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## PSMA PET/CT for treatment response evaluation at predefined time points is superior to PSA response for predicting survival in metastatic castration-resistant prostate cancer patients

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### ABSTRACT

**Background:** In metastatic castration-resistant prostate cancer (mCRPC), using serum prostate-specific antigen (PSA) levels to evaluate treatment response is not always accurate. This study aimed to assess the efficacy of PSMA PET/CT at specific time points for evaluating treatment response and predicting survival in mCRPC patients, compared to PSA.

**Methods:** Sixty mCRPC patients underwent [<sup>18</sup>F]PSMA-1007 PET/CT at baseline and for treatment response evaluation of either androgen receptor-targeted agents (after 3 months) or chemotherapy (after completion), and were retrospectively analysed. Visual assessment categorised overall response and response of the worst responding lesion as partial response, stable disease, or progressive disease, using the EAU/EANM criteria. Additionally, percentage changes in SUV<sub>max</sub>, total tumour volume and total lesion uptake (tumour volume \* SUV<sub>mean</sub>) were calculated. PSA response was defined according to the PCWG3 criteria. Cox regression analysis identified predictors of overall survival.

**Results:** PSMA PET/CT and PSA response were discordant in 47 % of patients, and PSMA PET/CT response was worse in 89 % of these cases. Overall response on PSMA PET/CT independently predicted overall survival (progression versus non-progression: HR = 4.05, p < 0.001), outperforming PSA response (progression versus non-progression: HR = 2.53, p = 0.010) and other PSMA PET/CT parameters. Among patients with a PSA decline of > 50 %, 31 % showed progressive disease on PSMA PET/CT, correlating with higher mortality risk (progression versus non-progression: HR = 4.38, p = 0.008). No flare in PSMA uptake was observed in this cohort.

**Conclusions:** PSMA PET/CT for assessing treatment response at predefined time points was superior to PSA-based response for predicting overall survival in mCRPC patients treated with androgen receptor-targeted agents and chemotherapy. PSMA PET/CT showed the ability to detect disease progression earlier than PSA levels, which can affect treatment decisions and has the potential to improve patient outcomes. We recommend further research to validate these findings in larger patient cohorts, to extend the number of treatments, and to evaluate cost-effectiveness and impact on patient outcomes.

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## 1. Introduction

Metastatic castration-resistant prostate cancer (mCRPC) is an advanced stage of prostate cancer characterised by resistance to androgen deprivation therapy, with a 5-year survival rate of approximately 30 % [1]. Treatment options for mCRPC mainly involve androgen receptor-targeted agents (ARTAs) and taxane-based chemotherapies [2]. As mCRPC is highly heterogeneous, evaluating treatment response is critical for disease management, with serum prostate-specific antigen (PSA) levels currently being the primary biomarker [2]. However, PSA levels do not always accurately reflect tumour burden. A PSA decrease can be seen in dedifferentiated prostate cancer [3] and a PSA increase can also have benign causes like prostatitis [4]. It is also known that time to PSA progression lacks correlation with overall survival in mCRPC patients and, therefore, is not a valid surrogate endpoint [5]. Additionally, PSA levels do not provide information about the location and biological behaviour of individual lesions, which can be particularly important in case of a mixed response. While in many other solid tumours treatment response is assessed using imaging modalities such as CT scans with RECIST criteria [6], in metastatic prostate cancer no imaging modality up to now has been effective enough to assess treatment response. Conventional imaging, i.e. CT and bone scans, has limited sensitivity in detecting lymph node and bone metastases, often showing no change in early bone metastases and missing more than half of lymph node metastases on CT scans [7]. It can also be complicated to distinguish between progressive and responsive bone lesions [8,9]. Due to the limitations of PSA and conventional imaging, there is a need to find a reliable alternative method for treatment response evaluation in mCRPC.

Prostate-specific membrane antigen (PSMA) positron emission tomography / computed tomography (PET/CT) may provide a solution. PSMA is a transmembrane protein that is expressed in the epithelial cells of prostatic tissue and is highly overexpressed in prostate cancer [10]. PSMA-targeted PET/CT imaging in prostate cancer offers improved diagnostic sensitivity and specificity compared to conventional imaging, and is currently used either for staging high-risk patients or for restaging patients with biochemical recurrence after primary therapy [2,11]. To date, however, there is limited data on the use of PSMA PET/CT for treatment response evaluation. It has been reported that PSMA PET/CT- and PSA-response differ in approximately 25 % of patients, but its impact on patient management and outcomes remains unclear [12,13]. We hypothesize that PSMA PET/CT offers improved treatment response evaluation compared to PSA, potentially leading to more effective treatment adjustments, improved survival outcomes, and reduced toxicity and costs. This study therefore aims to evaluate the effectiveness of PSMA PET/CT at specific time points in assessing treatment response and predicting survival in mCRPC patients as compared to PSA-based monitoring.

## 2. Materials and methods

### 2.1. Patient population

Since July 2019, [<sup>18</sup>F]PSMA-1007 PET/CT (in short: PSMA PET/CT) has replaced conventional imaging to assess treatment response in mCRPC patients at Leiden University Medical Centre (Leiden, The Netherlands) and Alrijne Hospital (Leiderdorp, The Netherlands). After approval of the study protocol by the local ethics committee on 03/03/2022, this bicentric study included patients who (1) had been diagnosed with mCRPC, (2) had received treatment with either ARTAs (enzalutamide, abiraterone) or chemotherapy (docetaxel, cabazitaxel) and (3) had undergone PSMA PET/CT at baseline and for treatment response evaluation. Patients with baseline PSMA PET/CT scans from other hospitals, i.e. other PSMA tracers and/or scanners, were excluded. Administered treatment dosages adhered to EAU guidelines [2] and androgen deprivation therapy was continued in all patients. Clinical

data, including medical history, laboratory tests, imaging results, overall survival (OS) and progression-free survival (PFS), were collected from electronic clinical records for retrospective analysis. All patients consented to the use of their data.

### 2.2. PSMA PET/CT imaging

Baseline PSMA PET/CT was performed within 8 weeks before treatment initiation. In case of ARTA treatment, the PSMA PET/CT for treatment response evaluation was performed after 3 months of treatment. This time point was chosen to avoid flare in PSMA uptake and/or PSA levels, which can occur in the weeks following ARTA initiation, but is not seen after 3 months [14–17]. In case of chemotherapy, PSMA PET/CT was performed 4–6 weeks (maximum: 8 weeks) after the last administered dose to evaluate treatment response. The PSMA PET/CT was performed earlier if disease progression was suspected after at least 3 chemotherapy cycles, also to avoid flare in PSMA uptake and/or in PSA levels [18,19]. Disease progression was suspected when PSA levels increased by > 25 % and > 2 ng/ml [19], or in case of clinical deterioration, such as new-onset pain.

PSMA PET/CT scans were performed 60–120 min after intravenous injection of [<sup>18</sup>F]PSMA-1007, depending on PSA (<4 ng/ml: 120 min, 4–40 ng/ml: 80 min, >40 ng/ml: 60 min). 1.5–2.1 MBq/kg body weight of [<sup>18</sup>F]PSMA-1007 was injected, depending on BMI (<25: 1.5 MBq/kg, 25–30: 1.8 MBq/kg, >30: 2.1 MBq/kg). All patients were scanned with the 5-Ring Discovery MI PET/CT (GE Healthcare, Chicago, Illinois, USA [20]) located at Alrijne Hospital (Leiderdorp, The Netherlands), covering the skull vertex to mid-thigh in a supine position. A low-dose CT (15–550 mA, 120 kV) was performed for attenuation correction, followed by a PET scan (120 s per bed position). CT images were reconstructed in 512 x 512 matrices with a slice thickness of 2.5 mm. PET images were reconstructed in 256 x 256 matrices with a slice thickness of 2.78 mm, and a Bayesian penalised-likelihood iterative image algorithm (Q.Clear with a beta value of 900) was applied.

### 2.3. Study endpoints

Overall response to treatment on PSMA PET/CT was assessed visually and reported for clinical use by one of our nuclear medicine physicians, who had 2–4 years of experience with this tracer at the start of this study period, according to the EAU/EANM criteria [21]. Imaging-based progressive disease (iPD) was defined as 2 or more new lesions or a > 30 % increase in uptake or tumour volume; partial response (iPR) as a > 30 % decrease in uptake or tumour volume; stable disease (iSD) as a change in uptake and tumour volume between –30 % and + 30 %. Additionally, our nuclear medicine physicians reported the response of the worst responding lesion using the same criteria (abbreviations: iPD<sub>worst</sub>, iPR<sub>worst</sub> and iSD<sub>worst</sub>). Complete response was not assigned due to the palliative setting. Potential flare in PSMA uptake was assessed by follow-up of PSA levels, subsequent PSMA PET/CT scans and clinical course.

Specifically for this research, additional quantitative PSMA PET/CT analyses were done. In each scan, SUV<sub>max</sub> (highest of all lesions), PSMA-TV (total tumour volume) and TL-PSMA (total lesion uptake: PSMA-TV \* SUV<sub>mean</sub>) were retrieved using LIFEX software [22] and the percentage changes in PET parameters were calculated as measures for treatment response ( $\Delta$ SUV<sub>max</sub>%,  $\Delta$ PSMA-TV% and  $\Delta$ TL-PSMA%). A fixed absolute threshold of SUV = 4 was used for semi-automatic scan delineation [23]. Further details on delineation methods are described in the [Supplemental Materials](#) [24].

Biochemical response was determined by comparing baseline PSA levels with those at the time of treatment response evaluation ( $\Delta$ PSA%). According to the PCWG3 recommendations, a > 25 % and > 2 ng/ml increase from the nadir indicated biochemical progressive disease (bPD), a > 50 % decrease indicated partial response (bPR), and a PSA change between –50 % and + 25 % indicated stable disease (bSD) [19].

### 2.4. Statistical analysis

Descriptive statistics were used to summarise the retrieved data. Patients were in follow-up until deceased or until the moment of data analysis. OS was defined as time from PSMA PET/CT for treatment response evaluation to death in months. PFS was defined as time from PSMA PET/CT for treatment response evaluation to either PSA progression or clinical deterioration in months. Censored data used the time to the last hospital visit. For the survival analyses, progressive disease (PD) was compared with non-progressive disease (non-PD: partial response or stable disease), as this guides treatment alteration or continuation in clinical practice [21]. Cox regression analyses were used to test the predictive value of input parameters for OS and PFS, and log-rank tests were used to compare survival distributions (PD versus non-PD). Statistical analyses were performed using SPSS version 29 (IBM Corporation, Armonk, New York, USA). Statistical significance was defined as a p-value < 0.05.

## 3. Results

### 3.1. Patient characteristics

From December 2019 to December 2023, 60 mCRPC patients underwent a PSMA PET/CT at baseline and at predefined time points, and were included in this study. Baseline characteristics are shown in Table 1. Thirty-one patients received ARTA treatment and twenty-nine received chemotherapy. The median time between baseline PSMA PET/CT and treatment initiation was 11 days (IQR 8 – 20 days). According to the local protocol, the response PSMA PET/CT was performed either after 3 months of ARTA treatment (median 95 days, IQR 82 – 110 days), or 3 weeks (median 21 days, IQR 16 – 31 days) after completion of

**Table 1**

Patient characteristics (n = 60). \* Gleason score unknown in 6 patients. \*\* As part of a clinical trial (EudraCT 2014–001161-27). ADT = androgen deprivation therapy. IQR = interquartile range. PSMA-TV = total tumour volume on PSMA PET/CT.

Characteristic	Value
Gleason score at diagnosis*, n (%)	
6	6 (10 %)
7	8 (13 %)
≥ 8	40 (67 %)
Metastatic status at diagnosis, n (%)	
M0	22 (37 %)
M1	38 (63 %)
Prior treatment of the primary tumour, n (%)	
Radical prostatectomy	4 (7 %)
Local radiotherapy	24 (40 %)
ADT only	18 (30 %)
ADT + docetaxel upfront	13 (22 %)
ADT + abiraterone upfront	1 (2 %)
Enzalutamide upfront**	6 (10 %)
Previous systemic therapy lines for mCRPC, n (%)	
0	37 (62 %)
1	23 (38 %)
Age at treatment initiation in years, median (IQR)	75 (68 – 78)
Serum PSA before treatment initiation in ng/ml, median (IQR)	21.1 (8.1 – 55.6)
PSMA-TV before treatment initiation in mL, median (IQR)	118 (41 – 328)
Site of disease on baseline PSMA PET/CT scan, n (%)	
Lymph nodes only	7 (12 %)
Bone only	18 (30 %)
Lymph nodes + bone	31 (52 %)
Bone + visceral	1 (2 %)
Lymph nodes + bone + visceral	3 (5 %)
Current treatment, n (%)	
Enzalutamide	25 (42 %)
Abiraterone	6 (10 %)
Docetaxel	24 (40 %)
Cabazitaxel	5 (8 %)

3–8 cycles (median 6 cycles) of chemotherapy. In 8 of 60 patients, the PSMA PET/CT was performed earlier than planned (after 3 or 4 cycles) due to either PSA progression (n = 6) or clinical deterioration (n = 2) during chemotherapy. At the time of analysis, 38 of 60 patients were deceased, and 47 of 60 patients showed either PSA progression or clinical deterioration. Median OS was 16.5 months and median PFS was 3.8 months. The median follow-up time was 26 months (range 7 – 35 months). One patient was transferred to another hospital during follow-up; no data was available on disease progression, but the date of death was reported. No other patients were lost to follow-up.

### 3.2. PSMA PET/CT response versus PSA response

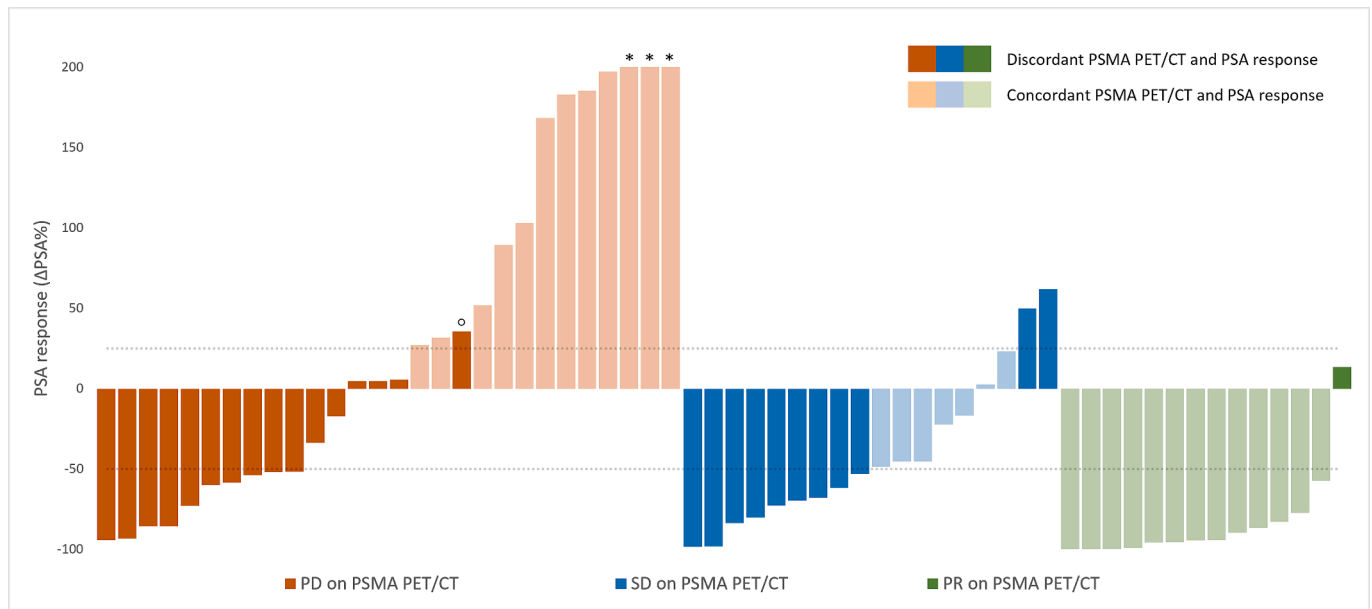
PSMA PET/CT response and PSA response were discordant in 28 of 60 patients (47 %). In 25 (89 %) of these patients, of which 15 received ARTA treatment and 10 chemotherapy, overall response on PSMA PET/CT was worse than PSA response: 10 had bPR and iPD, 9 had bPR and iSD, and 6 had bSD and iPD. In the other 3 patients, all receiving chemotherapy, PSA response was worse than overall response on PSMA PET/CT: 1 had bSD and iPR, and 2 had bPD and iSD. Strikingly, all three patients had decreasing PSA levels at the time of treatment response evaluation, so PSA flare could not be ruled out [25]. In the 32 patients with concordance between PSMA PET/CT response and PSA response (53 %), 12 patients had PD, 7 had SD and 13 had PR. In the 8 patients who underwent an early PSMA PET/CT for suspected progression, all were confirmed to have iPD. Fig. 1 shows the ΔPSA% and overall response on PSMA PET/CT for each patient. Supplemental Table S1 shows a direct comparison of all five PSMA PET/CT response parameters and ΔPSA% in each patient.

### 3.3. Survival outcomes

Univariate Cox regression analysis assessed the predictive value of all PSMA PET/CT response parameters, PSA response and age for OS (see Table 2). Overall response on PSMA PET/CT (iPD vs. non-iPD, p < 0.001), response of the worst responding lesion (iPD<sub>worst</sub> vs. non-iPD<sub>worst</sub>, p < 0.001), PSA response (bPD vs. non-bPD; p = 0.010), ΔPSA% (p = 0.027), ΔPSMA-TV% (p < 0.001) and ΔTL-PSMA% (p = 0.002) were significant predictors of OS, whereas age and ΔSUV<sub>max</sub>% were not. There was no significant difference in OS between patients treated with an ARTA and those treated with chemotherapy (p = 0.374). In multivariate Cox regression analyses using ΔPSA% as the first variable and a PSMA PET/CT response parameter as the second, overall response (HR = 4.05, p < 0.001) and response of the worst responding lesion (HR = 3.95, p < 0.001) remained the best predictors of OS, outperforming the quantitative PET response parameters ΔPSMA-TV% (p = 0.016) and ΔTL-PSMA% (p = 0.039), see Table 2. ΔPSA% became nonsignificant in these analyses (all p > 0.4).

Kaplan-Meier curves for OS illustrate the differences between bPD vs. non-bPD (Fig. 2A) and between iPD vs. non-iPD (Fig. 2B). Notably, overall response on PSMA PET/CT (X<sup>2</sup>(1) = 18.9, p < 0.001, median OS 12.3 versus 26.9 months) differentiated more effectively between short-term and long-term survivors than PSA response (X<sup>2</sup>(1) = 7.2, p = 0.006, median OS 12.3 versus 23.0 months). This was also the case when compared to response of the worst responding lesion on PSMA PET/CT (X<sup>2</sup>(1) = 14.9, p < 0.001).

Among all patients with a PSA decline of > 50 % (bPR, n = 32), PSMA PET/CT showed 10 with iPD (31 %), 9 with iSD (28 %) and 13 with iPR (41 %). In these 32 patients, overall response on PSMA PET/CT was the best predictor of OS (iPD vs. non-iPD: HR = 4.38 [1.47–13.05], p = 0.008) while ΔPSA% was not a predictor (p = 0.516). No flare on PSMA PET/CT was observed; all identified progression was confirmed as true disease progression, evident through multiple new PSMA-avid lesions, subsequent PSA progression, clinical deterioration, or further progression on a follow-up PSMA PET/CT. This suggests that PSMA PET/CT was able to detect progression earlier than PSA levels. The



**Fig. 1.** Waterfall plot of the percentage change in PSA level from before treatment initiation to the moment of treatment response evaluation in each included patient, grouped by the overall response on PSMA PET/CT. Discordance between PSMA PET/CT and PSA response was seen in 28 of 60 patients (47 %). Grey dotted reference lines: +25 % and -50 % change in PSA levels. ° The PSA response of this patient was classified as stable disease, because the absolute PSA increase was 0.5 ng/ml (PSA went from 1.4 to 1.9 ng/ml). \* ΔPSA% exceeded + 200 %. PD = progressive disease (orange), SD = stable disease (blue), PR = partial response (green).

**Table 2**

Univariate and multivariate Cox regression analyses for OS. \*HR = hazard ratio. \*\* p-values are only displayed when < 0.05.

Categorical variable	OS Univariate			Multivariate (ΔPSA% + PET parameter)		
	HR*	95 % CI	p-value**	HR*	95 % CI	p-value**
Overall response on PSMA PET/CT (iPD vs. non-iPD)	4.213	2.104–8.433	< 0.001	4.047	1.926–8.503	< 0.001
Response of the worst responding lesion on PSMA PET/CT (iPD <sub>worst</sub> vs. non-iPD <sub>worst</sub> )	4.251	1.922–9.401	< 0.001	3.948	1.747–8.920	< 0.001
PSA response (bPD vs. non-bPD)	2.529	1.253–5.103	0.010			
Continuous variable						
Age at treatment initiation (per year)	1.016	0.973–1.062				
ΔPSA% (per %)	1.001	1.000–1.003	0.027			
ΔSUV <sub>max</sub> % (per %)	1.004	0.999–1.009				
ΔPSMA-TV% (per %)	1.003	1.001–1.004	< 0.001	1.003	1.001–1.006	0.016
ΔTL-PSMA% (per %)	1.002	1.001–1.004	0.002	1.002	1.000–1.004	0.039

majority of patients with bPR and iPD were receiving first-line treatment (n = 8). An example patient with bPR and iPD is shown in Fig. 3.

45 Patients had no biochemical progression or clinical deterioration when response was evaluated. In these patients, overall response (HR = 6.88, p < 0.001) and response of the worst responding lesion (HR = 8.31, p < 0.001) on PSMA PET/CT were the best imaging-based predictors of PFS, independent of ΔPSA%. ΔPSA% was also a significant independent predictor of PFS. Detailed results are provided in Supplemental Table S2

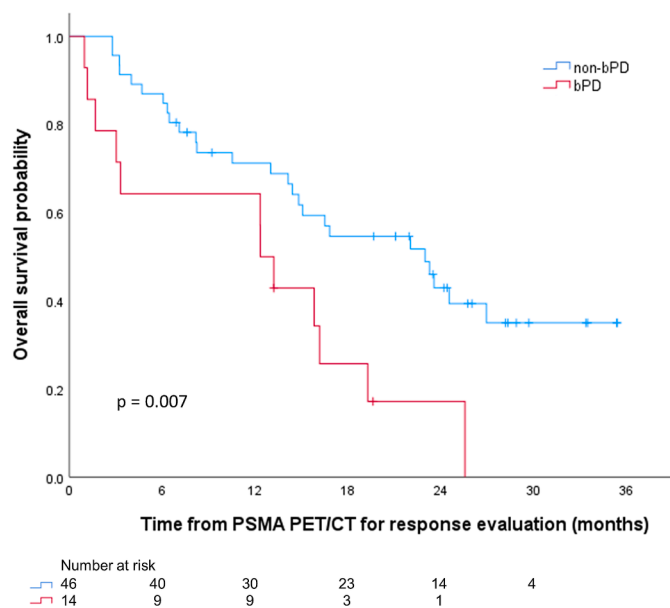
**4. Discussion**

In the management of mCRPC patients, accurate assessment of treatment response is essential to optimise treatment decisions and patient outcomes, and this study found PSMA PET/CT to be superior to PSA levels. We assessed the systematic use of PSMA PET/CT for response evaluation of treatment with ARTAs (after 3 months) or chemotherapy (after completion) in comparison to PSA response in 60 mCRPC patients. Discordance between PSMA PET/CT and PSA response was observed in 47 % of patients, and overall response on PSMA PET/CT was the best independent predictor of OS (iPD vs. non-iPD: HR = 4.05, p < 0.001), outperforming PSA (bPD vs. non-bPD: HR = 2.53, p = 0.010). This

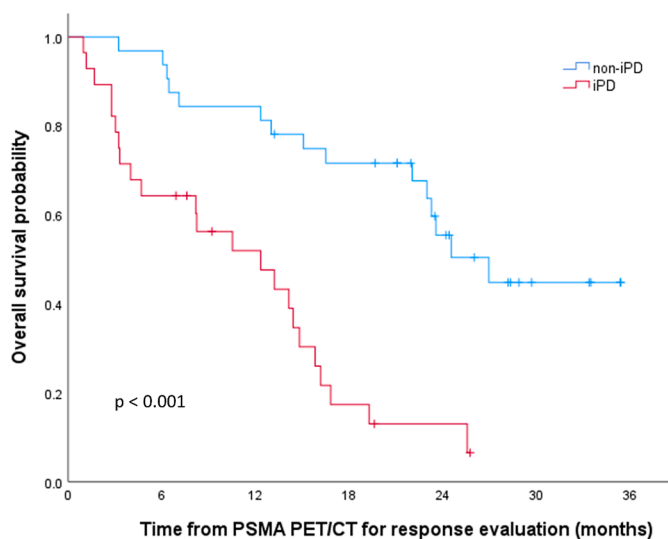
means that PSMA PET/CT could better differentiate between short-term and long-term survivors than PSA. Interestingly, among patients with a PSA decline > 50 %, 31 % showed progressive disease on PSMA PET/CT, which was significantly associated with worse OS (HR = 4.4, p = 0.008). These results suggest that the superior predictive ability of PSMA PET/CT for OS is due to its ability to detect progressive disease earlier than PSA in a significant proportion of patients. The systematic use of PSMA PET/CT for treatment response evaluation can allow for earlier discontinuation of ineffective treatments, minimising unnecessary toxicity and costs, and providing the opportunity to initiate potentially effective treatment earlier in these patients. It can also allow for continuation of treatment in those patients with the greatest survival benefit. In addition, PSMA PET/CT has the advantage over PSA of providing information on metastatic sites, so that e.g. metastasis-targeted treatments can be considered.

Previous studies have also reported discordance between PSMA PET/CT response and PSA response in mCRPC patients, with discordance rates ranging from 7-46 % [15,16,26–32]. However, most studies included fewer than 30 patients, introducing uncertainty, and variations in PSMA-tracers and PSMA PET/CT response definitions make direct comparisons difficult. Several articles investigated the predictive value of PSMA PET/CT for survival in mCRPC patients and found the following

## 2A. PSA response and overall survival



## 2B. Overall response on PSMA PET/CT and overall survival



**Fig. 2.** Kaplan-Meier plots showing the difference in overall survival between patients with progression (red) and patients without progression (blue), either based on PSA response (Fig. 2A) or on overall response on PSMA PET/CT (Fig. 2B). PSMA PET/CT better differentiated between short-term and long-term survivors than PSA. +: censored patients. bPD = PSA progression, non-bPD = no PSA progression. iPD = progressive disease as overall response on PSMA PET/CT, non-iPD = non-progressive disease as overall response on PSMA PET/CT.

significant predictors:  $\Delta$ PSMA-TV% for OS [26], PSMA PET/CT response for OS [16,27], and PSMA PET/CT response for PFS [28], all outperforming PSA as a parameter for treatment response. Additionally, Küper et al. [33] reported that absolute difference in PSMA-TV significantly predicted OS in 25 mCRPC patients. Our study provided robust and confirmatory results. In contrast to most previous studies, we used predefined fixed time points to assess treatment response in all mCRPC patients. By using PSMA PET/CT for treatment response evaluation regardless of PSA levels, our analysis could demonstrate its ability to detect progressive disease earlier than PSA levels in a proportion of the included patients. This study is also the first to use the radiotracer [ $^{18}$ F]PSMA-1007 for treatment response evaluation in this patient population, and its use is expected to increase due to its advantages over  $^{68}$ Ga-labelled tracers, including improved spatial resolution and a longer half-life (110 min vs. 68 min), which allows for wider distribution [34]. However, [ $^{18}$ F]PSMA-1007 has an increased risk of unspecific bone uptake, which requires increased awareness and accurate interpretation from nuclear medicine physicians to avoid false positives [35]. In case of a negative PSMA PET/CT at baseline or difficulty assessing liver lesions due to high background uptake, neither of which occurred in this study, other imaging modalities can be considered, e.g. whole body MRI or [ $^{18}$ F]FDG PET/CT.

By maintaining a minimum interval of 3 months (ARTA) or 3 cycles (chemotherapy) for treatment response evaluation, the risk of false-positive PSMA PET/CT results due to flare [36] was minimised. Importantly, none of the analysed PSMA PET/CT scans showed flare, and progression on PSMA PET/CT was confirmed to be true disease progression. Physicians should also be aware of PSA flare [25], which was suspected in the 3 patients with worse PSA response than PSMA PET/CT response. PSMA PET/CT imaging could potentially distinguish between PSA flare and genuine progression, but further research is necessary to validate this capability. Of course, in case of discordant results, it always remains important to consider clinical signs of deterioration, especially in case of tumour dedifferentiation [37].

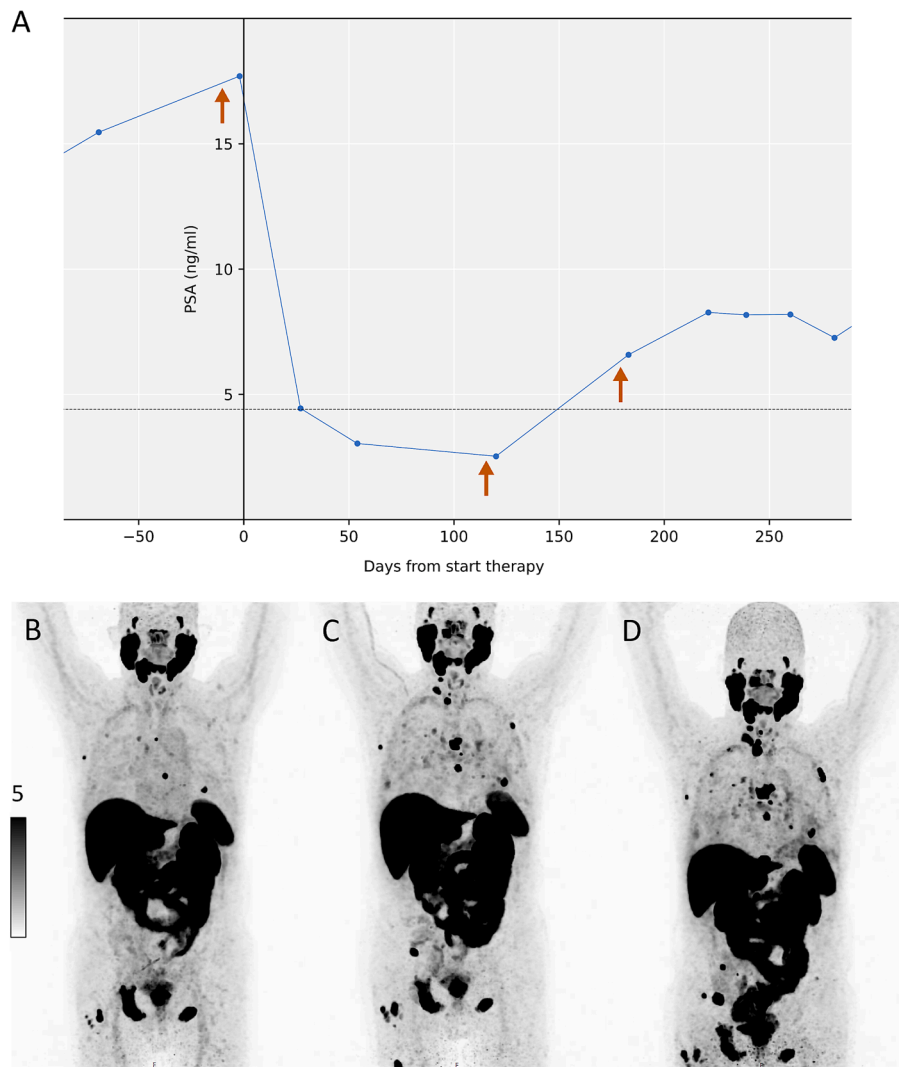
To the best of our knowledge, our study is the first to compare different qualitative and quantitative PSMA PET/CT response

parameters for predicting survival outcomes in mCRPC patients. Notably, the qualitative parameters (visual assessment of overall response and response of the worst responding lesion) clearly outperformed the quantitative parameters in predicting OS. We hypothesise that this can be explained by the heterogeneity of CRPC within patients in terms of genotype and response to treatment [38], and that a patient's prognosis primarily depends on the least treatment-sensitive cancer cells. Qualitative parameters took into account non-responding or new lesions, which appeared to be prognostically most unfavourable, whereas quantitative parameters assessed changes in total tumour burden. We recommend using the EAU/EANM criteria for response assessment [21] for further research and in clinical practice, as these criteria were easily usable and revealed to be the best predictor of OS. This study did not make a direct comparison with RECIP 1.0 [39] and did not assess interobserver variability. However, Shagera et al. [16] found that the EAU/EANM and RECIP 1.0 criteria performed equally well and were both good predictors of OS in mCRPC patients receiving ARTAs.

Limitations of this study include the relatively small bicentric cohort of 60 patients, its retrospective nature and the fact that no diagnostic CT or bone scans were performed, so PSMA PET/CT results could not be directly compared with conventional imaging. Furthermore, only mCRPC patients who were treated with an ARTA or chemotherapy were included. We recommend future research to include more types of mCRPC treatment, such as radium-223 therapy and PARP inhibitors, and to prospectively validate these findings in larger patient cohorts. In addition, cost-effectiveness and impact on treatment decisions and subsequent patient outcomes need to be assessed.

## 5. Conclusions

PSMA PET/CT response was superior to PSA-based response for predicting OS in mCRPC patients, likely due to its ability to detect disease progression earlier than PSA levels. Based on the results of this study, the systematic use of PSMA PET/CT for evaluating treatment response to an ARTA (after 3 months) or chemotherapy (after



**Fig. 3.** The PSA levels and [ $^{18}\text{F}$ ]PSMA-1007 PET/CT scans of a 72-year-old male with first-line enzalutamide treatment for mCRPC showed a discrepancy after four months: an 86% PSA decline, but disease progression on PSMA PET/CT with multiple new lesions. In a multidisciplinary team meeting it was decided to continue treatment as long as PSA values remained stable. After six months, treatment was stopped due to PSA progression and further progression on PSMA PET/CT. A: a graph of the patient's PSA levels, orange arrows indicate PSMA PET/CT scan times. B: baseline PSMA PET/CT showed a PSMA-avid primary tumour and multiple bone metastases. C: PSMA PET/CT after four months of treatment demonstrated an increase in total tumour volume and tracer uptake and over 6 new lesions. D: PSMA PET/CT after six months of treatment showed a further increase in total tumour volume and tracer uptake, and over 10 new lesions.

completion) should be considered, to provide better guidance for treatment decision-making and potentially improve patient outcomes and cost-effectiveness. In predicting OS, qualitative PSMA PET/CT criteria outperformed quantitative PSMA PET/CT criteria, and the EAU/EANM criteria for response assessment [21] had the best prognostic value in this study. Performing PSMA PET/CT after suspected disease progression was considered reliable. No flare on PSMA PET/CT was observed in this study where minimum intervals (3 months of ARTA or 3 chemotherapy cycles) were maintained. We recommend further research to focus on prospective trials of PSMA PET/CT-guided treatment strategies and their impact on survival, as well as evaluation of cost-effectiveness.

#### CRediT authorship contribution statement

**F. Kleiburg:** Writing – review & editing, Writing – original draft, Visualization, Project administration, Methodology, Investigation, Formal analysis, Conceptualization. **L.F. de Geus-Oei:** Writing – review & editing, Supervision, Methodology, Conceptualization. **S.A.C. Luelmo:** Writing – review & editing, Methodology, Conceptualization.

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#### Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

#### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ejrad.2024.111774>.

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