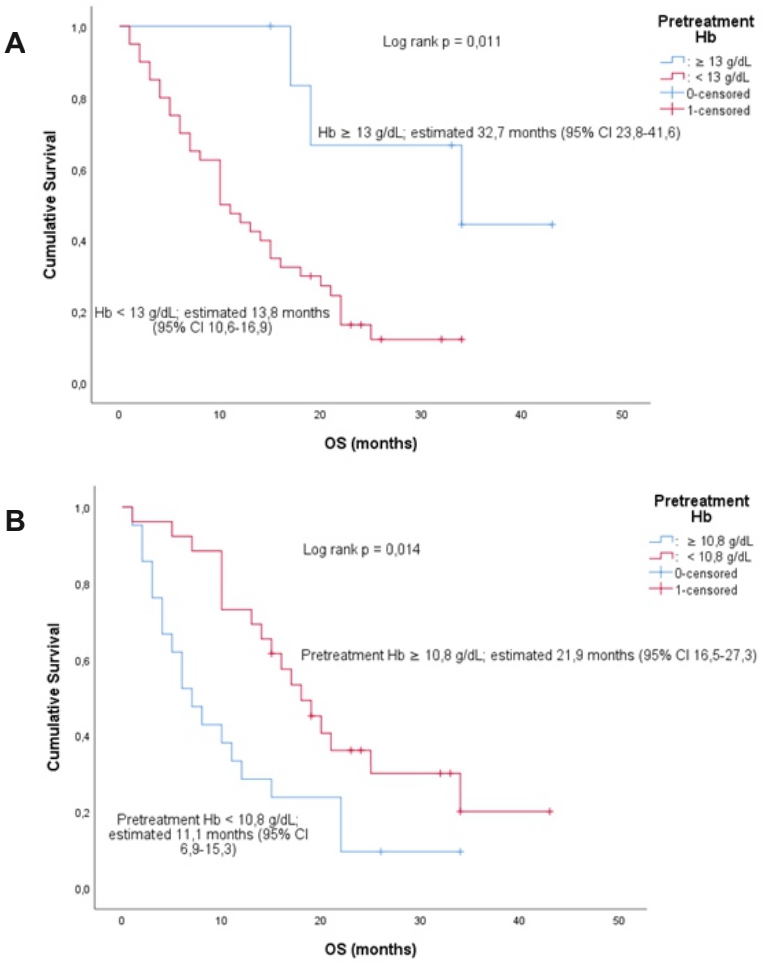

Figure 5. Kaplan-Meier plots of pretreatment hemoglobin and overall survival, cut-off value A) 13g/dL, B) 10,8g/dL.

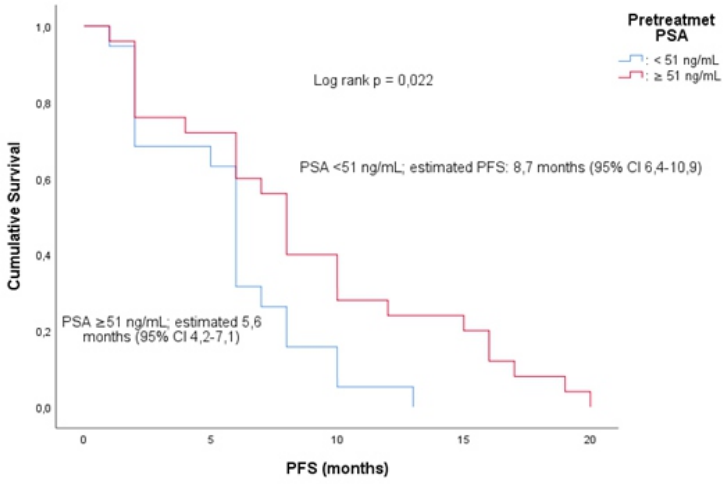

Figure 6. Pretreatment PSA and overall survival.

Table 3. *Relationship with treatment response after the first cycle and after the last cycle.*

		PSA changing after the last cycle compared to baseline PSA			
		Response n (%)	Stable n (%)	Progression n (%)	n
PSA changing after the firs cycle	Decline of ≥ 50%	9 (64,3)	4 (28,6)	1 (7,1)	14
	Any decline	12 (50)	8 (33,3)	4 (16,7)	24
	Decline of < 50%- increase of < 25%	3 (21,4)	4 (28,6)	7 (50)	14
	Increase of ≥ %25	1 (5,9)	2 (11,8)	14 (82,3)	17

Table 4. *Univariate analysis of overall and progression-free survivals.*

	Mean OS (months)	95% CI	P	Mean PFS (months)	95% CI	P
Age			0,827			0,677
<69	17,2	12,1-22,4		7,1	5,3-9,0	
≥69	15,5	10,8-20,3		7,7	5,2-10,2	
ISUP Gleason grade			0,824			0,174
≤2	13,6	5,9-21,1		5,8	4,1-7,5	
>2	16,1	11,7-20,5		7,5	5,8-9,3	
PSA			0,634			0,022
<51 ng/mL	19,3	12,3-26,2		8,7	6,4-10,9	
≥51 ng/mL	15,6	11,5-19,7		5,6	4,2-7,1	
LDH			0,378			0,215
<220 U/L	20,2	13,9-26,5		9,2	6,5-11,9	
≥220 U/L	14,2	10,2-18,3		6,6	4,9-8,3	
ALP			0,008			0,009
<120 U/L	23,7	17,4-30,1		9,8	7,3-12,5	
≥120 U/L	11,7	8,2-15,2		5,8	4,3-7,3	

(continued)

Hb			0,011			0,054
<13 g/dL	13,8	10,6-16,9		6,7	5,3-8,2	
≥13 g/dL	32,7	23,8-41,6		12,3	7,8-16,8	
<10,8 g/dL	11,1	6,9-15,3	0,014	7,1	5,9-8,6	0,072
≥10,8 g/dL	21,9	16,5-27,3		13,2	8,5-17,6	
Local recurrence			0,119			0,653
Yes	13,9	10,3-17,5		7,2	5,6-9,8	
No	21,5	14,5-28,5		7,7	5,2-9,1	
Extraabdominopelvic lymph node metastasis			0,930			0,506
Yes	13,6	9,3-17,8		6,8	4,9-8,7	
No	14,1	8,9-19,9		7,9	4,2-11,6	
Visceral metastasis			0,348			0,967
Yes	14,3	9,1-19,5		7,4	5,3-10,3	
No	19,1	13,8-24,5		7,8	5,5-9,3	
PSA decline of ≥50%			0,025			0,001
Yes	21,8	17,6-25,9		11,7	8,9-14,5	
No	13,7	8,9-18,6		5,6	4,1-7,1	
Any PSA decline			0,048			0,000
Yes	19,1	15,3-22,8		10,6	8,7-12,4	
No	13,8	7,2-20,4		4,0	2,8-5,2	
PSA increase of ≥25			0,001			0,000
Yes	8,7	22,2-15,1		2,3	1,3-3,3	
No	18,8	15,3-22,2		9,4	7,9-11,0	

OS: Overal survival,PFS: Progression-free survival,CI: Confidence interval,ISUP: International Society of Urological Pathology, LDH: Lactate dehydrogenase, ALP: Alkaline phosphatase, Hb: Hemoglobin

Table 5. Multivariate analysis of overal survival.

Factors	Grouping criteria	Hazard Ratio	%95 CI	P values
LDH_0	<220IU/L ≥220IU/L	1,610	0,729-3,554	0,2239
Hb_0	< 13 g/dL ≥13 g/dL	4,810	1,080-21,428	**0,039***
PSA decline of ≥ 50% after the firs cycle	Yes No	0,422	0,157-1,137	0,088
Any PSA decline after the firs cycle	Yes No	0,594	0,198-1,781	0,352
Visceral metastasis	Yes No	1,512	0,681-3,353	0,309

LDH_0: Pretreatment lactate dehydrogenase, Hb_0: Pretreatment hemoglobin

Discussion

Lutetium-177 PSMA RNT has been shown to be successful on mCRPC to accomplish PSA decline in multiple retrospective analyzes [13-20]. Also, some researchers investigated in factors could affect OS for ^{177}Lu PSMA RNT [13, 17, 25]. In our study, we assigned PSA response to therapy and had a focus on predictors about OS and PFS of ^{177}Lu PSMA I&T RNT on patients with mCRPC.

Baum et al. (2016) [16] reported PSA decline of ≥50% in 59,9% of patients and any PSA decline in 80% of patients in their precursor and valuable study. Bräuer et al. (2017) [13] reported PSA decline of ≥50% in 53% of patients and any PSA decline in 91% of patients in their study. Rahbar et al. (2018) [26] reported PSA decline of ≥50% in 56% of patients and any PSA decline in 66% of patients in their study that all 71 patients had 3 cycles of ^{177}Lu PSMA RNT. In our study, 33% of patients showed PSA decline of ≥50% and 51% of patients showed PSA decline. We thought the reason of lower therapy success that lower patients percent had lymph node metastasis (67%) regarding to report of Kulkarni et al. (2016) [19] showed that lymph nodes had homogenous PSMA expression and showed better therapy response with ^{177}Lu PSMA. Patients percent had lymph node metastasis mentioned studies were 95,7%, 80% and 80%, respectively.

Temporary high PSA levels can occur after therapies [27, 28] also known as "flare phenomenon". There was no study about flare phenomenon during ^{177}Lu PSMA RNT. Rahbar et al. (2018) [26] took attention to delay PSA response after ^{177}Lu PSMA RNT. They noticed that 29% of patients who had no PSA response after the first cycle showed PSA response after further cylces. Though small number of patient in the present study, patients who had PSA increase of ≥25% had significantly shorter OS and PFS than the others. We think that prominent PSA progression after the first cycle was a predictor of poor therapy response and it could be better not going on further cycles because of possible side effects and economic factors.

Prostate specific antigen change after first cycle of cytotoxic chemotherapy is an important predictor of therapy response [29, 30]. It was also cared for ^{177}Lu PSMA RNT since beginning of first administrations. Bräuer et al. (2017) [13] demonstrated different median OS between patients had any PSA decline and patients had PSA progression after the first cycle (56 weeks-29 weeks; P<0,001) and they showed no significant difference on median OS between patients had PSA decline of ≥50% and <50% after the first cycle. In the same way, Rahbar et al. (2018) [17] were analyzed 104 patients treated abiraterone and/or enzalutamide before ^{177}Lu PSMA. Median OS were significantly different between patients had any PSA decline and patients had PSA progression after the first cycle (62,9 weeks-47 weeks; P=0,004). But median OS were not different between patients had PSA decline of ≥50% and <50% after the first cycle. Ahmadzadehfar et al. (2017) [25] studied with 100 patients and demonstrated that both patients had any PSA decline and patients had PSA decline of ≥50% after the first cycle showed longer OS than patients had PSA progression and patients had PSA decline of <50% after the first cycle. In our results, median OS in patients had any PSA decline after the first cycle were compatible with mentioned analyzes above. Similar to results of Ahmadzadehfar et al. (2017) [25] mean OS were significantly different between patients had PSA decline of ≥50% and patients did not have PSA decline of ≥50% after the first cycle. In addition to all of these results, our analysis showed longer PFS in patients had any and ≥50% PSA decline after the first cycle.

Alkaline phosphatase is a marker can be used for liver and bone disease burden [31]. In their meta-analysis, Li et al. (2018) [32] showed that ALP is a prognostic factor for OS and PFS. Bräuer et al. (2017) [13], Ahmadzadehfar et al. (2017) [25] and Rahbar et al. (2018) [17] reported that patients had lower ALP showed significantly longer OS, their cut-off values for ALP were 220U/L, 220U/L and 140U/L, respectively. Our analysis confirmed their results. In our study, patients had pre-treatment ALP<120U/L had longer OS and PFS than patients had ALP ≥120.

Anemia has been identified 30%-90% of patients who have any type cancer, cause of anemia could be hemolysis, blood lose, impairment of red blood cell production or all of them [33]. It was reported as a predictor of OS for hormone-sensitive prostate cancer [34], mCRPC [35] and patients had mCRPC and treated with radium-223 (^{223}Ra) [36]. Ahmadzadehfar et al. (2017) [25] and Ferdinandus et al. (2017) [37] reported lower Hb as a predictor for longer OS for ^{177}Lu PSMA RNT on mRPC. Our results were parallel to these two analyzes. According to both of two different cut-off values of 10,8 g/dL and 13g/dL (lower limit of normal), patients who had lower Hb showed lower OS. Also, normal Hb values were found as an independent predictor of longer OS. Etiology of anemia was not be determined exactly (Secondary to recent therapies, related to bone marrow infiltration etc.).

Visceral metastasis shortens survival in mCRPC [38, 39]. Kessel et al. (2019) [40] treated 109 patients with totally 354 cycles of ^{177}Lu PSMA RNT and reported that patients had visceral metastasis showed shorter OS (7,1 months-13,1 months; P=0,029). Visceral metastasis stayed as an independent predictor of OS in Cox regression analysis. Liver metastasis had the most impact on survival. Conversely, Bräuer et al. (2017) [13] and Rahbar et al. (2018) [17] found no significant difference on OS between patients had visceral metastasis and had no visceral metastasis. Our analysis also showed no significant difference on OS between patients had visceral metastasis and had no visceral metastasis. Conflicting results were thought probably related to small number of patients in these studies.

Additionally according to our analyzes, OS and PFS were not associated to age at the first RNT, Gleason grade, local recurrence, extraabdominopelvic located lymph node metastasis according to ^{68}Ga PSMA PET/CT and pretreatment LDH value.

In conclusion, ^{177}Lu PSMA RNT therapy results are heterogeneous. It is important to determine patients can benefit from RNT. Any or ≥50% PSA decline after the first cycle, initial ALP <120U/L are associated with both longer OS and PFS. Initial Hb <13g/dL or <10,8g/dL predicts of longer OS, initial PSA <51ng/mL predicts of longer PFS. Also, Hb ≥13g/dL is an independent factor related to longer OS. Prostate specific antigen increase of ≥25% is associated with shorter OS and PFS.

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