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The prognostic role of ^{68}Ga-PSMA11 PET-based response in prostate cancer patients undergoing taxane-based chemotherapy

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ABSTRACT

To assess the prognostic utility of conventional biochemical and imaging response criteria and ^{68}Ga-prostate-specific membrane antigen (PSMA) 11 PET adapted or specific systems regarding overall survival (OS) in men with metastatic hormone-sensitive (mHSPC) and castration-resistant PC (mCRPC) treated with taxane-based chemotherapy.

Methods: A total of 103 patients (pts) (n=57 mHSPC, n=46 mCRPC) underwent taxane-based chemotherapy. All patients had a minimum of two PSMA PET scans (at baseline and up to 3 months post-treatment). PSMA PET response was assessed by Response Evaluation Criteria in Solid Tumors (RECIST 1.1), adapted Prostate Cancer Working Group Criteria 3 (aPCWG3, using PSMA PET instead of bone scan), adapted Positron Emission Tomography Response Criteria in Solid Tumors (aPERCIST) and PSMA PET Progression (PPP) criteria. Response by each criterion was stratified by either progressive disease (PD) versus non-PD. For aPERCIST, stratification by PD, stable disease (SD) and partial/complete remission (PR/CR) was performed. Biochemical response was determined by PSA decline ≥50%. Subgroup analyses were performed by castration-status. Univariable cox proportional hazard regression analyses including Harrell's concordance indices were calculated to investigate the association of PD by response criteria and OS. Kaplan-Meier tests including log-rank statistics were calculated for survival analyses.

Results: 26 (25%) of pts had non-measurable disease by RECIST 1.1. PD by any response criterion was associated with an at least 2.5-fold increased risk of death and was highest for PD versus CR/PR by aPERCIST (HR 11.4) on univariable regression. Stratified by castration status, a similar pattern was observed. PD by any criterion as associated with significantly shortened OS across overall and subgroup analyses. PR/CR by aPERCIST identified pts with lower risk of death and longer OS as compared to patients with PD or SD.

Conclusions: PSMA PET based response criteria (PPP, aPERCIST, aPCWG3) have high prognostic utility in men with metastatic PC undergoing taxane-based chemotherapy. PPP is simple to use, identified most patients with PD and showed best prognostic utility regarding OS. PR/CR by aPERCIST identifies a subgroup of responders (PR/CR) showing better outcomes than patients with PD or SD. Future studies are warranted to amend the current paradigm relying on mere differentiation of PD versus non-PD in metastatic PC and to identify true treatment responders by imaging criteria.

Key Words: metastatic prostate cancer; taxane-based chemotherapy; 68Ga-PSMA11 PET/CT; treatment monitoring; survival;

INTRODUCTION

Prostate cancer (PC) is the most common malignant tumor in men and the second most common cause of cancer associated mortality *(1)*. During the initial hormone-sensitive stage, metastatic PC (mHSPC) typically responds well to androgen deprivation. Nevertheless, the vast majority of patients will eventually progress despite androgen deprivation and metastatic castration-resistant PC (mCRPC) develops. This final stage of the disease is associated with poor prognosis and a significantly decreased overall survival (OS) *(2,3)*.

Despite the development of novel treatment strategies in both hormone-sensitive and castration-resistant PC, taxane-based chemotherapies remain a standard of care in metastatic PC treatment. Conventional assessment of treatment response in metastatic PC traditionally relies on radiographic criteria including CT and bone scan as proposed by the Prostate Cancer Working Group Criteria 3 (PCWG3) guidelines *(4)*. The PCWG3 imaging framework only allows the stratification of progressive disease (PD) versus non-progression (non-PD) and lacks identifying patients as responders by imaging criteria. The introduction of prostate-specific membrane antigen (PSMA) PET improved the detection of PC metastases as compared to conventional imaging *(5)*. Current guidelines recommend a PSMA PET in patients with rising or persistently elevated PSA after radical treatment *(6,7)*.

Whole body PET-imaging has evolved as reliable tool for assessing response in metastatic disease from various tumor entities *(8,9)*. Different frameworks exist for various tumor entities which employ either cross-sectional imaging (e.g. RECIST 1.1) or have been introduced for FDG PET (e.g. PERCIST). Most recently Fanti et al. proposed the PSMA PET progression (PPP)-criteria for potential use in metastatic PC (*(10)*). However, the use of PSMA PET imaging for assessing response in patients with metastatic PC undergoing systemic treatment is less explored *(11-14).* Despite the introduction of novel frameworks for

the application of PSMA PET in metastatic PC, especially data on the prognostic utility of such criteria in comparison to traditional frameworks for the monitoring of treatment response is limited.

The aim of this retrospective analysis was to investigate the comparative prognostic utility of traditional treatment response criteria with PSMA PET criteria regarding overall survival in metastatic PC patients (mHSPC and mCRPC) undergoing taxane-based chemotherapy. Traditional criteria comprised non-imaging PSA- based response and conventional-anatomy based RECIST 1.1 *(15)*. Specifically, PSMA PET criteria included ^{68}Gallium (^{68}Ga)-PSMA11 PET adapted PERCIST *(16)*, adapted PCWG3 *(4)*, and PPP-criteria *(10)*. In addition, we aimed to assess whether the definition of response employed in PERCIST would further add prognostic information in the group of patients with response.

MATERIAL AND METHODS

Patients

Patients with both mCRPC and mHSPC undergoing taxane-based chemotherapy and a ^{68}Ga-PSMA11 PET pre- and post-treatment between January 2014 and December 2018 at the Technical University Munich were included. The term PSMA PET is used throughout the remaining manuscript and refers to the use of ^{68}Ga-PSMA11 PET/CT in the setting of this retrospective analysis.

We included only patients with pairs of PSMA PET which were performed within a maximum interval of 3 months prior to initiation of chemotherapy and up to 3 months after completion of treatment. Patients without follow-up information and survival data were excluded. Patients with mCRPC underwent up to one additional interim PSMA PET after 3 months from initiation of treatment due to the high risk of progression in these patients. Clinical characteristics as well as serum PSA level were collected both at baseline and at the post-treatment visit.

All reported investigations were conducted in accordance with the Declaration of Helsinki and with national regulations *(17)*. The retrospective study was approved by the Ethics Committee of the Technical University Munich (permit 5665/13) and a waiver of consent was granted. The administration of PSMA11 complied with The German Medicinal Products Act, AMG §13 2b, and the responsible regulatory body (Government of Oberbayern).

Response Assessment

Biochemical response was defined as a PSA-decline ≥50% following chemotherapy. PET-based response was evaluated as follows: all patients underwent PSMA PET from the skull base to the mid-thigh using a previously described protocol *(11)*. In brief, PET scans were acquired in 3D mode, combined with an intravenous and oral contrast-enhanced CT scan. Images were reviewed by an experienced, board-certified nuclear medicine physician using the Prostate Cancer Molecular Imaging Standardized Evaluation (PROMISE) criteria for lesion assessment. Any focal uptake higher than that of the surrounding background and not associated with physiological uptake was considered suspicious for malignancy *(18)*. The post-treatment response was subsequently assessed in accordance with RECIST 1.1 (*15*), PPP *(10)*, adapted PERCIST *(16)*, adapted PCWG3 *(4)* criteria as described below.

RECIST 1.1

The revised RECIST1.1 criteria are widely used for response assessment in solid tumors *(19)*. The two morphologically largest lesions per organ system were selected in CT as target lesions with a maximum of five lesions in total. For targeted tumor lesions, the longest diameter with a minimum size of 10 mm by CT scan was measured. For targeted pathological nodes, the lesions must meet the criterion of short axis >15 mm by CT images. In final, a sum of the diameters of all target lesions is evaluated, and the results categorizes patients into complete response (CR), partial response (PR), stable disease (SD), and

progressive disease (PD). Patients who had only non-target lesions in the pre-chemotherapy PET scan, without clear progression or disappearance in post-chemotherapy PET were classified as non-measurable.

PSMA PET Progression (PPP) criteria

The PPP criteria were recently proposed by Fanti S, et al. *(10)*. Progression using PSMA PET was defined as follows: a) appearance of 2 or more new PSMA positive distant lesions, b) appearance of 1 new PSMA positive lesion plus consistent clinical and/or laboratory data. Clinical and laboratory data included changes in ECOG score, the record of any improving or worsening of bone pain or changes in PSA level before and after treatment c) increase in size or PSMA uptake of 1 or more existing lesions of at least 30% plus consistent clinical and/or laboratory data, together with the confirmation by biopsy or correlative imaging within 3 months. For the last criterion, SUVmax was used to evaluate changes in PSMA uptake and lesion size was measured according to the RECIST 1.1 protocol.

Adapted PERCIST

PERCIST 1.0 criteria *(16)* were adapted to the use of PSMA PET as follows: five organ systems (prostate or prostate bed, lymph nodes, bone, liver, and other visceral metastatic sites) were recorded per patient. For each organ system, up to two lesions with the highest PSMA PET uptake identified on maximum intensity projection PET images were selected on the pre-chemotherapy PET scan (PET1). To measure the SUVpeak, a circular 1.2-cm diameter volume region of interest was placed over the transaxial slice with maximum ^{68}Ga-PSMA-11 PSMA uptake. The post-therapeutic PET (PET2) was compared with the pre-chemotherapy PET scan (PET1) and finally interpreted as follows: the absence of any PSMA uptake on PET2 in all target lesions seen on PET1 was considered CR; a decrease in the SUVpeak sum of ≥30% (minimum decrease in SUVpeak of 0.8) was considered PR; the appearance of a new PET positive lesion on PET2 or an increase in SUVpeak sum of ≥30% (minimum increase in SUVpeak of 0.8) was considered

PD; an intermediate change in summed SUVpeak between −30% and +30% without the appearance of new target lesions was considered SD.

Adapted PCWG3 criteria

PCWG3 criteria *(4)* were adapted to the use of PSMA PET as follows: application of RECIST 1.1 for soft tissue lesions remained unchanged and information from PSMA PET was used for assessment of bone lesions instead of bone scan. Patients who exhibited progression according to RECIST 1.1 and/or had ≥ 2 new bone lesions on PET2 were classified as PD. Other conditions were defined as non-PD. Given the high specificity of PSMA PET, no additional confirmation of new bone lesions was demanded.

Statistical Analysis

All values are reported as average (SD) or median (IQR) for continuous variables and as number and percentage for categorical variables. All statistical tests were conducted for the overall collective as well as following stratification by castration status. Kaplan-Meier tests including log-rank statistics were calculated for survival analyses. Overall survival was defined as the time from initiation of chemotherapy until death from any causes. Patients who were alive or lost to follow-up were censored at the last date they were known to be alive.

The association between biochemical response and PET-based criteria (aPCWG3, aPERCIST and PPP) with OS was evaluated using univariate cox regression analyses and reported as hazard ratio (HR) and 95% confidence interval (95% CI). To evaluate the goodness of fit of performed cox-regression analyses the Harrell's concordance index (C-index) was calculated. Ties were included in the calculation of the C-index. A P-value <0.05 was considered statistically significant. All statistical analyses were performed using SPSS v26 (SPSS, Chicago, IL, USA).

RESULTS

Patients and Disease Characteristics

A total of 103 patients (n=57 mHSPC, n=46 mCRPC) were included. Clinical characteristics are outlined in table 1. The majority of the patients had bone metastasis (M1b) (N=80/103, 78%), and extrapelvic lymph node metastasis (M1a) (N=72/103, 70%).

Median duration from pre-chemotherapy PSMA PET to initial chemotherapy was 27 days (IQR 14 - 49), while the median duration from last chemotherapy application to post-treatment PET was 27 days (IQR 18 - 39).

Biochemical Response

Overall, 61 patients (59%) had a PSA decrease ≥ 50% following taxane-based chemotherapy. Stratified by castration status, 45 (79%) of mHSPC patients and 16 (35%) of mCRPC patients had a PSA decrease ≥ 50%.

For mHSPC, median pre- and post-chemotherapy PSA values were 14.9 ng/ml (IQR 1.9 – 39.3) and 0.6 ng/ml (IQR 0.04 – 3.5), respectively. For mCRPC, median pre- and post-chemotherapy PSA values were 45 ng/ml (IQR 9.5 – 154.5) and 34 ng/ml (IQR 6.7 – 153.8), respectively.

Imaging-based Response

By RECIST 1.1 criteria, 26 (25% of all patients) had non-measurable disease. Of those, 5 patients had isolated bone metastases without soft tissue component, 6 patients had non-target lymph nodes with or without non-target prostatic bed lesions, and 15 patients had coexisting non-target nodes and bone lesions. Survival and further response analyses for RECIST 1.1 were therefore omitted. An overview of response rates by PET-response criteria is given in table 2.

Overall, by adapted PERCIST criteria, PD was observed in 33 (32%) of patients. For mHSPC and mCRPC, PD was observed in 8 (14%) and 25 (54%) of patients, respectively. By aPCWG3 criteria, PD was observed in 34 (33%) of patients. For mHSPC and mCRPC, PD was observed in 9 (16%) and 25 (54%) of patients, respectively. By PPP criteria, PD was observed in 41 (40%) of patients. Stratified by castration status, PD was observed in 11 (19%) of mHSPC patients and 30 (65%) of mCRPC patients.

Survival Analyses by Response Criteria

Median OS of all patients was 50 months (95% CI 31 – 69). Median OS for patients with mCRPC was 18 months (15 – 21) and was not reached (n.r.) for patients with mHSPC.

Kaplan Meier analyses by biochemical response and imaging-based response criteria are shown in figures 1A-D. Progression by any investigated criterion was associated with a significantly shorter OS as compared to response (median survival ranging from 14-17 months (PD) versus median survival ranging from 57 months – not reached. (No-PD)). Additional survival analyses for stratification by castration status are shown as a cumulative illustration in supplementary figure 1.

Prognostic value of response criteria

Cox – regression analyses investigating the associations of PET-based response criteria and biochemical response with OS are given in table 3. Of note, on univariable analysis, PD (independent of castration status) as defined by any of the investigated PET-criteria in this study was associated with a significantly increased risk of death (HR range 4.1 – 8.1 (95% CI 2.5 – 16.7). C-index analyses revealed the strongest prognostic values for PPP (0.77 (95% CI 0.72 – 0.81) and aPERCIST (0.75 (95% CI 0.69 – 0.80). Details are presented in table 3.

Stratified by castration status, for mHSPC, aPCWG3 and PPP criteria showed a strong prognostic value with a C-index >0.73). For mCRPC status, aPERCIST and PPP criteria C-indices were highest (> 0.69, see supplementary table 1 and 2 for more detailed results).

DISCUSSION

The objective and reliable evaluation of response to systemic treatment is critical to both clinical research and practice. To date, a variety of frameworks exist to determine response to PC treatment, but data on their prognostic value and use in routine clinical practice is limited. Here, we present a considerably large and evenly balanced cohort including both mCRPC and mHSPC patients to retrospectively compare the prognostic utility of response to taxane-based chemotherapy by serum PSA decrease, RECIST 1.1, aPERCIST, aPCWG3 and PPP criteria regarding overall survival. Within the used imaging biomarkers aPERCIST offer the possibility not only to detect PD versus non-PD, but also to identify PR/CR.

Overall, PD (independent of castration status) as defined by traditional and PSMA PET frameworks was associated with an at least 2.5-fold increased risk of death by univariable analyses in this study. PD by aPERCIST was associated with the highest risk of death (HR 11.4, 95% CI: 4.7-27.1) as compared to patients with PR/CR ($P < 0.001$). To compare the prognostic utility of reported hazard ratios, C-index analyses were carried out. Based on its C-index PPP was the framework with the highest prognostic value as compared to the other investigated criteria – however not statistically different. Overall, Kaplan-Meier-curve (KM) analyses revealed that PD by any investigated criterion was associated with significantly reduced overall survival. Of interest, across all criteria, only in patients classified as having PR/CR by aPERCIST, median overall survival was not reached and was significantly shorter in patients with PD and SD (14 months (95%CI 12 – 16) and 55 months (95% CI 18 – 92), respectively, $P < 0.001$). The same pattern was observed following stratification by castration status (see supplementary figure 1).

A recent review investigated the role of PET-based imaging for response to systemic treatment in metastasized PC *(14)*. The results suggest that the volumetric extent of metastatic burden and/or the total lesion PSMA estimated by PSMA PET may have prognostic value in patients undergoing taxane-based

chemotherapy *(14)*. However, the evidence backing this conclusion is sparse and relying on a limited number of studies with small sample sizes. Moreover, most studies investigate different endpoints and lack standardized definitions of response and comparable follow-up. Similarly, two works by Simsek and Shagera et al most recently aimed to investigate the prognostic role of total metastatic burden *(12,13)*. Of interest, both studies found that PD by PSMA total tumor volume was associated with a significantly shortened overall survival. Yet, the significance of presented results appears limited by the overall small sample size, the lack of post-treatment PET-scans and the combination of both mCRPC and mHSPC patients in one cohort. In contrast, we focused on the use of different diagnostic frameworks for response assessment. Here, we assessed response by comparing a limited number of lesions across two different timepoints and assessing the presence of new lesions in follow-up scans. Of note, the investigated methods in our study did not require the determination of the whole-body tumor volume. Still, our data clearly indicate that PD as defined in PPP, PCWG3 and aPERCIST was associated with shorter overall survival. Yet, future prospective studies are warranted to validate and determine the prognostic benefit of one framework over the other, including a definition of reliable cut-offs for the measurement of whole-body metastatic tumor volume.

Comparing the investigated frameworks provided novel insights and, in contrast to previous studies *(11)*, our analysis is based on long-term follow-up, allowing a comparison of results from different frameworks with overall survival as clinically most meaningful outcome parameter. First, our results showed that PPP and aPERCIST had the highest comparative prognostic value. Still, while response assessment using PPP is much more feasible in routine practice given its simple application, aPERCIST provides the potential not only to discriminate between PD and non-PD, but also to identify responders (CR/PR) within this group with substantially better outcome as compared to SD. This finding highlights an important aspect of aPERCIST worth investigation in further prospective studies. Still, to date, the use of software solutions (semi-) automatically detecting, quantifying and following tumor lesions over time is

required to facilitate its adoption. Such tools are currently under development by various vendors but are not yet fully implemented in standard software solutions. Thus, the application of aPERCIST criteria remains currently limited to scientific investigations until automated analyses are routinely available.

On the other hand, response by aPCWG3 as a straight-forward adoption of PCWG3 for the use with PSMA PET did not outperform aPERCIST or PPP in terms of prognostic utility in this study. In addition, despite the incorporation of similar criteria as compared to PPP for bone assessment, the application remains time-consuming and is hampered by the manual, quantitative measurement of soft-tissue metastases. Similar to previous investigations, response by traditional RECIST 1.1 is not useful for metastasized prostate cancer *(20)*. In our cohort 25% of included patients only had non-measurable disease confirming a major limitation of this framework for response assessment in metastatic PC. Furthermore, typical for metastasized prostate cancer, 78% of patients had bone metastases in this study. However, these lesions cannot be assessed quantitatively within this framework in the absence of extra-osseous soft-tissue extension and osteolytic lesions. Progression of sclerotic bone metastases in RECIST 1.1 can only be determined in the case of "unequivocal progression" of non-target lesions, which is prone to subjective interpretation. These observations led to its combination with bone scintigraphy and their combined use within the PCWG framework *(4)*. Taken together, our results suggest that PPP appears most useful for determination of treatment response of metastasized PC in routine clinical practice, given its easy adoption and its comparable prognostic utility to aPCWG3 or aPERCIST.

Here, we also analyzed the utility of traditional response by serum PSA reduction as a prognostic biomarker. While serum PSA measurement effectively stratified patients in PD and non-PD, its C-index was lower as compared to the other imaging-based response criteria. In addition, it is known that its sole use is hampered by the known inter- and intratumor heterogeneity associated especially with mCRPC *(21)*,

as well as its inability to detect clinically relevant complications (e.g. fractures, embolism, ...) as compared to imaging-based response assessment.

Several limitations of this study are noteworthy including the small cohort size and the retrospective study design, associated with selection and misclassification bias. Additionally, the current study reflects a single center experience and all imaging data-sets were reviewed by a single physician only. One particularly relevant limitation concerns the study population: here, both patients with mCRPC and mHSPC were included for survival analyses. The inclusion of mHSPC patients might have introduced substantial bias of obtained univariable regression results due to the small study population and the low rate of PD events as compared to mCRPC patients alone. Nevertheless, all results followed a similar trend even following stratification by castration status and expand the available knowledge on the prognostic role of PSMA PET-based response criteria regarding overall survival in a large cohort of metastatic PC patients.

CONCLUSION

The PSMA PET-based response criteria PPP, aPERCIST and aPCWG3 are reliable and prognostic tools for the assessment of treatment response following taxane-based chemotherapy in both mHSPC and mCRPC patients. PPP appears most useful for determination of treatment response of metastasized PC in routine clinical practice. PPP is easy to adopt and implement in clinical routine and its prognostic utility was similar to aPCWG3 or aPERCIST in this study while lacking the need of (semi)-automated software applications. In contrast, aPERCIST offers the possibility to also identify a subgroup of responders (PR/CR) showing reduced risk of death and associated with a significantly longer OS compared to patients with PD and SD. Its further prospective investigation is warranted to potentially expand the current paradigm assessing only PD versus non-PD to the identification of true response by an imaging biomarker for response in metastasized prostate cancer.

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KEY POINTS

QUESTION: To investigate the comparative prognostic utility of traditional treatment response criteria with PSMA PET criteria for overall survival in metastatic PC patients undergoing taxane-based chemotherapy.

PERTINENT FINDINGS: This retrospective cohort study on (n=103) metastatic PC patients showed that progressive disease by any response criterion was associated with an at least 2.5-fold increased risk of death and was highest for PD versus CR/PR by aPERCIST. PPP as an easy to determine parameter showed best prognostic utility regarding overall survival.

IMPLICATIONS FOR PATIENT CARE: PSMA PET based response criteria have high prognostic utility in men with metastatic PC undergoing taxane-based chemotherapy and may help to identify patients at high risk for reduced overall survival.

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Table 1. Clinical characteristics

Age (years), median (range)	71 (43-85)
Pre-CTX PSA level (ng/ml) (median (IQR))	
mHSPC	15 (2 - 39)
mCRPC	45 (10 – 155)
Gleason score (no. (%))	
≤7	31 (30)
≥8	67 (65)
NA	5 (5)
ECOG performance status, no. (%)	
0	53 (52)
1	26 (25)
2	1 (1)
NA	23 (22)
Castration status (no. (%))	
mHSPC	57 (55)
mCRPC	46 (45)
Pre-CTX miTNM staging (no. (%))	
No distant metastasis (M0)	6 (6)
Extrapelvic node metastasis (M1a)	72 (70)
Bone metastasis (M1b)	80 (78)
Visceral metastasis (M1c)	16 (16)
Pattern of metastatic spread (no. (%))	
LN only	21 (21)
Bone only	9 (9)
Visceral only	1 (1)
LN and bone	54 (52)
LN and visceral organs	1 (1)
LN, bone and visceral organs	14 (14)
LN, bone and others (subcutaneous, skin metastasis)	2 (2)
Bone and others (penis)	1 (1)
Local treatment for PC (no. (%))	
Prostatectomy ± lymphadenectomy	58 (56)
Primary EBRT	13 (13)
Type of Chemotherapy (no. (%))	
Docetaxel	95 (92)
Cabazitaxel	7 (7)
Docetaxel and Cabazitaxel	1 (1)
Reduction in serum PSA ≥50% (no. (%))	61 (59%)

Abbreviations: CTX, chemotherapy; ECOG, Eastern Cooperative Oncology Group; EBRT, external beam radiotherapy; mHSPC, metastatic hormone-sensitive prostate cancer; mCRPC, metastatic castration-resistant prostate cancer; NA, not available; LN = lymph nodes;

Table 2 Overall response rates by imaging response criteria.

Criteria	Response	N (%)
RECIST 1.1	n/m	26 (25)
	PD	20 (19)
	SD	38 (37)
	PR	15 (15)
	CR	4 (4)
aPERCIST	PD	33 (32)
	SD	18 (18)
	PR	45 (44)
	CR	7 (7)
aPCWG3	PD	34 (33)
	No-PD	69 (67)
PPP	PD	41 (40)
	No PD	62 (60)

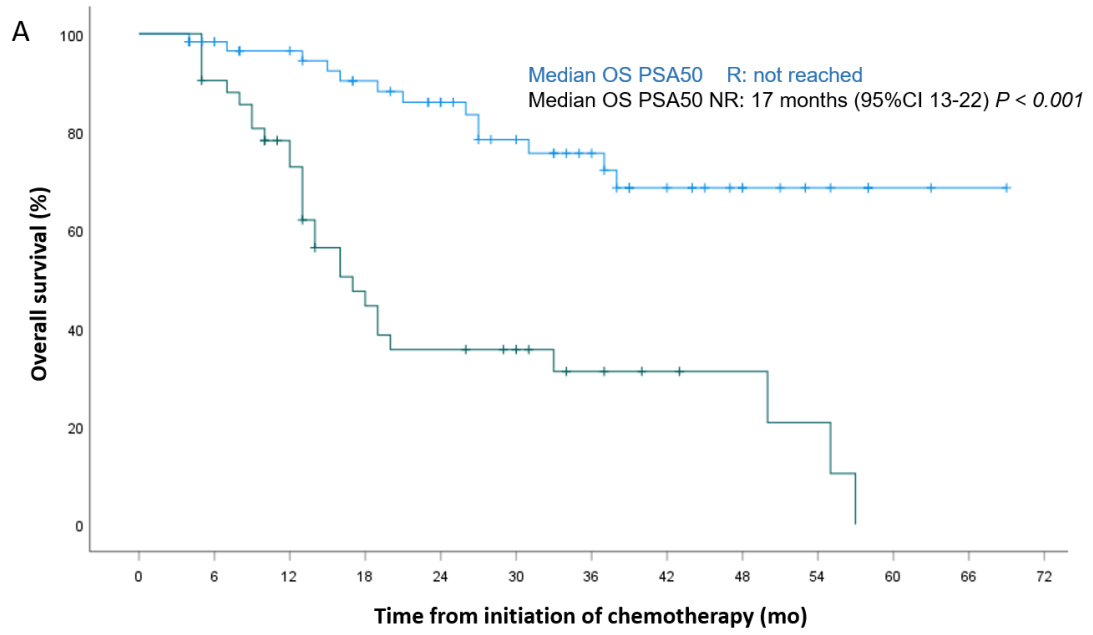
Abbreviations: n/m, non-measurable disease; PD, progressive disease; SD, stable disease; PR, partial remission; CR, complete remission; No-PD, no progressive disease which includes complete response, partial response and stable disease; N, number of patients; %, percentage;

Table 3 Univariable cox-regression analyses for the association of response criteria with overall survival, all patients (mCRPC and mHSPC) included.

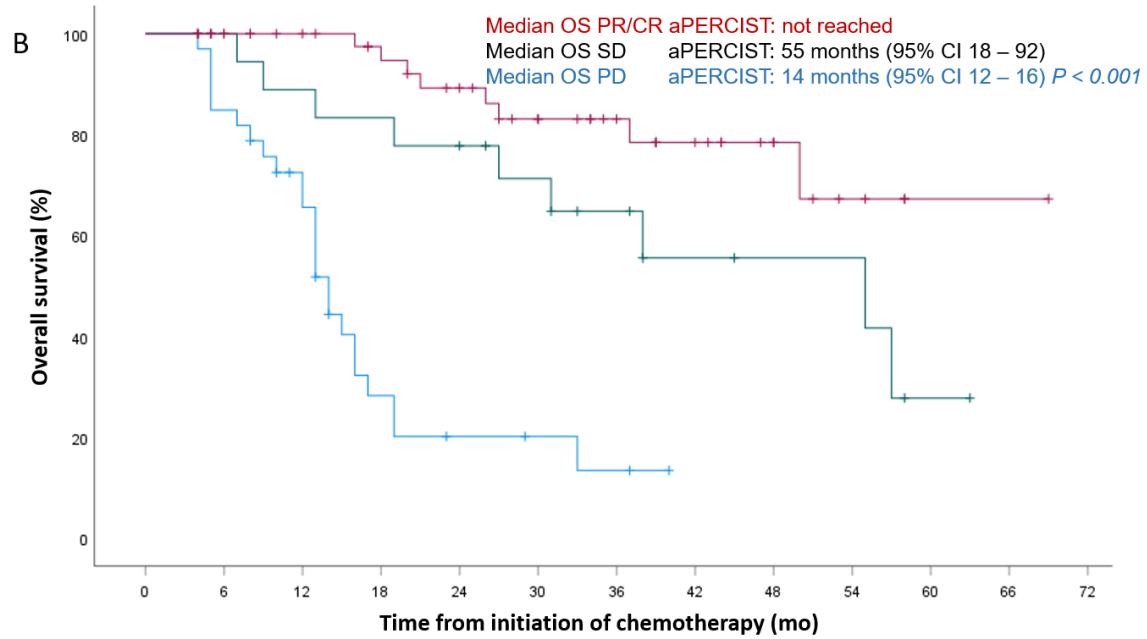
Criteria	Response	N*	HR	95% CI	P value	C-index
PSA50	PD vs No-PD	42 vs 61	4.8	2.5 – 9.3	<*0.001*	0.695 (0.629-0.761)
aPERCIST	PD vs No-PD	33 vs 70	8.1	4.1 – 16.2	<*0.001*	0.746 (0.690-0.802)
	PD vs SD	33 vs 18	4.1	1.7 – 10.1	<*0.001*	
	PD vs PR/CR	33 vs 52	11.4	4.7 – 27.1	<*0.001*	
aPCWG3	PD vs No-PD	34 vs 69	7.1	3.5 – 14.2	<*0.001*	0.729 (0.670-0.788)
PPP	PD vs No-PD	41 vs 62	8.1	4.0 – 16.7	<*0.001*	0.765 (0.721-0.808)

Abbreviations: C-index, Harrell's concordance index (C-index); CR, complete remission; HR = Hazard ratio; n/m, non-measurable disease; PD, progressive disease; PSA50, dichotomous, biochemical response with PSA reduction ≥ 50%; PR, partial remission; No-PD, no progressive disease which includes complete response, partial response and stable disease; N, number of patients; SD, stable disease; %, percentage; vs, versus;

Figure 1. Kaplan–Meier estimates of overall survival by biochemical response (A), adapted PERCIST (B), adaptedPCWG3 (C) and PPP (D).

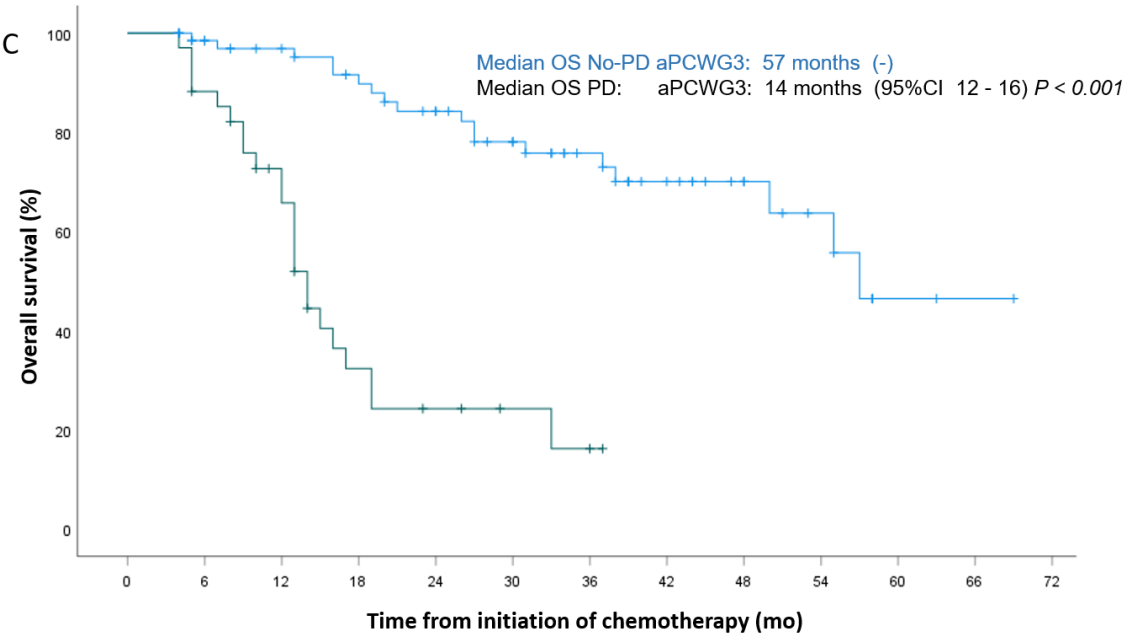


Pts. at risk													
PSA 50 NR	42	37	29	16	12	10	6	4	3	2	-	-	-
PSA50 R	61	55	49	42	37	29	23	15	10	6	2	1	-



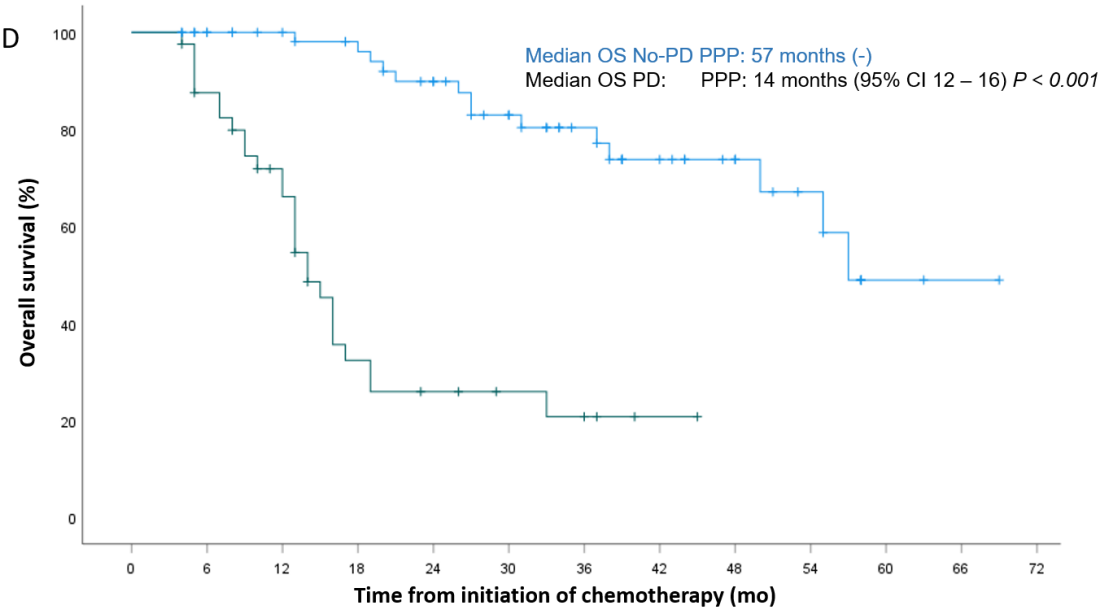
Pts. at risk													
PD	33	28	21	7	4	3	2	-	-	-	-	-	-
SD	18	18	16	15	14	11	8	5	4	4	1	-	-
PR/CR	52	46	41	36	31	25	19	14	9	4	1	1	-

C



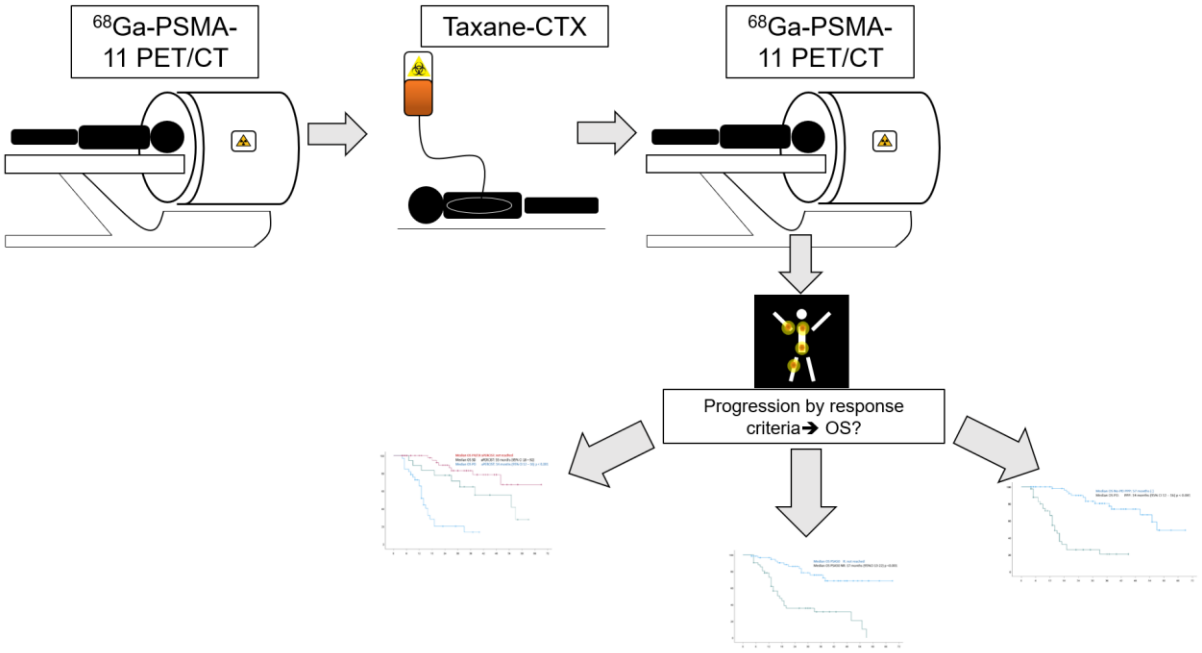
Pts. at risk													
PD	34	29	21	8	5	3	2	-	-	-	-	-	-
No-PD	69	63	57	50	44	36	27	19	13	8	2	1	-

D



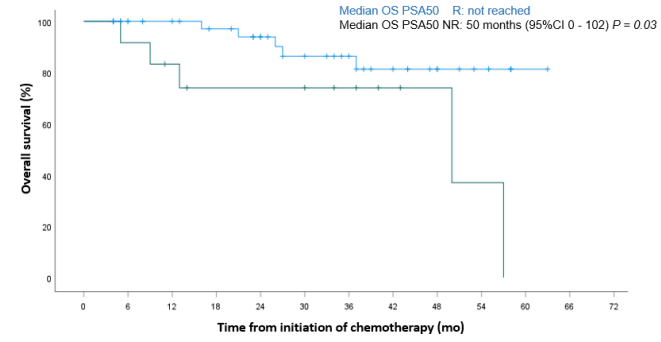
Pts. at risk													
PD	41	34	25	10	7	5	4	1	-	-	-	-	-
No-PD	62	58	53	48	42	34	25	18	13	8	2	1	-

Graphical abstract



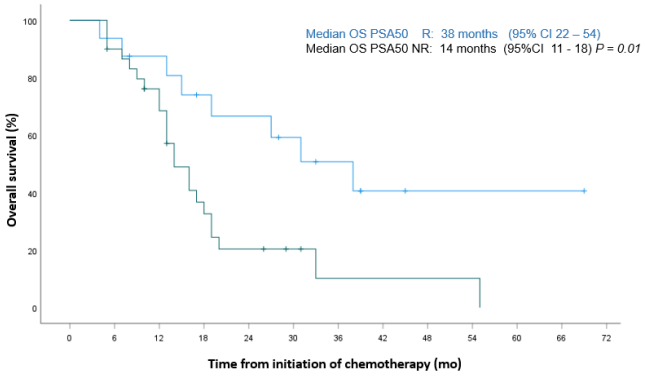
Supplementary figure 1: Kaplan Meier estimates of overall survival by PSA reduction ≥50%, adapted Prostate Cancer Working Group Criteria 3 (aPCWG3), adapted Positron Emission Tomography Response Criteria in Solid Tumors (aPERCIST) and PSMA PET Progression (PPP) criteria, stratified by castration status.

PSA50 Response: mHSPC



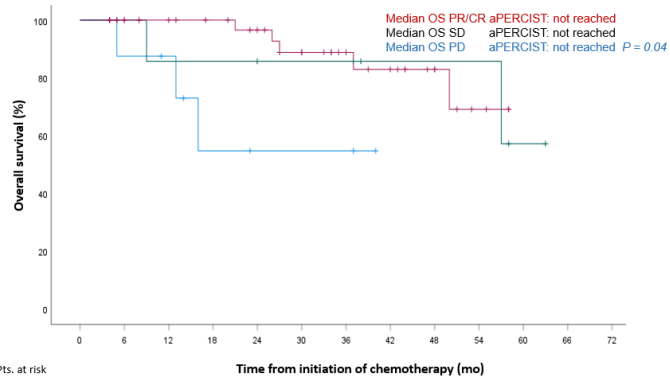
Pts. at risk													
PSA 50 NR	12	11	9	7	7	7	5	3	2	1	-	-	-
PSA50 R	45	40	36	32	28	22	18	13	9	5	1	-	-

PSA50 Response: mCRPC



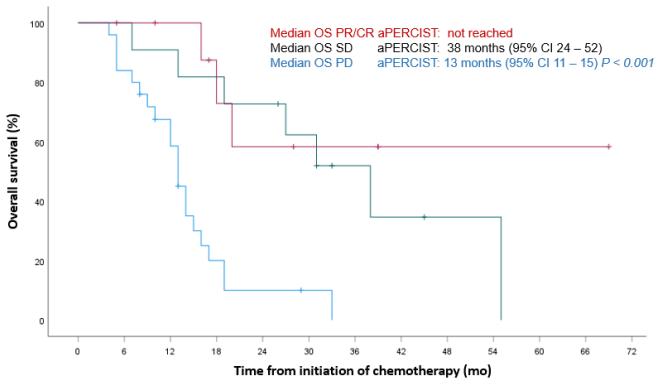
Pts. at risk													
PSA 50 NR	30	26	20	9	5	3	1	1	1	1	-	-	-
PSA50 R	16	15	13	10	9	7	5	2	1	1	1	1	-

aPERCIST: mHSPC



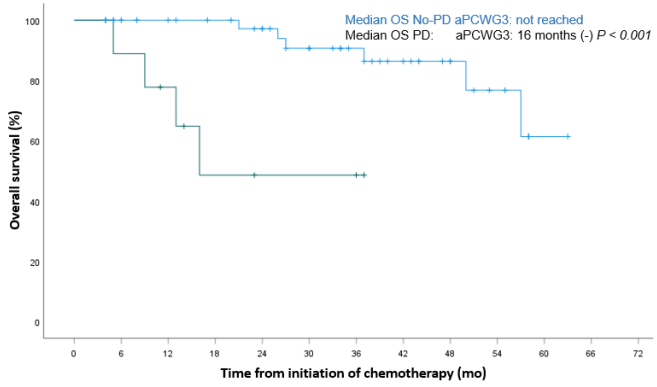
Pts. at risk													
PD	8	7	6	3	2	2	2	-	-	-	-	-	-
SD	7	7	6	6	6	5	5	3	3	3	1	-	-
PR/CR	42	37	33	30	27	22	16	13	8	3	-	-	-

aPERCIST: mCRPC



Pts. at risk													
PD	25	21	15	4	2	1	-	-	-	-	-	-	-
SD	11	11	10	9	8	6	3	2	1	1	-	-	-
PR/CR	10	9	8	6	4	3	3	1	1	1	1	1	-

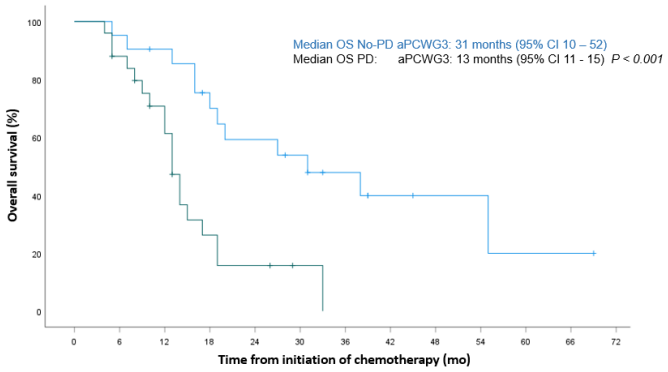
aPCWG3: mHSPC



Pts. at risk

PD	9	8	6	3	2	2	2	-	-	-	-	-	-
No-PD	48	43	39	36	33	27	21	16	11	6	1	48	43

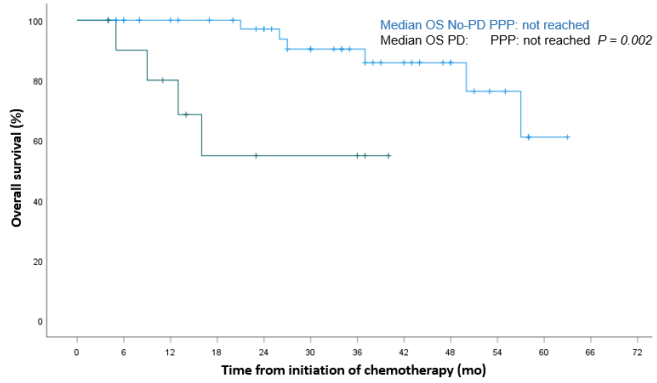
aPCWG3: mCRPC



Pts. at risk

PD	25	21	15	5	3	1	-	-	-	-	-	-	-
No-PD	21	20	18	14	11	9	6	3	2	2	1	1	-

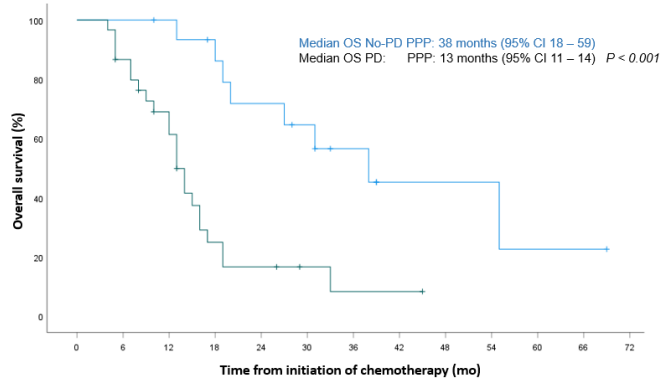
PPP: mHSPC



Pts. at risk

PD	11	9	7	4	3	3	3	-	-	-	-	-	-
No-PD	46	42	38	35	32	26	20	16	11	6	1	-	-

PPP: mCRPC



Pts. at risk

PD	30	25	18	6	4	2	1	1	-	-	-	-	-
No-PD	16	16	15	13	10	8	5	2	2	2	1	1	-

Supplementary table 1 Univariable cox-regression analyses for the association of response criteria with overall survival for patients with mHSPC.

Criteria	Response	N*	HR	95%CI	P value	C-index	95%CI
PSA50	PD vs No-PD	12 vs 45	3.8	1.1 – 13.0	*0.03*	0.645	0.489-0.801
aPERCIST	PD vs No-PD	8 vs 49	5.4	1.3 – 23.0	*0.02*	0.668	0.517-0.818
	PD vs SD	8 vs 7	3.2	0.3 – 31.5	*0.3*		
	PD vs PR/CR	8 vs 42	4.5	1.3 – 27.3	*0.02*		
aPCWG3	PD vs No-PD	9 vs 48	9.7	2.3 – 40.4	*0.002*	0.743	0.611-0.874
PPP	PD vs No-PD	11 vs 46	7.0	1.7 – 28.3	*0.007*	0.730	0.595-0.864

Abbreviations: C-index, Harrell's concordance index (C-index); CR, complete remission; HR = Hazard ratio; n/m, non-measurable disease; PD, progressive disease; PSA50, dichotomous, biochemical response with PSA reduction ≥ 50%; PR, partial remission; No-PD, no progressive disease which includes complete response, partial response and stable disease; N, number of patients; SD, stable disease; %, percentage;

Supplementary table 2 Univariable cox-regression analyses for the association of response criteria with overall survival for patients with mCRPC.

Criteria	Response	N*	HR	95%CI	P value	C-index	95%CI
PSA50	PD vs No-PD	30 vs 16	2.8	1.2 – 6.5	*0.02*	0.609	0.524-0.693
aPERCIST	PD vs No-PD	25 vs 21	5.6	2.4 – 13.3	*< 0.001*	0.706	0.651-0.760
	PD vs SD	25 vs 11	4.9	1.8 – 13.8	*0.002*		
	PD vs PR/CR	25 vs 10	6.3	1.8 – 21.8	*0.003*		
aPCWG3	PD vs No-PD	25 vs 21	3.6	1.6 – 8.1	*0.002*	0.659	0.589-0.730
PPP	PD vs No-PD	30 vs 16	4.5	1.8 – 10.9	*< 0.001*	0.693	0.647-0.739

Abbreviations: C-index, Harrell's concordance index (C-index); CR, complete remission; HR = Hazard ratio; n/m, non-measurable disease; PD, progressive disease; PSA50, dichotomous, biochemical response with PSA reduction ≥ 50%; PR, partial remission; No-PD, no progressive disease which includes complete response, partial response and stable disease; N, number of patients; SD, stable disease; %, percentage;