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TITOLO TESI

Impact of ^{68}Ga-PSMA PET/CT in patients with metastatic castration-resistant prostate cancer (mCRPC) treated with enzalutamide

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1. Introduction

Prostate cancer (PC) is the second most common malignancy worldwide, with an estimated 288.300 new diagnoses in 2023[1]. Although 5-year survival rate for patients with localized disease is almost 100%, this figure dramatically drops to 30% in the metastatic setting[2]. Androgen deprivation therapy (ADT) has long been the mainstay of treatment by decreasing endogenous androgen levels; however, vast majority of patients eventually progress on ADT and develop resistance despite low levels of serum testosterone. Thereby, the disease state changes to castration resistant prostate cancer (CRPC), which ultimately reflects poor prognosis and survival[3].

Treatment of metastatic CRPC (mCRPC) has considerably evolved in the past years with the approval of several novel agents based on the outcomes of large randomized clinical trials. Current standard therapy options in the first-line setting of patients with mCRPC include docetaxel[4,5], abiraterone acetate[6,7], enzalutamide[8] and olaparib[9]. Enzalutamide is a second-generation androgen receptor antagonist and it was approved for use in pre-docetaxel setting for mCRPC based on the results of Prevail[8] trial. Enzalutamide is a rationally designed oral androgen receptor (AR) inhibitor that inhibits multiple steps in the AR signaling pathway[10]. The mechanism of action for enzalutamide is threefold. It is a potent, competitive binder of androgens at the level of the AR. It prevents the translocation of the AR from the cytoplasm to the nucleus. Within the nucleus, it inhibits AR binding to chromosomal Deoxyribonucleic acid (DNA), which prevents further transcription of tumor genes.

A wide range of available therapeutic options and highly variable disease course in patients with mCRPC make it challenging to select the most effective management strategy and evaluate treatment response. Functional status of patients, prostate-specific antigen (PSA) levels and imaging findings appear to play a role in decision making at this point. In clinical practice, however, novel

biomarkers are certainly required to provide a dynamic and powerful approach to disease management in patients with mCRPC.

Prostate specific membrane antigen (PSMA) is a membrane-bound glycoprotein that is an expressed 100- to 1000-fold higher in PC cells than in benign prostate tissue or normal tissue of most other organs and its expression rises with Gleason score (GS) of PC, tumor aggressiveness, androgen independence, recurrence, and metastatic disease[11]. As a result, PSMA has recently been the focus of interest as a molecular target for PC imaging and radionuclide therapy[12,13].

Gallium-68 (^{68}Ga)-PSMA positron emission tomography/computed tomography (PET/CT) is a highly sensitive diagnostic tool to detect prostate metastatic sites even at low levels of PSA. PSMA PET/CT imaging has demonstrated greater sensitivity compared to conventional imaging modalities with CT and whole-body bone scan (WBBS)[14,15] and choline PET in the detection of metastatic PC[16].

The impact of PSMA PET/CT on the clinical management of PC patients has been investigated in intermediate- and high-risk disease at initial staging[17-20] and after biochemical recurrence (BCR)[21-27] but not in patients who undergo imaging for other indications. PSMA PET/CT can also be used to select patients for PSMA-targeted radioligand therapies, as well as for subsequent therapy response evaluations[28]. Specifically, the impact on management of patients whose PSA has not risen to or beyond the threshold to define BCR[29,30], those with known mCRPC, and those with primary treatments other than surgery or radiation therapy is unknown.

In mCRPC, the role of PSMA PET/CT imaging is less clear. A small prospective cohort demonstrated that PSMA PET/CT use changed management in 61% of patients with mCRPC[31]. However, the benefits of PSMA PET-CT compared to conventional CT and WBBS have not been well established.

In the current study, we aimed to investigate whether baseline volumetric parameters obtained from ^{68}Ga-PSMA PET/CT could be used as a predictive and prognostic biomarker in patients treated with enzalutamide as first-line therapy for mCRPC.

2. Materials and methods

2.1 Study design and patient selection

We retrospectively reviewed medical records of patients diagnosed with mCRPC who were followed-up in Istituto Romagnolo per lo Studio dei Tumori "Dino Amadori - IRST IRCCS between August 2017 and September 2022. Patients who received first-line treatment with enzalutamide were eligible for the study, in case a ^{68}Ga-PSMA PET/CT scan was performed before starting systemic treatment. Patients were treated with enzalutamide 160 mg once daily in combination with ADT in the first-line setting until disease progression, intolerable toxicity or death. The exclusion criteria were absence of GS or pre-treatment PSA value, metastatic castration sensitive prostate cancer (mCSPC), no treatment with enzalutamide in the first-line setting of mCRPC, unavailability of ^{68}Ga-PSMA PET/CT scan at baseline and lack of follow-up data. Patients receiving novel antihormone therapies (abiraterone, enzalutamide or apalutamide) in the castration-sensitive period were excluded from the study due to the potential effects of the therapy on the treatment of subsequently developed mCRPC and the associated outcomes. Patients who received docetaxel therapy during the castration-sensitive period were included.

^{68}Ga-PSMA PET/CT was performed at baseline and at the discretion of the treating physician, which was in general 1 and 3 months after initiation of therapy and at PSA/clinical progression. Metastatic disease was determined from radiological findings using ^{68}Ga-PSMA PET/CT imaging. Patients were evaluated on a monthly basis for serological PSA response and safety. CT scan, WBBS and Flourine-18 fluorodeoxyglucose (^{18}F-FDG) were performed at the discretion of the treating physician.

We collected data about demographic, clinicopathologic, and treatment-related factors that could affect prognosis. In this context, we recorded age, Eastern

Cooperative Oncology Group performance status (ECOG PS), GS, metastatic sites and previous treatments.

2.2 Image analysis

All ^{68}Ga-PSMA PET/CT images were reanalyzed by two experienced nuclear medicine physicians who re-evaluated the PET/CT images for local recurrence, malignant lymph nodes involvement and distant metastases. Any focal tracer uptake higher than surrounding background activity was considered as malignant based on the location, intensity, shape, and size[32]. All lesions suggestive of recurrent PC, their localizations as well as the number of detected metastases per patient were recorded. Volumetric PET parameters, the maximum standardized uptake volume (SUVmax) and mean standardized uptake volume (SUVmean) were measured on attenuation-corrected images. A volume of interest (VOI) around the outline of a lesion was set and then VOI was automatically drawn along the margin of the tumor uptake. The SUVmax shows the highest ^{68}Ga-PSMA uptake in a VOI. SUVmean refers to the average SUV concentration in a VOI. The metabolic total volume (MTV) represents the total volume of the tumor cells having PSMA uptake greater than a threshold of 45% of SUVmax in the VOI[33-35]. The SUVmax, SUVmean and MTV were produced automatically from the VOIs by the workstation and then total lesion activity (TLA) was calculated by multiplying the SUVmean by the MTV of the lesions. All these parameters were calculated for a maximum of 20 lesions.

2.3 Statistical analysis

Descriptive data were recorded as frequencies and percentages for categorical variables. Continuous variables were presented as median and ranges (minimum-maximum). The normality of data was tested by the Kolmogorov-Smirnov and Shapiro-Wilks test and the parameters did not show normal

distribution. Continuous variables of two independent groups were compared with Mann-Whitney *U* test. Categorical variables were compared with Fisher's exact test. Correlation of whole-body volumetric parameters with PSA levels was investigated by Spearman's rank correlation test. Time-dependent variables were estimated using Kaplan–Meier method and compared with log-rank test. Overall survival (OS) was defined as the interval from the start of first-line treatment until death from any reason or last visit of follow-up for survivors. Progression free survival (PFS) was defined as the interval from the start of first-line treatment until progression of disease or death from any reason or last visit. Univariate and multivariate analyses were carried out using the Cox regression models to evaluate factors that predict PFS and OS and to estimate Hazard Ratio (HR) and their 95% Confidence interval (CI). All statical analyses were two-sided and *p* value less than 0.05 was accepted as the level of significance. All statistical analyses were performed using SPSS version 22.0 (SPSS Inc., Chicago, IL, USA).

3. Results

3.1 Characteristics of the study population

In the observational prospective study, 67 consecutive mCRPC patients were treated with enzalutamide 160 mg once daily in first-line for mCRPC. At the moment of the present analysis, 58 mCRPC patients were considered fully evaluable. Clinicopathologic and treatment characteristics of the study population are presented in Table 1. Median age was 75 years (Interquartile Range [IQR] 67.3-80.9), most of the patients had an ECOG PS of 0 (81%), GS 8-10 was reported in 62% of the patients. All patients received ADT before developing resistance, only one patient received docetaxel in mCSPC. The median baseline PSA was 2.66 ng/mL (IQR 1.14 - 6.19). All patients presented with positive PSMA PET/CT with significantly overexpressing metastatic lesions. As defined by ^{68}Ga-PSMA PET/CT, bone metastases were present in 52% of the patients, with the majority having less than 5 metastases. The median total number of metastases was 3. Since there is no established definition of high *versus (vs)* low volume disease in mCRPC, the CHARTEED definition of high and low volume used for mCSPC was applied. In the specific, high volume was defined as more than 4 bone metastases and/or visceral disease, and low volume was defined as 4 or fewer bone metastases with no visceral disease[36]. The main part of patients (81%) was classified as low disease.

At baseline PSMA PET/CT, we observed a median MTV of 73 cm^3 (IQR 2.49-15.40), median SUVmax of 44.85 (IQR 26.60-96.80), median SUVmean of 25.80 (IQR 15.30-58.80) and median TLA of 59.66 (IQR 26.58-146.00).

Table 1. Demographic and clinical characteristics of patients (n = 58)

Characteristics	**N (%)**
Median age (IQR), years	75 (67-80)
ECOG PS	
0	47 (81%)
1-2	11 (19%)
GS	
6-7	22 (38%)
8-10	36 (62%)
Baseline PSA	
Median (IQR), ng/mL	2.66 (1.14 - 6.19)
Docetaxel for mCSPC	
Yes	1(2%)
No	57 (98%)
Median number of lesions, (IQR)	3 (2-7)
Disease volume	
Low	47 (81%)
High	11 (19%)
Metastatic locations as defined by ^{68}Ga-PSMA PET/CT	
Local disease	16 (34%)
Bone only	16 (28%)
Lymph nodes only	24 (41%)
Bone plus lymph nodes	11(19%)
Visceral involvement	3 (7%)
lung	4 (100%)

Bone plus visceral lung	3 (5%) 3 (100%)
Number of bone lesions None <5 5-10 >10	 28 (48%) 23 (40%) 5 (9%) 2 (3%)
Baseline MTV IQR <5.73 (median value) ≥5.73	5.73 (2.49-15.40) 29 (50%) 29 (50%)
Baseline TLA IQR <59.66 ≥59.66	59.66 (26.58-146.00) 29 (50%) 29 (50%)
Baseline SUVmean IQR <25.80 ≥25.80	25.80 (15.30-58.80) 29 (50%) 29 (50%)
Baseline SUVmax IQR <44.85 ≥44.85	44.85 (26.60-98.80) 29 (50%) 29 (50%)

3.2 Correlation between baseline clinical parameters and PSMA expression

Baseline PSA and the number of lesions at baseline were positively associated with all PSMA PET/CT parameters (table 2). In the specific, PSA and number of lesions at baseline had a strong correlation with MTV, TLA, SUV mean and SUV max. There was not a correlation between baseline PSA and number of lesions (p=0.115) (table 2).

Table 2. Correlation between baseline PSA and baseline MTV, TLA, SUV mean, SUV max and number of lesions

	MTV		TLA		SUVmean		SUVmax		N of lesions	
	r_s	p	r_s	p	r_s	p	r_s	p	r_s	p
PSA	0.26	0.046	0.45	0.0004	0.32	0.013	0.41	0.001	0.21	0.115
MTV	-	-	0.62	<0.0001	0.46	0.0003	0.40	0.002	0.53	<0.0001
TLA	-	-	-	-	0.79	<0.0001	0.81	<0.0001	0.45	0.0004
SUVmean	-	-	-	-	-	-	0.93	<0.0001	0.70	<0.0001
SUVmax	-	-	-	-	-	-	-	-	0.65	<0.0001

3.3 Correlation between volume of disease and PSMA expression

Only 11 patients (19%) were classified as high volume according to CHARTEED classification, while the main part (81%) was classified as low volume disease. There was a strong correlation between volume of disease and SUV mean and SUV max, but there was not a correlation between volume of disease and TLA and MTV (table 3-4).

Table 3. Correlation between TLA, MTV, SUV mean, SUV max and volume

	VOLUME		
	Low (n=47)	High (n=11)	
	Median value (IQR)	Median value (IQR)	p
TLA	41.43 (24.00-117.50)	242.40 (322.14-616.50)	0.097
MTV	5.00 (2.35-12.60)	13.96 (4.19-44.95)	0.097
SUVmean	22.40 (13.93-50.50)	113.50 (34.90-248.40)	0.020
SUVmax	37.70 (24.50-88.90)	184.40 (53.30-407.90)	0.020

Table 4. Association between TLA, MTV, SUV mean, SUV max and volume

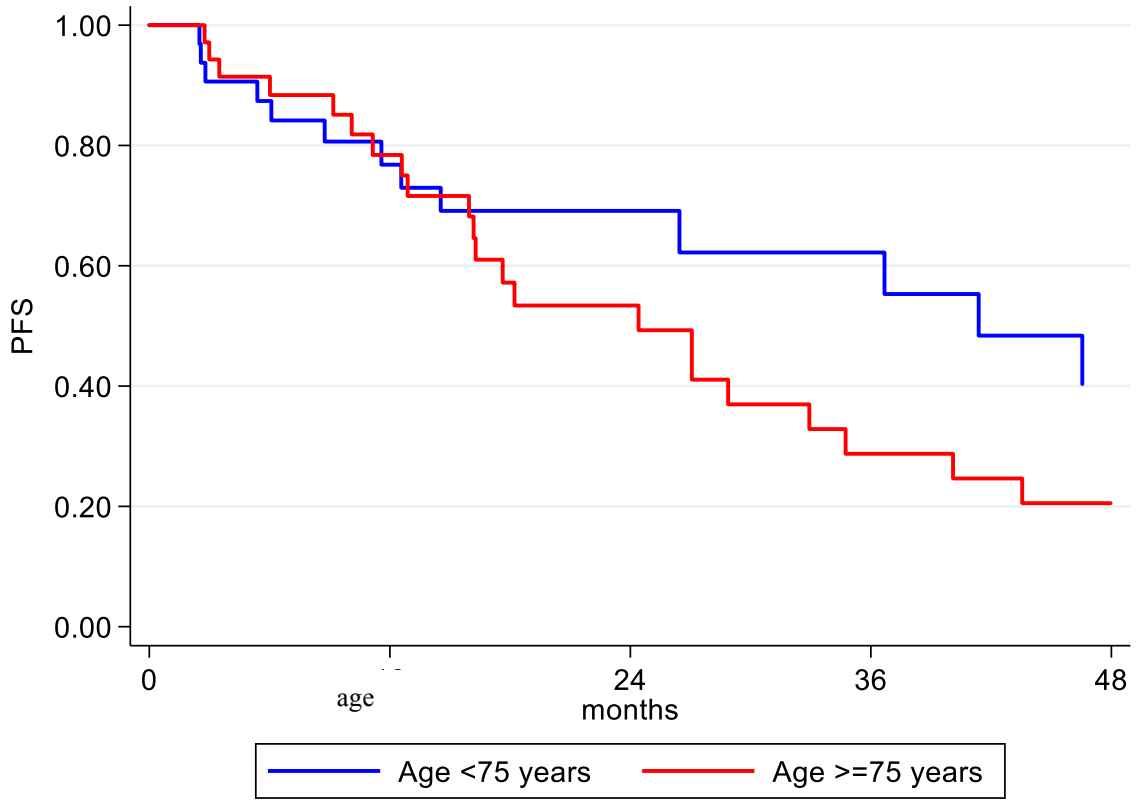
	VOLUME		
	Low (n=47)	High (n=11)	
	n. (%)	n. (%)	p
TLA			
<59.66 (median value)	26 (55.3)	3 (27.3)	
≥59.66	21 (44.7)	8 (72.7)	0.094
MTV			
<5.73 (median value)	26 (55.3)	3 (27.3)	
≥5.73	21 (44.7)	8 (72.7)	0.094
SUVmean			
<25.80 (median value)	27 (57.5)	2 (18.2)	
≥25.80	20 (42.5)	9 (81.8)	0.019
SUVmax			
<44.85 (median value)	27 (57.5)	2 (18.2)	
≥44.85	20 (42.5)	9 (81.8)	0.019

3.4 Survival outcomes

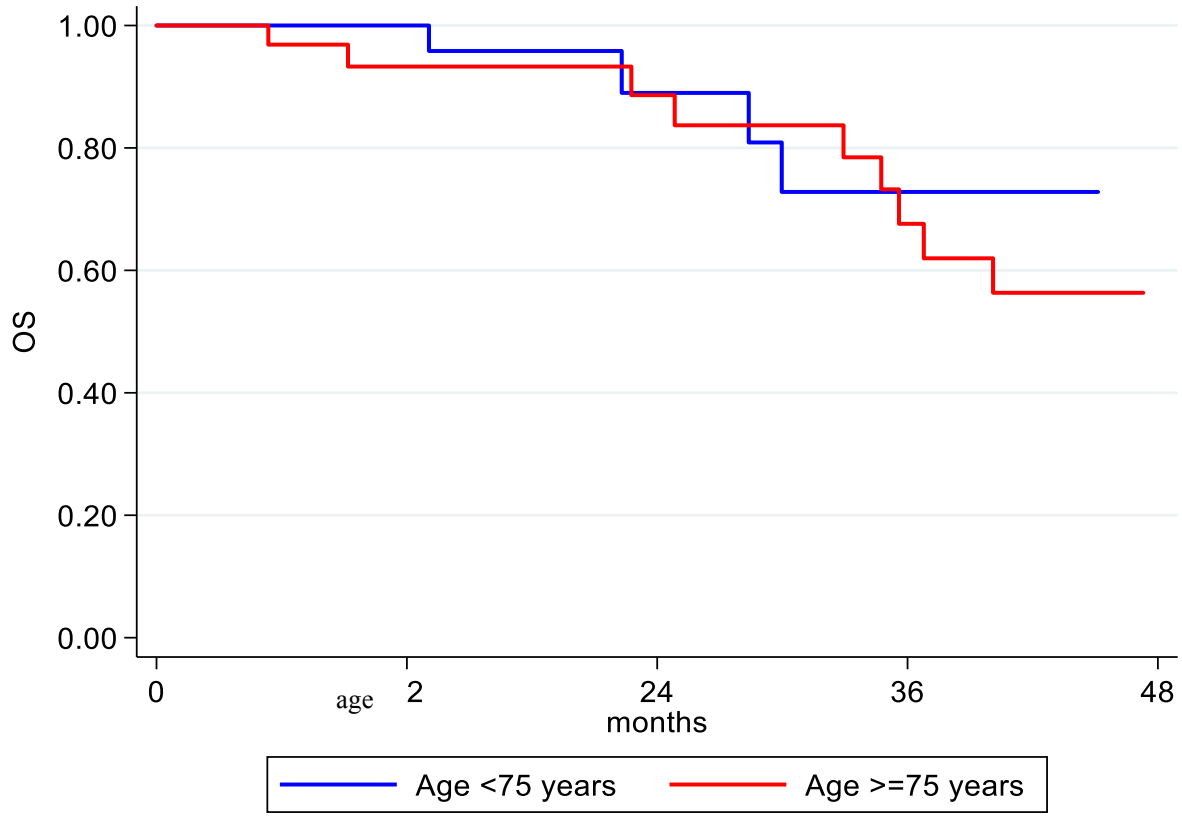
At the median follow-up of 52 months, median PFS was 28.9 months (95% CI 16.3-43.6), median OS was not reached (95% CI 36.8-not reached [NR]). Among total study population, 21% (12/58) died during follow-up period.

In univariate analysis, median PFS and OS were significantly longer in patients with SUVmax <44.85 compared to SUVmax ≥44.85 (41.4 *vs* 17.6 months, *p*=0.015 and NR *vs* 40.1 months, *p*=0.026, respectively). Likewise, median PFS and OS were significantly longer in patients with TLA <59.66 compared to TLA ≥59.66 (43.5 *vs* 15.9 months, *p*=0.001 and NR *vs* 36.8 months, *p*=0.019, respectively). Median OS was significantly longer in patients with SUVmean <25.80 when compared to patients with SUVmean ≥25.8 (NR *vs* 40.1 months, *p*=0.028) and in patients with 3 or less metastases compared to patients with more than 3 metastases (HR 19.94, 95% CI 2.56-155.57, *p*=0.004). Multivariate analysis confirmed TLA as the only independent predictor of PFS (HR: 4.16, 95% CI 1.88-9.21, *p*=0.0004) and OS (HR: 4.79, 95% CI 1.29-17.79, *p*=0.019), while ECOG PS is an independent predictor of PFS (HR 3.07, 95% CI 1.23-7.67, p=0.016) (figure 1, table 5).

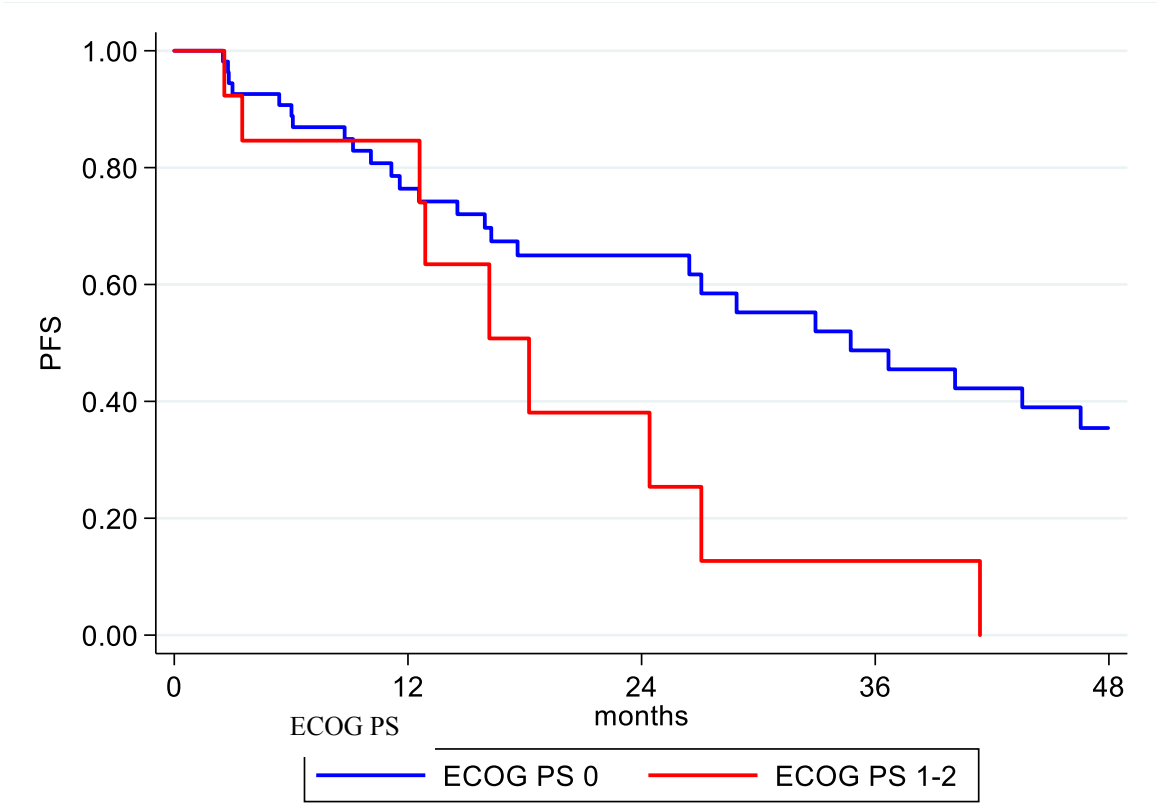
Figure 1. Kaplan–Meier curves according to **a** age (**a1** PFS and **a2** OS), **b** ECOG PS (**b1** PFS and **b2** OS)**, c** GS (**c1** PFS and **c2** OS), **d** PSA (**d1** PFS and **d2** OS), MTV (**e1** PFS and **e2** OS), SUVmean (**f1** PFS and **f2** OS), SUVmax (**g1** PFS and **g2** OS), TLA (**h1** PFS and **h2** OS), number of lesions (**i1** PFS and **i2** OS) and volume of disease (**l1** PFS and **l2** OS)


1.00
0.80
0.60
0.40
0.20
0.00
PFS
0
age
24
36
48
months
Age <75 years
Age >=75 years

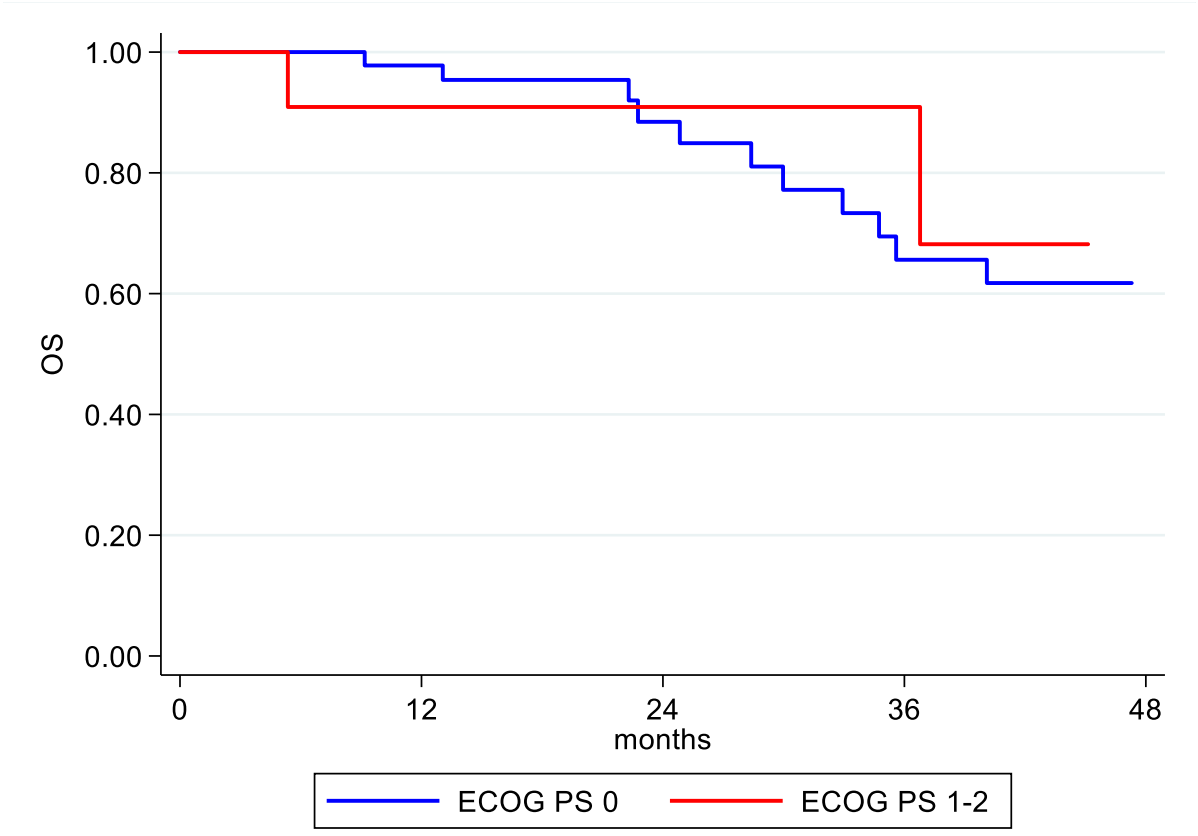
a1


1.00
0.80
0.60
0.40
0.20
0.00
OS
0
age
2
24
36
48
months
Age <75 years
Age >=75 years

a2


1.00
0.80
0.60
0.40
0.20
0.00
PFS
0
12
24
36
48
months
ECOG PS
ECOG PS 0
ECOG PS 1-2

b1


1.00
0.80
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OS
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12
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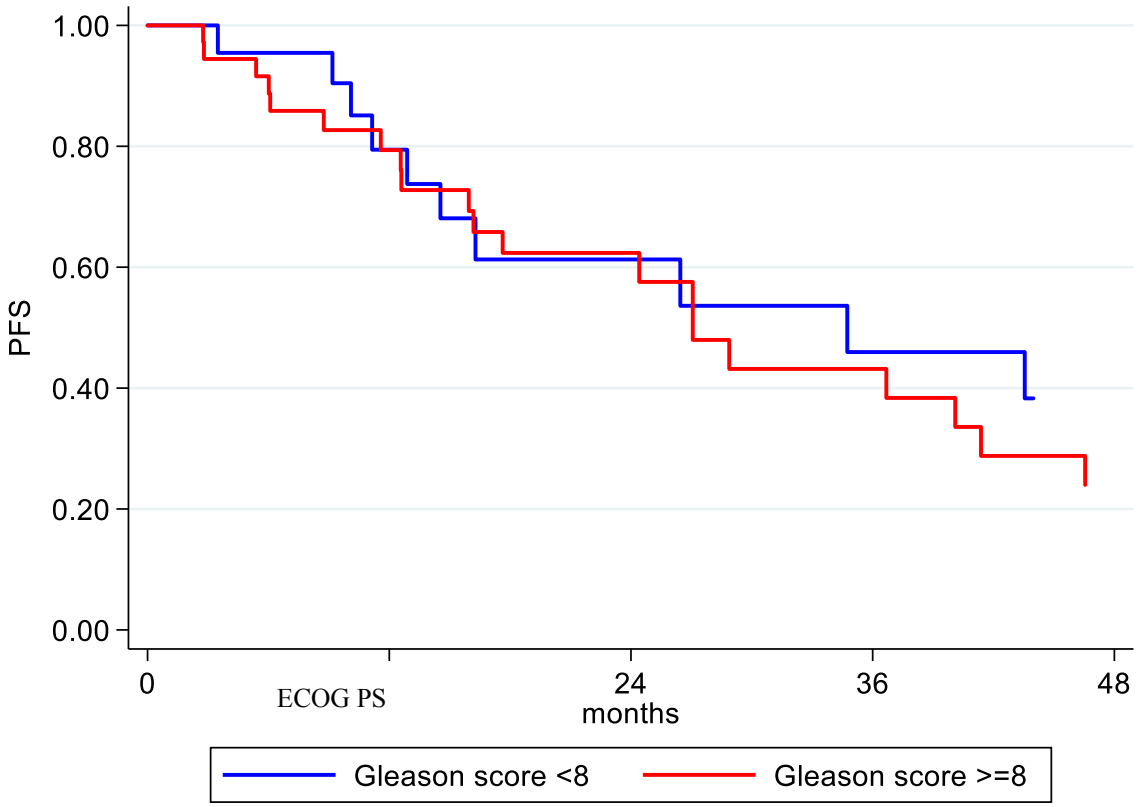
months
ECOG PS 0
ECOG PS 1-2

b2


1.00
0.80
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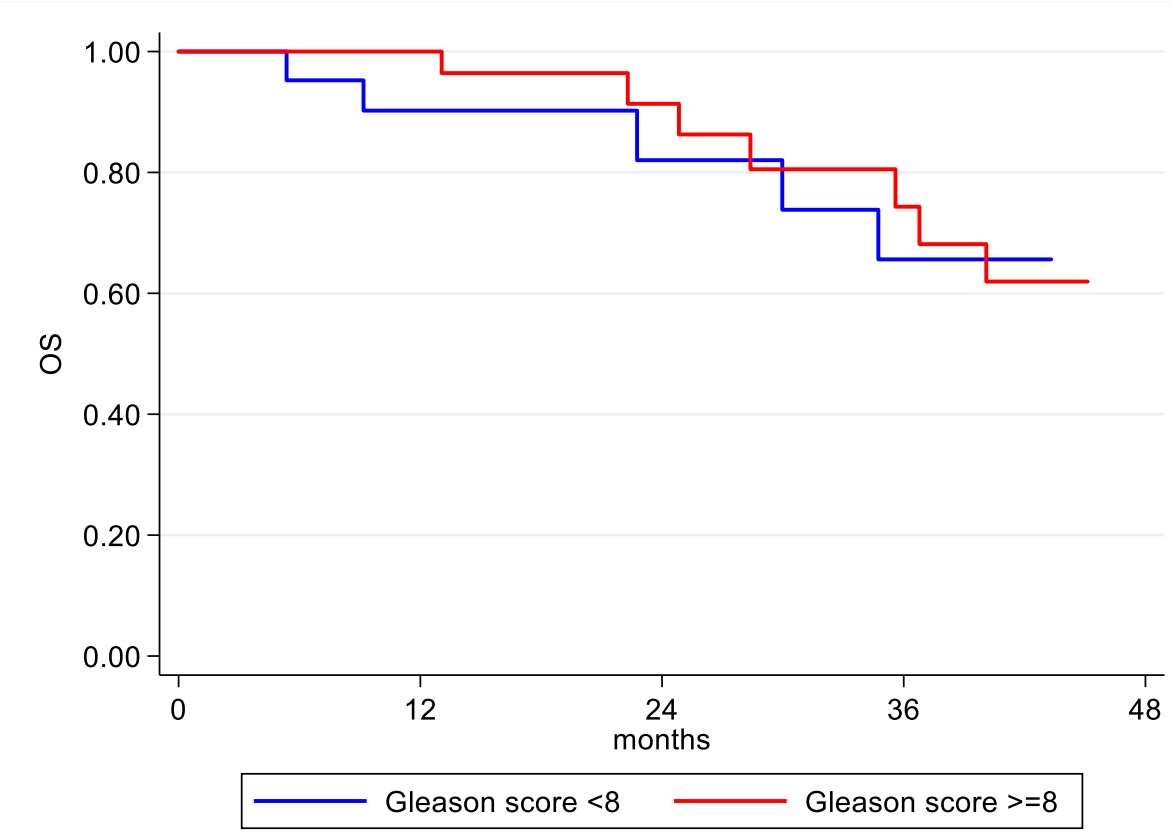
0.20
0.00
PFS
0
ECOG PS
24
months
36
48
Gleason score <8
Gleason score >=8

c1


1.00
0.80
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OS
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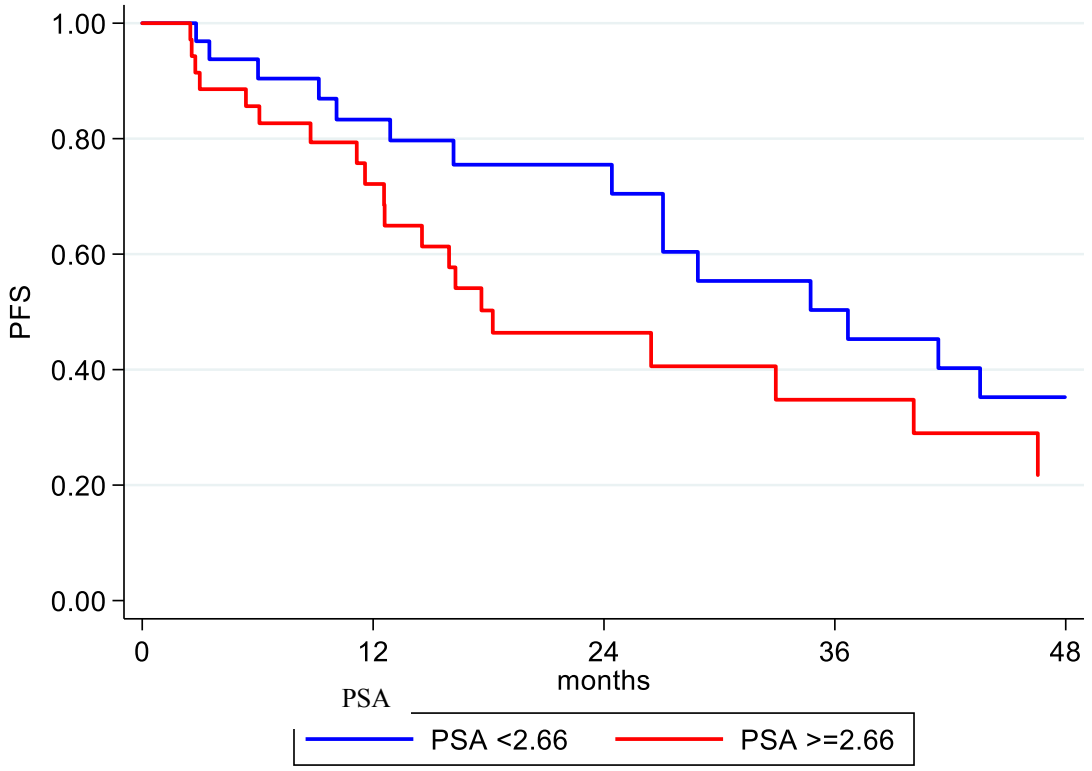
months
36
48
Gleason score <8
Gleason score >=8

c2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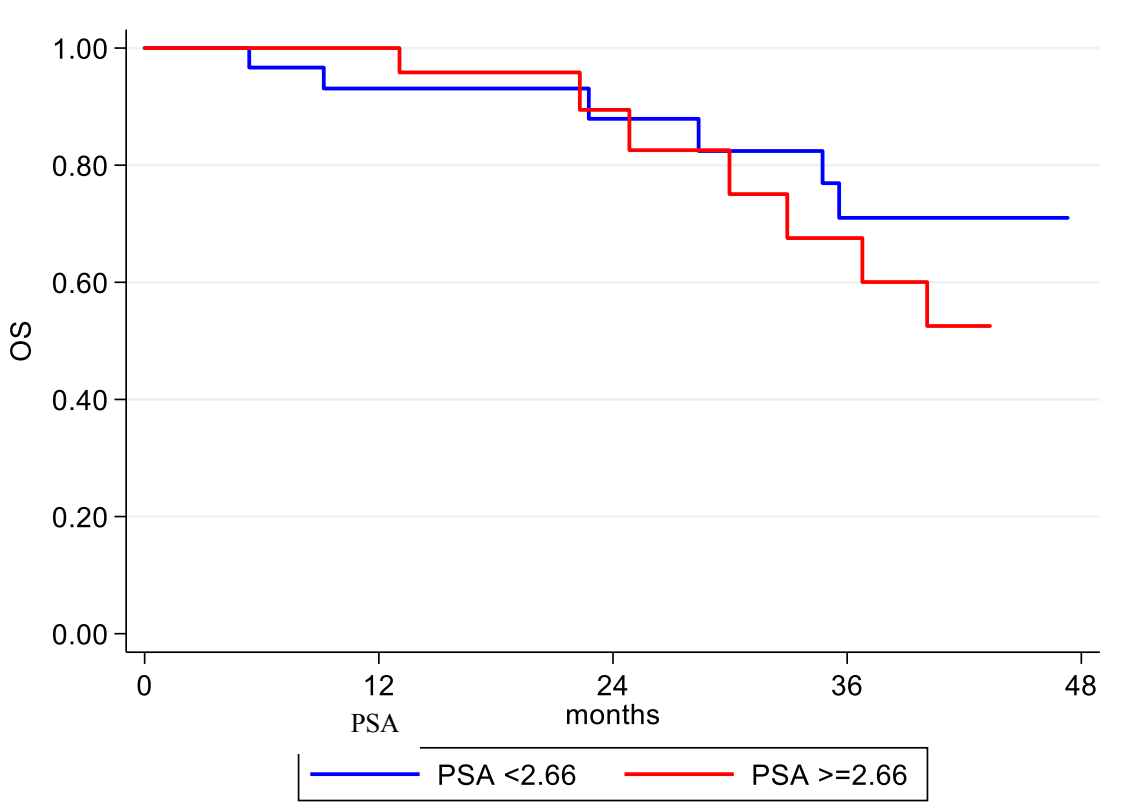
months
PSA
PSA <2.66
PSA >=2.66

d1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PSA
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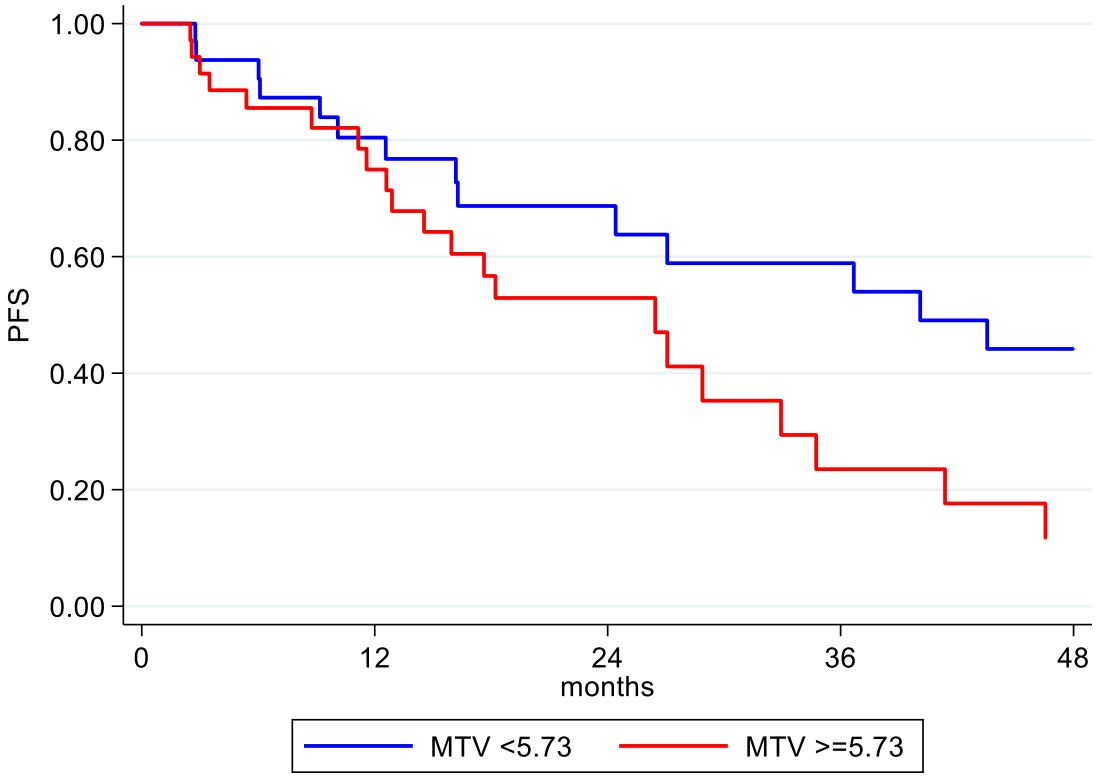
PSA >=2.66

d2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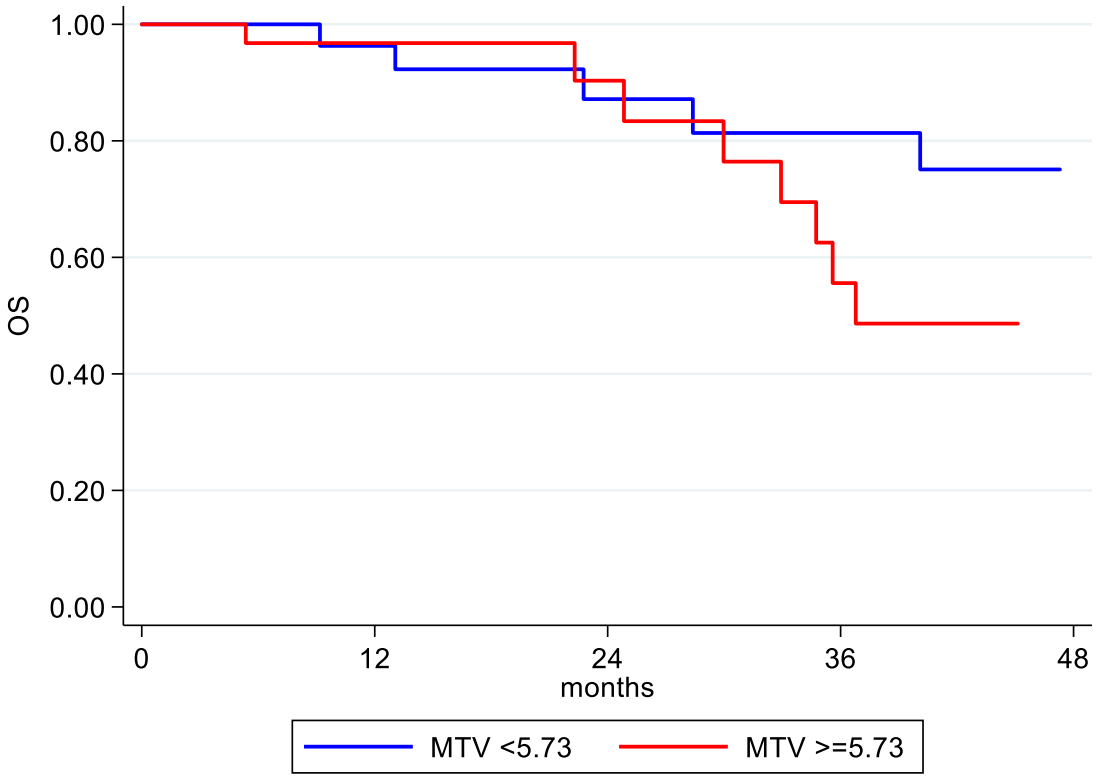
MTV <5.73
MTV >=5.73

e1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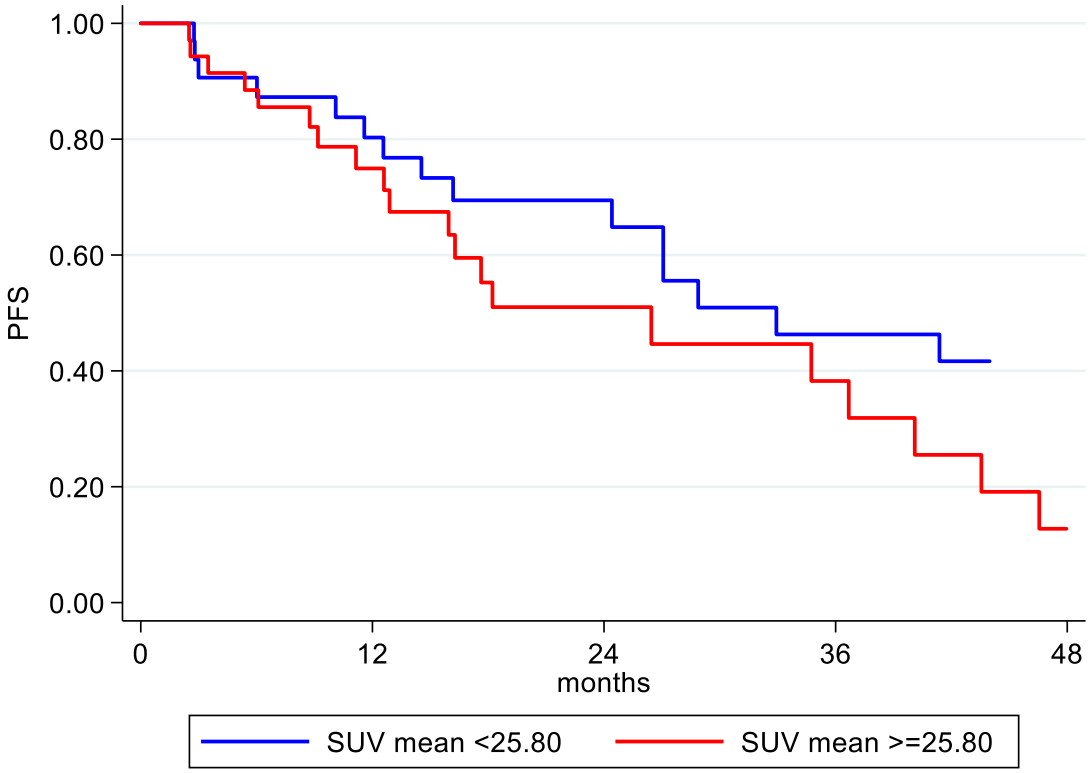
MTV <5.73
MTV >=5.73

e2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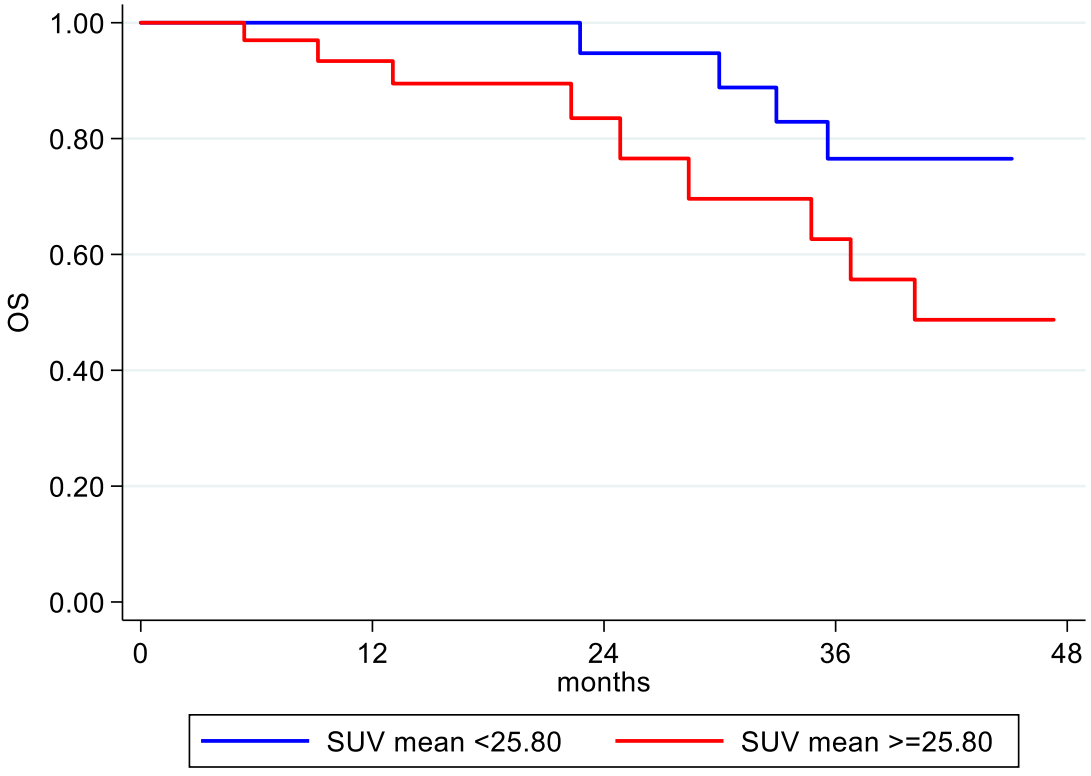
SUV mean <25.80
SUV mean >=25.80

f1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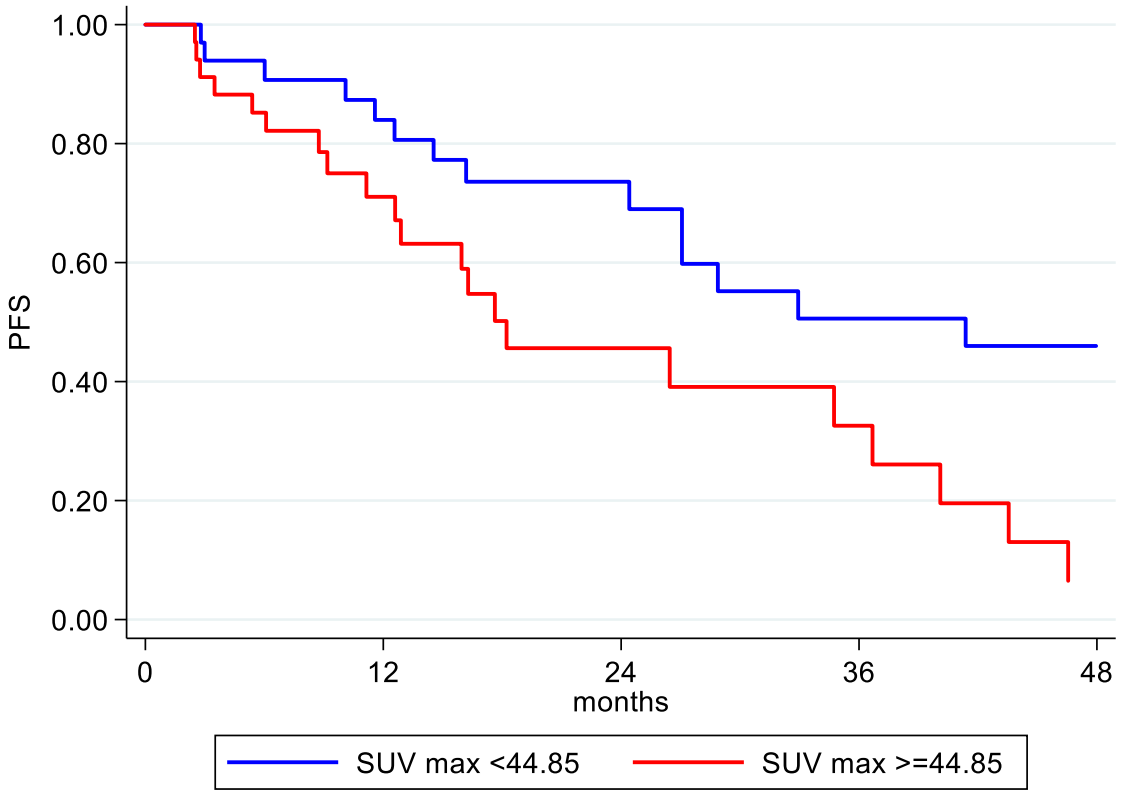
f2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PFS
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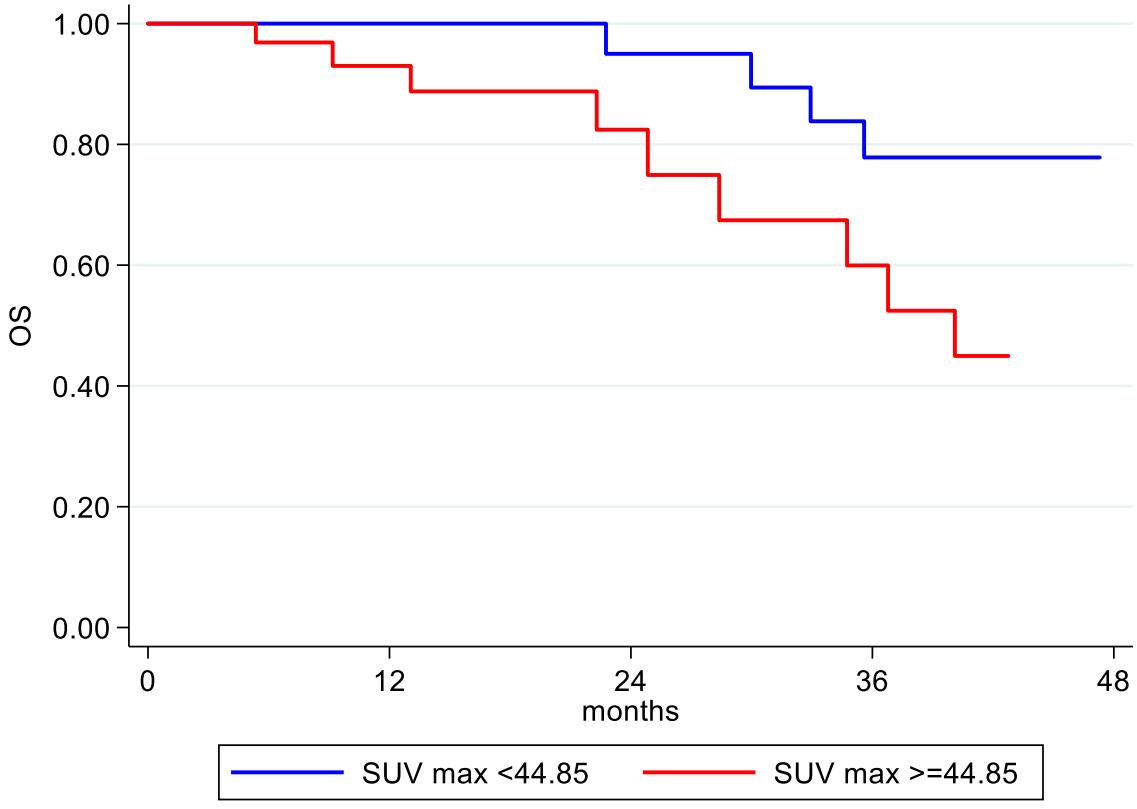
months
SUV max <44.85
SUV max >=44.85

g1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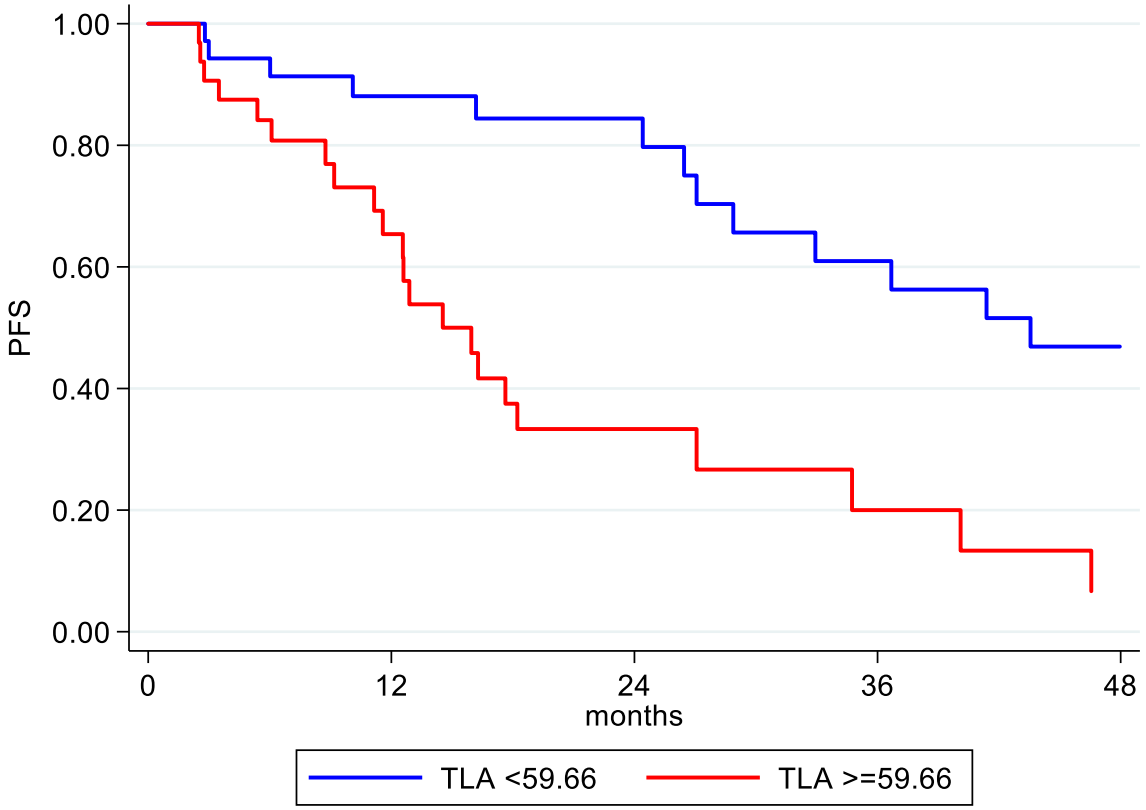
SUV max >=44.85

g2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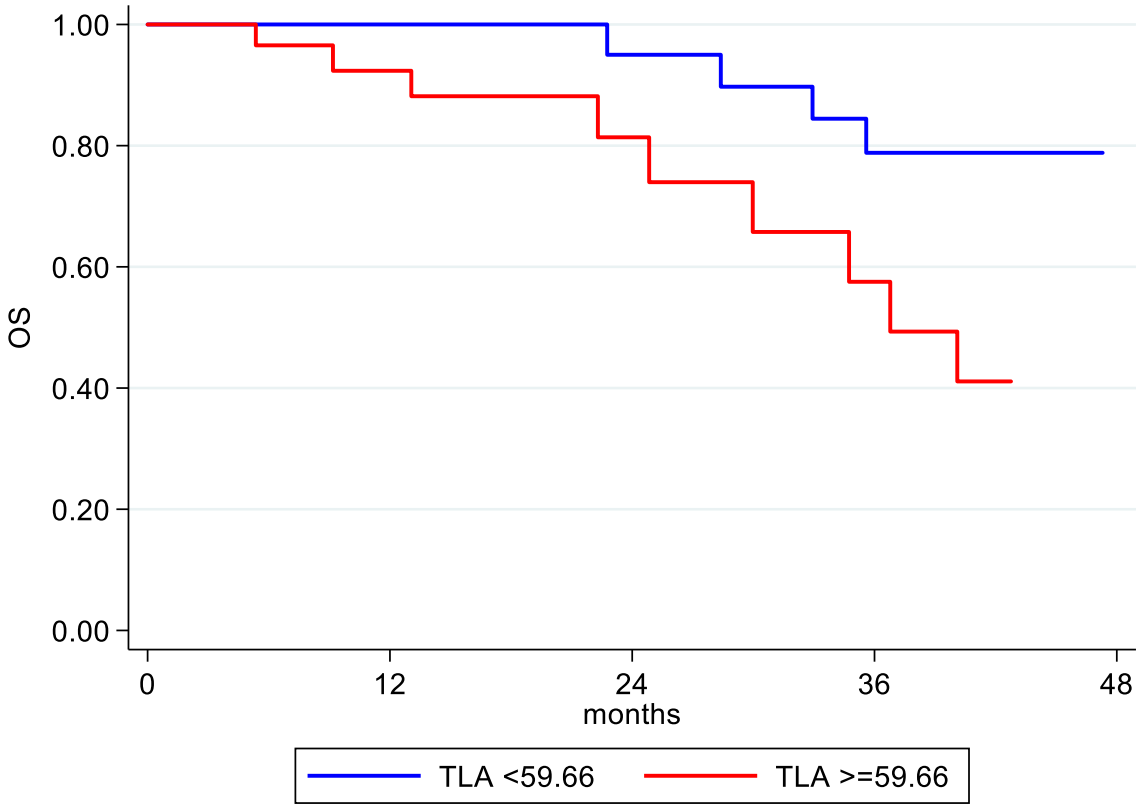
TLA <59.66
TLA >=59.66

h1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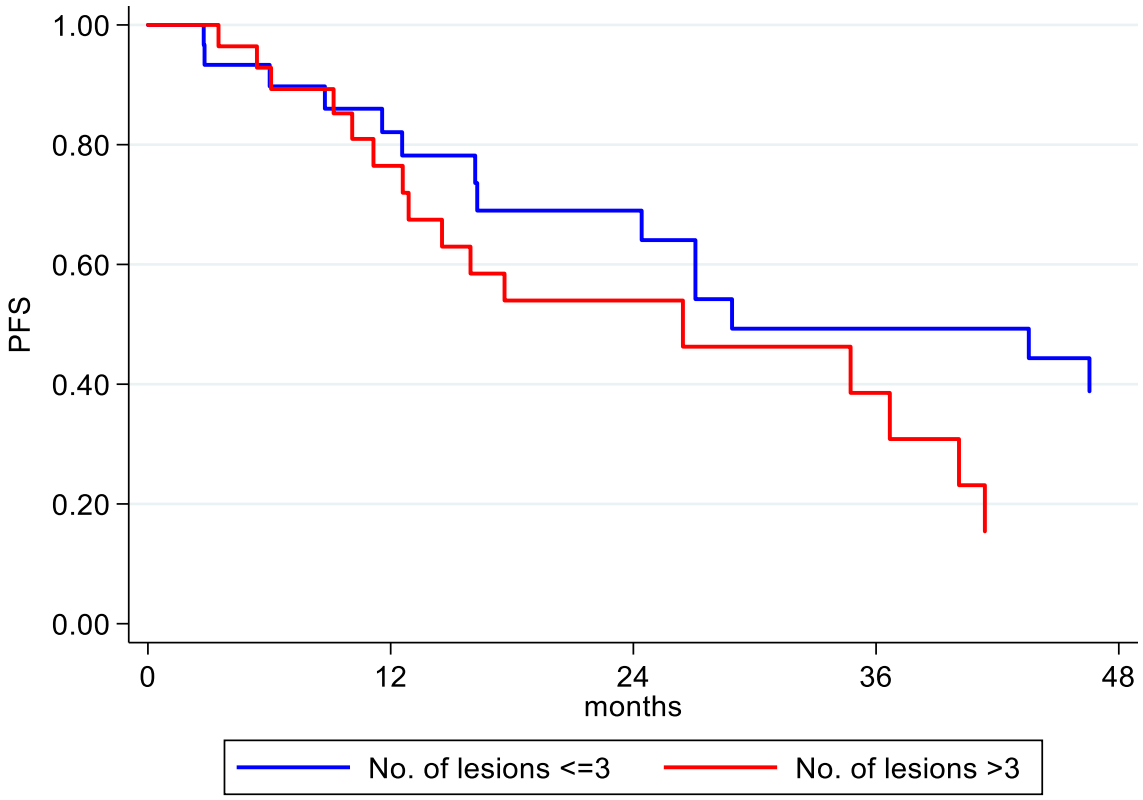
months
TLA <59.66
TLA >=59.66

h2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PFS
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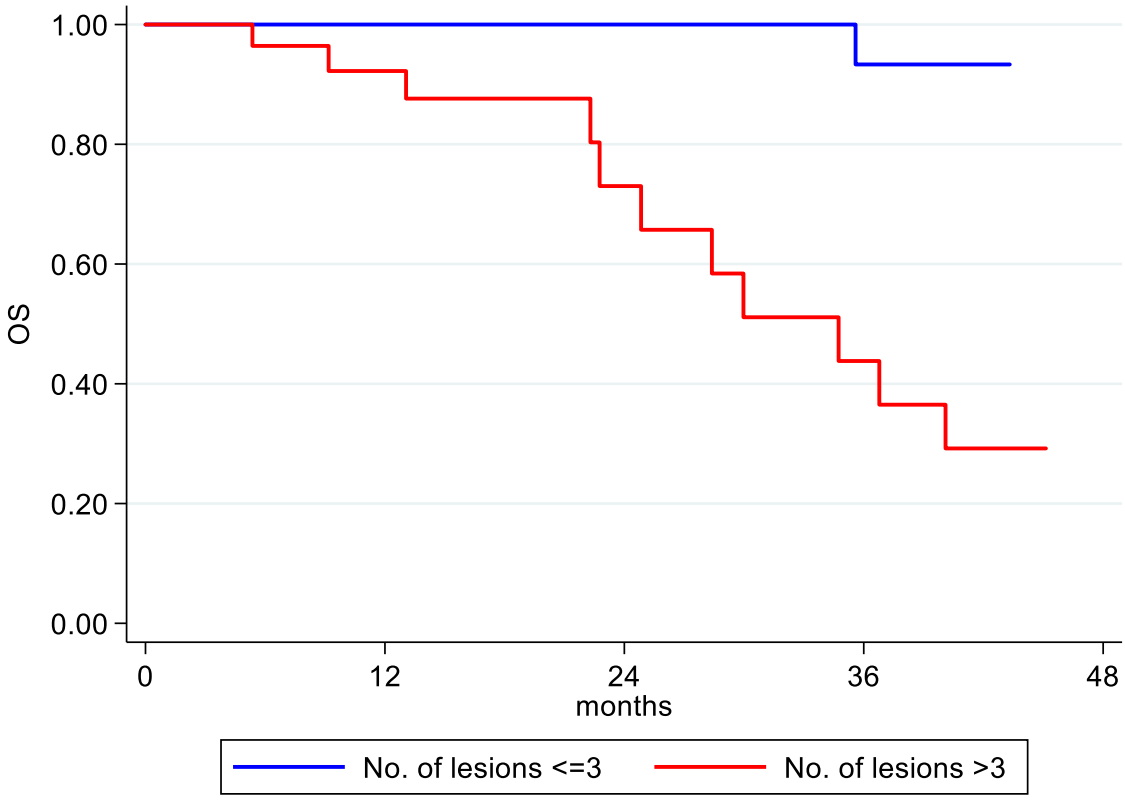
months
No. of lesions <=3
No. of lesions >3

i1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0.00
OS
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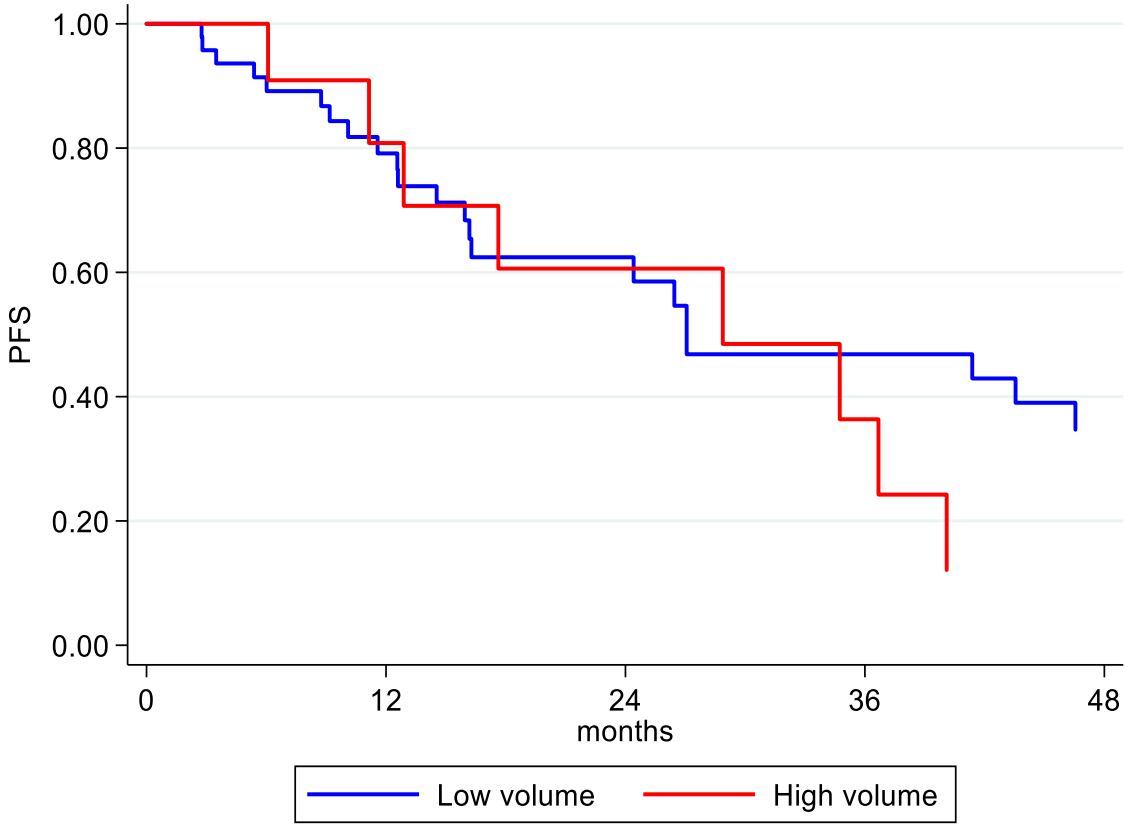
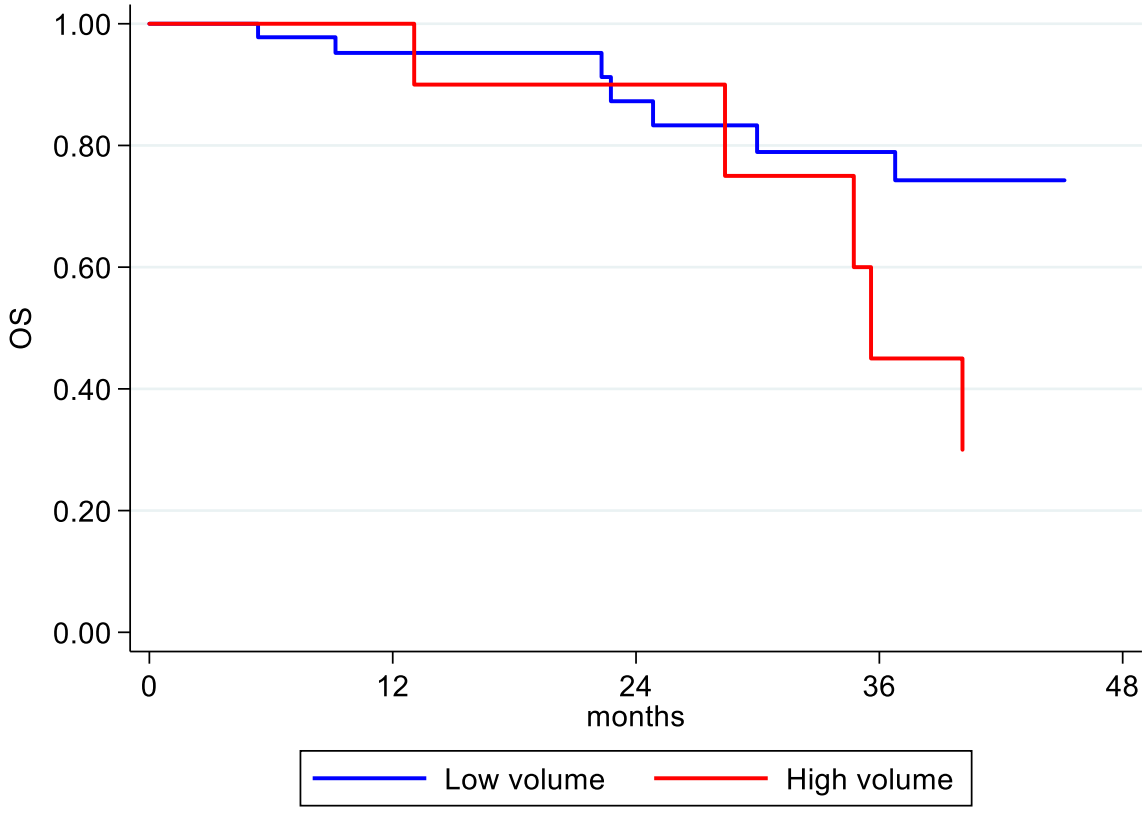
36
48
months
No. of lesions <=3
No. of lesions >3

i2


1.00
0.80
0.60
0.40
0.20
0.00
PFS
0
12
24
36
48
months
Low volume
High volume

I1


1.00
0.80
0.60
0.40
0.20
0.00
OS
0
12
24
36
48
months
Low volume
High volume

I2

Table 5. Univariate and multivariate analyses of PFS and OS

Variables	Univariate analysis				Multivariate analysis			
	PFS		OS		PFS		OS	
	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
ECOG PS (1-2 *vs* 0)	2.13 (0.89-5.06)	0.088	0.91 (0.20-4.17)	0.906	2.95 (0.96-9.13)	0.060	0.96 (0.12-7.73)	0.967
GS (≥8 *vs* <8)	1.28 (0.60-2.74)	0.526	0.88 (0.28-2.79)	0.834	1.24 (0.54-2.84)	0.603	1.09 (0.26-4.51)	0.907
Age (continuous variable)	1.016 (0.978-1.056)	0.413	1.050 (0.978-1.128)	0.179	1.01 (0.97-1.05)	0.515	1.03 (0.95-1.11)	0.515
PSA baseline (≥2.66 *vs* <2.66)	1.33 (0.65-2.73)	0.440	1.29 (0.42-4.01)	0.658	0.97 (0.40-2.36)	0.952	0.42 (0.08-2.11)	0.294
MTV (≥5.73 *vs* <5.73)	1.50 (0.72-3.11)	0.278	1.76 (0.56-5.57)	0.336	0.81 (0.32-2.02)	0.647	1.10 (0.25-4.77)	0.900
TLA (≥59.66 *vs* <59.66)	3.48 (1.62-7.49)	0.001*	4.79 (1.29-17.79)	0.019*	3.68 (1.34-10.10)	0.012	3.44 (0.66-18.08)	0.144
SUVmean (≥25.80 *vs* <25.80)	2.05 (0.98-4.28)	0.055	4.36 (1.17-16.14)	0.028*	-	-	-	-
SUVmax (≥44.85 *vs* <44.85)	2.52 (1.20-5.28)	0.015*	4.41 (1.19-16.34)	0.026*	1.88 (0.67-5.33)	0.232	3.60 (0.55-23.45)	0.180

No. of lesions (>3 vs ≤3)	1.72 (0.82-3.57)	0.148	19.94 (2.56-155.57)	0.004*	-	-	-	-
VOLUME (high vs low)	1.40 (0.62-3.17)	0.418	2.85 (0.90-9.00)	0.075	0.75 (0.27-2.09)	0.585	1.12 (0.24-5.19)	0.882
After backward stepwise procedure								
TLA (≥59.66 vs <59.66)					4.16 (1.88-9.21)	0.0004	4.79 (1.29-17.79)	0.019
ECOG PS (1-2 vs 0)					3.07 (1.23-7.67)	0.016	-	-

*Significant values ($p < 0.05$) are highlighted

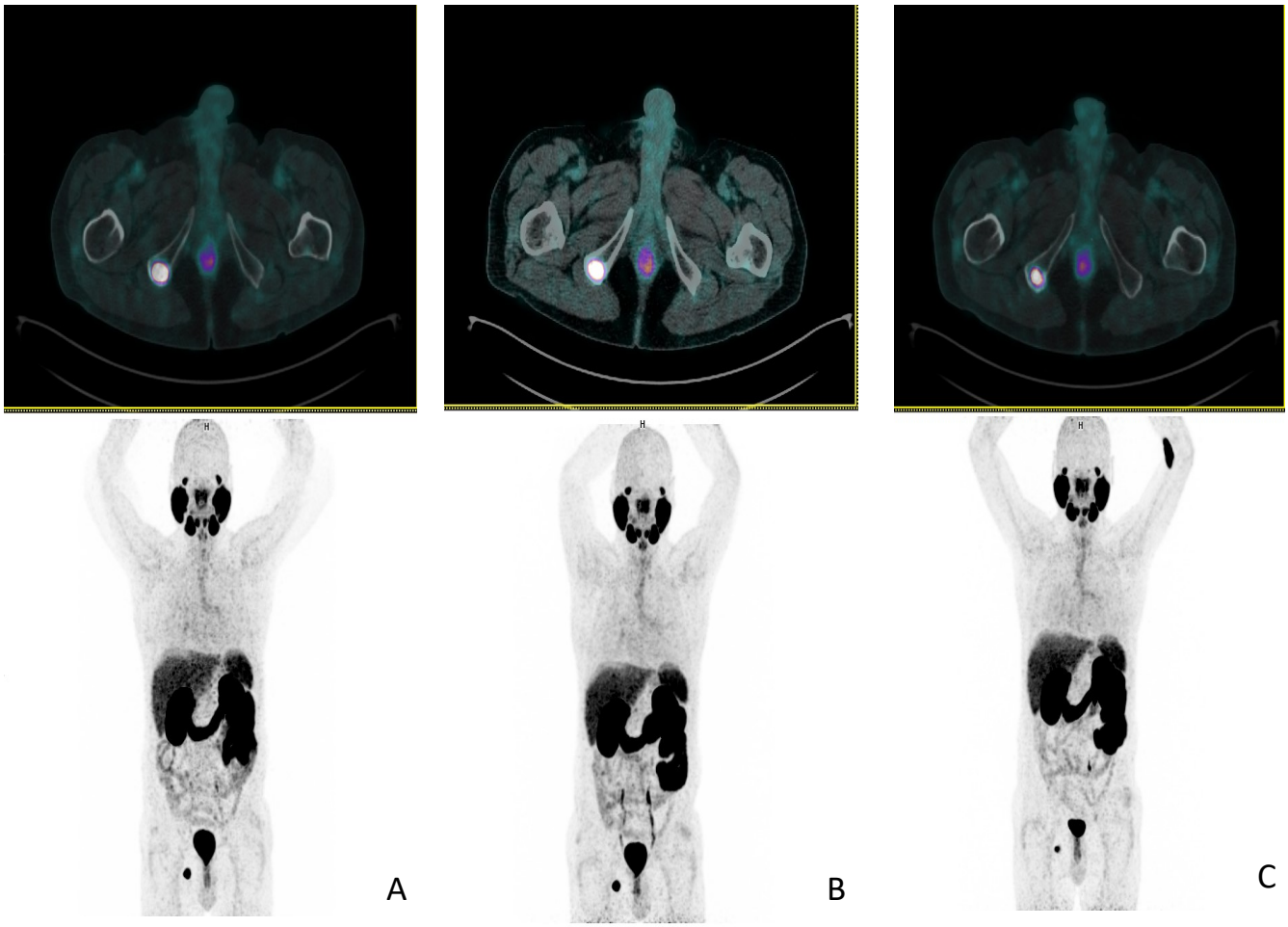
No (additional) effects met the 0.05 level for removal from the model.

Only variables with $p< 0.05$ at univariate analysis and low intercorrelation were included in the multivariable analysis.

3.5 Role of subsequent PSMA PET/CT

On 58 fully evaluable patients, 33 patients (57%) repeated ^{68}Ga-PSMA PET/CT after 1 month of treatment and in 7 patients (21%) we observe a PSMA flare (figure 2).

Figure 2. PSMA flare during treatment with enzalutamide. Baseline ^{68}Ga-PSMA PET/CT before starting enzalutamide (A), ^{68}Ga-PSMA PET/CT after 1 month (B) and 3 months (C) of treatment with enzalutamide.



Furthermore, 54 patients (93%) performed a PSMA PET/CT after 3 months from starting enzalutamide.

Biochemical responses at 1 and 3 months were assessed, patients were classified as PSA responders in case of PSA decrease ≥ 50% and PSA non-responders in all other cases. On the basis of EAU/EANM criteria, patients were categorized as PSMA responders in case of complete/partial response or stable disease or PSMA non-responders in case of progressive disease.

After 1 months, 39 patients (67%) were PSA responders, while 19 patients (33%) were not. At this time-point there was a concordance between PSA response and PSMA PET/CT response.

After 3 months, 42 patients (72%) were PSA responders, while 14 patients (28%) were not. At this time-point there was not a concordance between PSA response and PSMA PET/CT response

Table 6. Association between PSMA PET/CT-based and PSA-based response status at 1 month

	PSA response (-50%) – 1 month		**Phi-coefficient**
	No	**Yes**	
	(N=19)	**(N=39)**	
PET response – 1 month			
Partial response	0	9 (23.1)	
Stable Disease	3 (15.8)	7 (17.9)	
Progressive Disease	8 (42.1)	6 (15.4)	
NA	8 (42.1)	17 (43.6)	
PET response – 1 month			
Nonresponse (PD)	8 (72.7)	6 (27.3)	
Response (PR+SD)	3 (27.3)	16 (72.7)	0.43 (p=0.013)

Table 7. Association between PSMA PET/CT-based and PSA-based response status at 3 months

	PSA response (-50%) – 3 months		Phi-coefficient
	No	**Yes**	
	(N=14)	**(N=42)**	
PET response - 3 months			
Complete response	0	2 (5.0)	
Partial response	3 (21.4)	23 (57.5)	
Stable Disease	7 (50.0)	11 (27.5)	
Progressive Disease	4 (28.6)	4 (10.0)	
NA	0	0	
Missing/unknown	0	2	
PET response – 3 months			
Nonresponse (PD)	4 (28.6)	4 (10.0)	
Response (CR+PR+SD)	10 (71.4)	36 (90.0)	0.23 (p=0.092)

4. Discussion

The impact of tumor burden on cancer prognosis has been well documented and volumetric parameters obtained from ^{18}F-FDG PET/CT such as metabolic tumor volume and total lesion glycolysis have been shown to reflect tumor load and found to be associated with prognosis in a variety of malignancies[37,38]. As for PC, the CHAARTED trial effectively highlighted the importance of metastatic burden by defining high and low volume disease based on the number and location of bone or visceral metastases in a group of patients with mCSPC, and high volume disease was shown to be predictive of docetaxel benefit[36]. However, this study considered as low-volume disease cases without visceral metastases and with less than four bone lesions, instead of disease burden. A similar definition of metastatic burden was also adopted in the LATITUDE and STAMPEDE trials, and abiraterone was approved for mCSPC after these randomized phase 3 clinical trials, regardless of disease burden[39,40]. In patients with mCRPC, however, the concept of tumor burden did not receive much consideration when determining prognosis or treatment strategy. Furthermore, it is obvious that more quantitative descriptors of tumor burden are required in clinical practice and clinical trials, instead of considering only the number or location of lesions. Volume-based metabolic parameters generated from ^{68}Ga-PSMA PET/CT are some of those tools with very few studies in the literature. Therefore, we conducted the present study to investigate whether ^{68}Ga-PSMA PET/CT-derived volumetric parameters could predict survival outcomes and response to therapy in mCRPC patients receiving first-line treatment. According to our findings, TLA, expression of both volume and intensity of ^{68}Ga-PSMA uptake, appeared the strongest parameter able to predict PFS and OS. Furthermore, the CHARTEED classification in high and low volume disease is not useful in the setting of mCRPC. In our analyses patients where evaluated with PSMA PET/CT only then further evaluation is

needed to understand if the same classification obtained through CT scan and WBBS have the same impact on prognosis.

The first evidence of ^{68}Ga-PSMA PET/CT-derived volumetric parameters as a quantitative imaging biomarker was provided by the study of Schmuck et al.[33]. This retrospective study included 101 patients who had elevated PSA levels after primary surgery and underwent a ^{68}Ga-PSMA PET/CT. Neither SUVmax nor SUVmean correlated significantly with PSA levels. PSMA-derived tumor volume (PSMA-TV) and total lesion PSMA (TL-PSMA), on the other hand, were found to be significantly correlated with PSA levels, suggesting that these imaging parameters had the potential to reflect whole-body tumor burden. Furthermore, a significant concordance was observed between changes in PSMA-TV and TL-PSMA and changes in PSA levels, in a small group of patients (n=10) who had a baseline and follow-up PET/CT scan.

Brito et al.[41] and Schmidkonz et al.[34], respectively, published similar findings, focusing on the evaluation of whole-body tumor burden with ^{68}Ga-PSMA PET/CT in patients with BCR. In the former study, a total of 100 PC patients who had a ^{68}Ga-PSMA PET/CT because of a BCR, were included. The detection rate of malignant lesions with ^{68}Ga- PSMA PET/CT was 72%. Since PSMA-TV and TL-PSMA showed a strong correlation, they used only TL-PSMA in further analysis. A strong correlation was reported between TL-PSMA and PSA levels (rho=0.73, p<0.0001). The latter study, evaluated the role of ^{68}Ga-PSMA PET/CT in determining treatment response, as well as its ability to assess whole-body tumor burden. The study population was chosen similar to Brito el al. and 142 PC patients who underwent a ^{68}Ga-PSMA PET/CT due to BCR were enrolled. Both PSMA-TV and TL-PSMA showed a significant correlation with PSA levels (p <0.0001). Data of 23 patients who underwent a baseline and follow-up ^{68}Ga-PSMA PET/CT after external beam radiotherapy, ADT or chemotherapy were analyzed for therapeutic response evaluation. A higher rate of agreement (87%) was noted between biochemical response

defined by changes in PSA levels and TL-PSMA (95% CI 0.66-0.97; Cohen's κ=0.78; p<0.01), when compared to the rate of agreement (74%) for SUVmax (95% CI 0.52-0.90; κ=0.55; p<0.01).

To date, limited research has investigated the role of ^{68}Ga-PSMA PET/CT-derived volumetric parameters in predicting survival outcomes in metastatic setting and very few studies addressed this issue in patients with mCRPC. Can et al. evaluated the predictive value of volumetric parameters in terms of survival, as well as their efficacy in monitoring treatment response[42].This retrospective study included 151 mCRPC patients who were treated with docetaxel or abiraterone/enzalutamide and underwent ^{68}Ga-PSMA PET/CT before and after treatment. The findings of this study showed a correlation and concordance between both PSA response and MTV response (r=0.66, p<0.01 and k=0.454, p<0.001), and PSA response and total lesion PSMA response (r=0.71, p<0.001 and k=0.541, p<0.001). The results were more significant when PSA levels were above 10 ng/mL. Pre-treatment MTV (p=0.003) and MTV change (p=0.001) were independent prognostic factors for mortality. In terms of treatment types, our study sample was similar to Can et al.'s, but we only included patients who received first-line treatment with enzalutamide in first-line setting, which made our cohort more homogeneous and allowed for more reliable survival analyses.

Second study from the same center included 44 mCRPC patients who were treated with abiraterone or enzalutamide and had two consecutive ^{68}Ga-PSMA PET/CT scans performed within 1 month before treatment and at least 3 months after treatment[43]. Pre-treatment PSA and MTV, as well as PSA change, were found to be independent prognostic factors associated with mortality.

In the study of Karyağar et al. MTV was shown to predict PSA response in mCRPC patients treated with enzalutamide after docetaxel failure[44]. PSMA-TV was significantly higher in non-responder group (p=0.028).

Another study[45] of 54 mCRPC patients treated in first-line setting with docetaxel, abiraterone or enzalutamide demonstrated that PSMA-TV (rho=0.582, *p*=0.004) and TL-PSMA (rho=0.564, *p*=0.007) showed moderate positive correlations with PSA levels. Older age (*p*=0.02), higher PSMA-TV (*p*=0.007), higher PSA (*p*=0.01), higher number of bone metastases (*p*=0.02), and lack of PSA response (*p*=0.03) were significantly associated with an increased risk of mortality. Multivariate analysis determined PSMA-TV (HR 1.003, 95% CI 1.001-1.004, *p*=0.001) and PSA response (HR 2.241, 95% CI 1.189–4.222, *p*=0.01) as independent predictors of OS.

In the study of Grubmüller et al.[46] in which patients with mCRPC receiving different treatments were included, the authors found that the use of SUVmean, SUVmax, SUVpeak and PSMA total tumor volume parameters derived from ^{68}Ga-PSMA-11 PET/CT were suitable for assessing treatment response; however, they found no association with OS.

In another study[47] of 71 mCRPC men treated with taxane, the volumetric parameters obtained by ^{68}Ga-PSMA PET/CT showed to have an impact on OS on univariate but not on multivariate analysis. Shagera and collegues[48] analyzed a population of mCRPC treated with cabazitaxel and demonstrated that high PSMA-TV before treatment initiation is associated with shorter PFS and OS.

Recently, volumetric parameters were furthermore reported as negative prognostic factors of OS in patients receiving [177Lu]Lu-PSMA-617 radioligand therapy[49].

The limitations of our study are the relatively small sample size and its retrospective and single-center design. For these reasons, the reported findings need to be confirmed and results have to be interpreted with caution. Larger, ideally prospective trials are needed to help to reveal the full potential of metabolic parameters derived from PET imaging with ^{68}Ga-PSMA.

In our study population, median baseline PSA was 2.66 ng/mL while in the enzalutamide arm of Prevail trial[8] median PSA was 54.1 ng/mL. Furthermore, 41% of our patients had lymph nodes only disease, 48% of them did not have bone metastases (compared to 15% of patients in the enzalutamide arm of Prevail trial[8]), 41% of them have less than 5 bone lesions and median OS was not reached after 52 months follow-up. These data reflect an earlier disease state probably due to the use of ^{68}Ga-PSMA PET/CT instead of conventional imaging to stage CRPC patients. Weber et al.[50] evaluated the detection rate of PSMA PET/CT in early 55 CRPC with low PSA values (<3 ng/mL). PSMA PET/CT resulted positive in 75% of patients and in 45% of them metastatic disease was detected. Fendler et al.[51] evaluated 200 patients with non-metastatic CRPC (nmCRPC) and PSA >2 ng/mL. All of them underwent PSMA PET/CT and 196 of 200 presented a PSMA-positivity. Overall, 55% had metastatic disease despite negative conventional imaging and a previous diagnosis of nmCRPC.

The therapeutic landscape of metastatic prostate cancer has broadened recently, with multiple new therapeutic options demonstrating survival benefits in patient outcomes. Therefore, identifying patient candidates most likely to benefit from a particular therapy is clinically essential to decide on the optimal therapeutic strategy. ^{68}Ga-PSMA PET/CT can accurately determine the total tumor burden before starting treatment with enzalutamide. This parameter can be used as a prognostic biomarker allowing the detection of those patients less benefiting from enzalutamide with a higher risk of progression or death. Therefore, considering the TLA before starting enzalutamide may help choose the best first-line treatment in mCRPC patients.

5. Conclusion

Despite its limitations, the findings of this study support the role of ^{68}Ga-PSMA PET/CT parameters in predicting survival and response to treatment among mCRPC patients treated with enzalutamide.

Our findings suggest that ^{68}Ga-PSMA PET/CT-derived volumetric parameters, notably TLA, appear to be useful tools to assess tumor burden and predict long-term survival and response to treatment in patients with mCRPC. TLA, expression of both volume and intensity of ^{68}Ga-PSMA uptake, appeared the strongest parameter able to predict clinical outcome in patients treated with enzalutamide in first-line setting.

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