PSMA PET Before and After Initial Long Term Androgen Deprivation in Patients With Newly Diagnosed Prostate Cancer

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Original research

Keywords: PSMA, 68Ga, ADT, Prostate cancer, PET

DOI: https://doi.org/10.21203/rs.3.rs-60507/v1

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Abstract

**Purpose:** The study aimed to evaluate the effect of androgen deprivation therapy (ADT) on PSMA imaging and its correlation to the PSA concentration comparing qualitative and quantitative parameters: SUVmax, SUVmean, PSMA-derived tumor volume (PSMA-TV), total lesion PSMA (TL-PSMA) and metabolic imaging (mi)PSMA score.

**Methods:** Retrospective analysis of 19 therapy-naïve and oligometastatic prostate cancer patients (median age 73 years) who underwent either $^{68}$Ga-PSMA-11-PET/CT or -PET/MRI before initiation (T1) of as well as during ADT (T2). The median duration of ADT was 156 days (range: 61-289 days). All lesions were analyzed using several qualitative and quantitative PET parameters.

**Results:** During long term ADT occurred a relevant decrease of lesion count and PSMA expression.

A total of 104 PSMA-positive lesions (21 intraprostatic, 54 lymphonodal, 29 osseous) were visually detected at each of the two points, while at T2 two new bone lesions were detected in one patient. All analyzed PET parameters, which correlated strongly with each other.

During ADT, all patients experienced a decrease of their PSA level (median: 29.1 before vs. 0.69 after; p<0.001). The PSA level at T2 correlates modestly with the decrease of PSMA expression and its derived volumes.

**Conclusion:** Post ADT scans detected less PSMA-positive lesions with overall lower PSMA expression, regardless of primary tumor site or metastatic sites. None of the PET parameters has proven to be superior, as they all correlated modestly with the PSA value at T2. Thus, the simply acquirable miPSMA score seems to be the most suitable for evaluating the effect of ADT on PSMA expression.

Introduction

Prostate cancer (PCa) is the world's most common cancer in men (1). $^{68}$Ga-labeled PSMA ligands have become state of the art in molecular imaging of PCa in primary and recurrent diseases as well as in therapy monitoring (2–5).

In the high risk or oligometastatic situation therapy includes androgen deprivation therapy (ADT) and radiation therapy (6,7). Recently, docetaxel chemotherapy or enhanced ADT (i.e. abiraterone, enzalutamide or apalutamide) are recommended in castration sensitive metastatic prostate cancer (8–12).

As PSMA-based imaging becomes more and more important for planning local ablative therapy, the influence of ADT on PSMA-expression is of high relevance (13).

On a cellular level ADT upregulates the folate hydrolase 1 (FOLH1) gene and thus increases PSMA expression (14).

The influence of ADT on the PSMA expression has been evaluated in several studies that showed conflicting results. In a preclinical study Murga et al. (15) showed a PSMA upregulation of both androgen sensitive and androgen resistant prostate cancer cells. In an animal study Evans et al. (16) reported a decreasing cell count under ADT and a higher PSMA expression per cell. These parallel developments affect imaging: The effect of increased PSMA expression in surviving cells may be overcompensated by induced cell death in the vast majority of cells.

In the present study the influence of ADT on the PSMA expression in the primary tumor as well as in lymphatic and osseous metastases in exclusively untreated, hormonally naïve, oligo-metastasized patients was evaluated.

As surrogate parameters for the PSMA expression we compared the change of SUVmax, SUVmean, PSMA-derived tumor volume (PSMA-TV) and total lesion PSMA (TL-PSMA) (23), and the miPSMA score (24) under ADT were compared for the primary tumor as well as the lymphatic and bone metastases within each other and the respective PSA values.

Materials And Methods

**Patients**

Nineteen therapy-naïve, oligo-metastasized, biopsy proven prostate cancer patients with a median age of 73 years (range: 57-80 years) who were foreseen for local ablative radiotherapy underwent $^{68}$Ga-PSMA-11-PET for primary staging before start of androgen deprivation therapy (median: 14, range 0-59 days). All patients were discussed in an interdisciplinary tumor board. After six months a local ablative radiotherapy to all known lesions was planned, and a re-staging PET was performed (median: 156, range: 61-289 days after start of ADT). The two time points were labeled as T1 and T2, respectively. The data were obtained between 11/2016 and 01/2020 and were retrospectively analyzed.

Written informed consent was obtained from all patients for the clinically indicated examination and the consecutive scientific analysis of their clinical and imaging data. The institutional review board of the local ethics committee at our medical faculty approved this analysis.

**Radiotracer preparation**

The radiotracer $^{68}$Ga-PSMA-11 was synthesized as in clinical routine and as previously described (25).
**Imaging protocol**

No specific patient preparations were required for \(^{68}\)Ga-PSMA-PET.

For the 19 examinations at T1 a median of 153 MBq (range: 90-206 MBq) was applied and acquisition started with a median of 115 min p.i. (range: 89-168 min), while for the examinations at T2 a nearly equal median of 155 MBq (range: 62-190 MBq) was applied and imaging started with a median of 116 min p.i. (range: 92-140 min).

The 38 examinations were performed on either PET/MRI or PET/CT 1 or PET/CT 2. Ten out of the 19 patients underwent both examinations on the same device.

The PET/CT scans until 08/2019 (PET/CT1) were acquired with a Biograph 16 (Siemens CTI, Knoxville, Tennessee, USA). Eight to 9 bed positions were obtained with 3 min scan time each. The PET/CT scans after 08/2019 (PET/CT2) were acquired with a Biograph Vision 600 (Siemens Healthineers, Knoxville, USA). The emission PET scan was obtained using continuous bed motion with a speed of 2.9 mm/s being equivalent to 1.5 min per bed position.

The PET/MRI scans were acquired with a 3 Tesla Ingenuity TOF PET/MR (Philips Medical Systems, Best, Netherlands). Ten bed positions were acquired with a scan time of 3 min each.

**Imaging reconstruction**

The CT 1 images were reconstructed using an ordered-subset expectation maximization (OSEM) algorithm with 6 iterations and 4 subsets with a 168x168 matrix. Plain CT scans for attenuation correction were performed in a craniocaudal direction from the skull base to the upper thighs. Scanning parameters included 100 mAs, 120 kV, online tube current modulation, 1.5 mm slice collimation, 0.5–0.75 s rotation time, and reconstruction of 5 mm slices.

The CT 2 images were reconstructed using the TRueX algorithm with 4 iterations, 5 subsets, Time-of-flight (TOF) application and without filtering. The resulting PET images had an image matrix size of 440x440 with a voxel size of 1.65 x 1.65 x 3.0 mm. A standard low dose CT was acquired from the whole body (X-ray tube current of 10 mAs, tube voltage of 100 kV, spiral pitch factor of 1.5, 3.0 mm slice thickness) and used for scatter correction of the subsequent PET scan.

**Image analysis**

A Nuclear Medicine physician (SH) and a Radiologist (RW) both experienced in PSMA-PET reporting used Syngo.via Software (VB30a, Siemens Healthineers, Erlangen, Germany) to determine pathologic uptakes and to identify the reference lesions. Senior Consultants in Nuclear Medicine (KZö) and Radiology (DF) retrospectively confirmed the findings of both of them.

At first, all scans were evaluated visually. Pathologic uptakes were initially assumed if a lesion shows a tracer uptake higher than the local background \((26)\). Depending on the localization, they were rated as local (prostate) tumor, lymphonodal or bone metastasis. For subsequent quantitative analysis, volumes of interest (VOI) sufficiently large for covering the whole lesion were inserted over each pathologic lesion and SUVmax as well as SUVmean of each lesion were acquired. The resulting volumetric parameters were the PSMA-derived tumor volume (PSMA-TV) based on a 45% cut-off of the SUVmax, as suggested by Schmuck et al. \((23)\), and the total lesion PSMA (TL-PSMA), which is a product of PSMA-TV and the SUVmean of that lesion. The concept of these metabolic volumes is adapted from FDG imaging and PSMA-TV calculation is equivalent to the metabolic tumor volume (MTV) while TL-PSMA is calculated equally to the total lesion glycolysis (TLG) \((28)\).

Sufficiently large \((27)\) VOIs were further inserted in reference regions: liver (3 cm diameter), the thoracic aorta (2 cm diameter) and the parotid glands (1.5 cm diameter), and the SUVmax and SUVmean values were calculated. For the parotid glands the values were averaged.

In order to make the uptake values more comparable between the different devices and different reconstruction algorithms ratios to the respective liver SUVmean were calculated (LQ) for SUVmax, SUVmean and TL-PSMA and compared.

For the same reason, each lesion was scored according to the miPSMA expression score \((27)\). The score ranges from 0 (uptake < blood pool) to 3 (uptake ≥ parotid gland). It was determined based on the SUVmean of both the lesions and the reference lesions. If a lesion was not separable from the local background in one time point it was scored as 0, regardless of its SUVmean. To evaluate the patients total tumor burden the sum of the score of all lesions was calculated as well.

Furthermore, each patient was staged using the miTNM expression score. Since there was no contrast enhanced CT or MRI simultaneously acquired after ADT, there was no T Stage to be compared.

**Statistical analysis**

To compare different PSMA parameters lesion-based characteristics and the PSA value between the two time points T1 and T2, the paired Wilcoxon signed-rank test was applied. For the comparison of parameters between independent patient groups or lesions, the Mann-Whitney-U test was used. Correlations between PSMA parameters, lesion-based characteristics and PSA values were evaluated by the Spearman correlation coefficient \(r\). All
statistical analyses were performed using SPSS 25 (IBM Corporation, Armonk, NY, USA). Two-sided tests were performed and \( p \)-values below 0.05 were considered as statistically significant.

**Results**

As Table 1 shows 19 patients received ADT for a median of 156 days (range: 61-289 days) prior to local ablative radiotherapy. Meanwhile, the median PSA value dropped from a median value of 29.1 ng/ml (range: 2.5-107.0 ng/ml) to 0.69 (0.05-4.91) ng/ml \( (p=0.001) \). Accordingly, the number of both the PSMA-expressing intraprostatic and extraprostatic tumor manifestations dropped as well as the number of patients in whom they were detectable. A total of 102 different lesions were identified at T1, while only 45 lesions (43.2\%) were detectable at T2. The latter included two new bone metastases occurred in the same patient (Figure 1), resulting in 104 lesions to analyse.

Table 2 gives further details of patients’ disease, ADT duration and treatment history as decided by the interdisciplinary tumor board. Five patients received additionally a chemotherapy (CTx, docetaxel 75 mg/m² q3wk). It outlines the PSA decrease in every single patient, even though not all patients showed a complete PSA response.

In a patient based analysis the summed tumor burden decreased in both number and size from T1 to T2. The summed PSMA derived tumor volume (PSMA-TV) dropped from nearly 498.51 ml to 116.47 ml and the total lesion PSMA decreased as well (8845.18 ml vs. 1189.33 ml). Table 3 outlines additionally that the patient wise metabolic tumor volumes dropped in all but one patient.

In 16 of 19 patients the number of lesions was lower at T2 compared to T1. Two patients even had no longer any pathologic PSMA expression after ADT, one patient is exemplarily shown in Figure 2. For a lesion-based assessment, the different quantitative parameters were obtained and correlation with the SUVmean of the liver was performed in order to minimize the effect of different reconstruction algorithms in the three different devices. Lesion-based analysis revealed that the PSMA expression summed and in all types of lesions separately was reduced at T2, no matter what surrogate parameter was evaluated.

Table 4 displays the individual characteristics of the prostatic, lymphatic and osseous lesions in both scans. For all 5 response parameter analyzed, there was a statistical significance reduction from T1 to T2. I.e. the average SUVmax value of all lesions dropped from 19.56 (CI: 16.04 - 23.08) prior ADT to 7.86 (CI: 4.69 - 11.04) after initiation of ADT.

If analyzed separately at both T1 and T2 the primary intraprostatic tumor manifestations showed higher PSMA expression and higher PSMA derived volumes than the bone metastases. The average SUVmax of all intraprostatic lesions decreased under ADT from 28.47 (CI: 18.27 - 38.67) to 13.69 (CI: 7.71 - 19.68). The mean SUVmax of bone metastases dropped from 12.84 (CI: 8.27 - 17.41) to 3.48 (1.3 - 5.65).

The PSMA expression in lymph node metastases ranged in-between the primary tumors and the bone metastases.

The visually obtainable miPSMA score as a surrogate parameter for the decrease of PSMA expression during therapy correlates very strongly with the quantitative PET parameters SUVmax, SUVmean, regardless of the additional intraindividual correction with the liver uptake. The decrease of derived metabolic tumor volumes PSMA-TV and TL-PSMA showed a slightly lower but still strong correlation with the miPSMA score. As shown in detail in Table 5 these strong correlations can be reproduced for the primary tumor, the lymph node metastases and the bone metastases separately. However, the lowest but still moderate correlation was found in the primary tumor site. With decreasing PSMA-expression in the primary tumor, the SUVmax dependent metabolic tumor volumes overestimate the tumor burden due to a lowered tumor to background ratio and a resulting blurred tumor delineation. Please note that intraindividual correction with liver SUVmean in a reference region did not lead to better correlation coefficients.

Even though ADT lead to a decrease in PSA expression in the vast majority of the lesions, a certain degree of heterogeneity could be shown in a separate comparison of each single lesion. There is a small number of lesions showing higher uptake values under ADT (Table 6). It is noteworthy that there are two bone metastases newly occurring at T2. Please note the metabolic volumes as well as the miPSMA score were decreased in more lesions at T2 compared to the SUV parameters. Intraindividual liver correction did not change the results relevantly. Table 6 provides further details. The SUVmax \( (p=0.554) \) and SUVmean \( (p=0.487) \) of the three reference regions mediastinal blood pool, liver and salivary glands did not differ between both time points.

As both the PSA value and the PSMA decreased several analyses of the correlations between the surrogate parameters of PSMA expression and the PSA concentrations at both time points were performed. In the primary staging (T1) of the 19 therapy naïve oligometastatic prostate cancer patients neither of the SUV parameters nor the PSMA derived tumors volumes nor the summed miPSMA score correlated with initial PSA concentration (Table 7). In contrast, there was an at least moderate correlation \( (p=0.022, r=0.523) \) between the PSA level under ADT (T2) and summed total lesions PSMA volume, while the other surrogates failed to have significant correlations at T2 as well as at T1. Stronger correlations were observed between the PSA value after ADT (T2) and the T2/T1-quotients of the PSMA-derived tumor volumes. There were moderate to strong correlations between the total PSMA derived tumor volumes, the total lesions PSMA and the summed score of all lesions and if analyzed separately the prostatic primary tumors alone. The same tendency becomes apparent in a separate analysis of each the osseous and lymphonodal tumor volumes alone, although the significance threshold was failed in these cases. Interestingly, the simple summation of the miPSMA score of all lesions correlates not relevantly lesser with the PSA value under ADT than the far more elaborated metabolic volumes PSMA-TV and TL-PSMA.

Fewer and lower correlations emerged between the PSA decrease (T2/T1) and the reduced tumor volumes at T2 suggesting that the influence of the initial (T1) PSA value can be neglected in favor of the post ADT PSA value.
Similar to the patient-based evaluation the lesion-based analysis revealed no relevant association between the initial PSA value prior to ADT (T1) and the different obtained PSMA parameters. In contrast, the PSA value after ADT (T2) correlated at least moderately with all of the PSMA parameters at T2 and their quotient T2/T1. Further details for both time points are listed in Table 8.

Discussion

As expected, long term ADT in oligometastatic castration sensitive prostate cancer patients resulted in a distinct decrease of the PSA concentration (29). It could be demonstrated that this PSA response corresponded with the decline of PSMA PET parameters and their derived tumor volumes.

Recently, Yaz et al (13) summarized the currently available clinical (n=9) and in vitro and in vivo (n=10) studies investigating the effect of ADT on PSMA expression. They outlined the high heterogeneity of these 19 reports in terms of study design, numbers of patients or cell lines, hormone sensitivity, ADT type and duration of application. Besides these heterogeneous study designs, even the PSMA expression itself was not measured identically, as it was either measured immunohistochemically or by metabolic imaging using PET or SPECT.

Nevertheless, the majority of the collected studies (n=13 reports) indicated an increased PSMA expression under ADT in general, including the description of a flare phenomenon (17).

Emmet et al (18) conducted serial PSMA-PET examinations in patients with both castration sensitive and resistant PCa within 9 to 28 days after the onset of ADT. They described a reduction of the SUVmax as a surrogate of the PSMA expression in most of the castration resistant patients after day 9 with a positive PSA response. However, in castration resistant individuals the PSMA expression raised, while the PSA response occurred later and not in all patients. The remaining case reports or small studies supposed a time dependence in which the PSMA expression raised under short-term ADT (i.e. 2 to 6 weeks) and lowered after long-term ADT (i.e. 3 to 4 months) (19,20).

The duration of ADT is a key point to be considered when interpreting the influence of ADT and PSMA expression and is the main reason for the diverging results. The studies assembled by Yaz et al. (13) suggesting an increased PSMA expression under ADT had in most cases a therapy duration of only one month or shorter, while in our study the median therapy duration was 156 days with only two patients having ADT for less than two months. We affirm the assumption of Afshar-Oromieh et Al. (21) that the term of ADT is a key factor in the influence of ADT on PSMA expression, and long-term ADT inverts the initial effect of stimulating it (30).

Afshar-Oromieh et al (21) reported reduced PSMA expression in PET/CT after long-term (median 230 days) ADT in 10 differently pretreated patients. Recently, Gupta et al (22) published a lesion-wise analysis of 43 patients therapy naïve PCa patients of any stage prior and after a median of 6 months under ADT with heterogenic results. The response on ADT measured as PSMA expression was different in the primary tumor from the lymphonodal and the bone metastases. While the primary tumor remained visible in all cases, there was complete metabolic remission, especially in oligometastatic disease, in about 20% of the lymphonodal and osseous metastases. Nevertheless, even in the primary tumors the decrease of SUVmax correlated with the PSA response. However, there was a relevant number of both local and distant lesions presented with higher PSMA expression. The PSMA-derived tumor burden for each patient was not analyzed.

The analysis of the primary tumor and the metastatic sites prior and after ADT revealed a decrease of the PSMA expression in both primary tumor and metastases, whereby the primary tumor site had higher PSMA-ligand accumulation compared to metastases. The strong correlation between the different PET parameters indicated that concordant changes of (metabolic) volume and PSMA expression occurred and the choice of the quantification method is secondary. The use of the simply and visually obtainable miPSMA score (27) is practical and did not lead to a clinically relevant loss of information compared to the SUV parameters, not even if separate imaging devices are in use.

Long-term ADT impaired the PSMA expression in the vast majority of the primary tumor sites as well as the metastases resulting in a relevant underestimation of the patient's tumor burden, especially in the metastatic sites and in lower tumor stages in 10 out of the 19 patients. Only 43% of the lesions remained detectable under therapy, which corresponds with the results Afshar-Oromieh et al. (21) observed in their mostly pre-treated patient population.

However, in our study one patient developed under ADT two newly detectable bone metastases, while the initially PSMA-positive bone metastases vanished completely under ADT. In other patients, a few metastases showed increased PSMA-uptake. These lesions probably bore, as previously postulated, castration resistant cell clones (27) and could have serious implications for their further therapeutic management (31). Oppositely to our results in therapy naïve patients larger, recently published studies (32,33) dealing with biochemically recurrent prostate cancer reported from higher tumor detection rates in patients under ADT suggesting the assumption that the effect of ADT on the PSMA expression changes within the course of the disease. Or in other words – as demonstrated in our study and in the study by Gupta et al. (22) ADT masks the PSMA-expression in early / therapy naïve stages and thus persisting PSMA expression under therapy may be an indicator for early castration resistance. These lesions are not sufficiently controlled by ADT, and may require further therapeutic approaches. The success of these further, however featured, therapeutic approach is assumable of high prognostic importance. In short, in our therapy naïve setting under ADT far less lesions could be seen in PSMA PET but these lesions may be those that become prognostically relevant in the course of the disease, as they are not sufficiently controlled by ADT alone.

Limitations of our present study are the low number of patients, the retrospective study design, the heterogeneous ADT and CTx and of course the lack of histologic confirmation of the lesion's malignancy in follow up.
However, the influence of different devices can be neglected and is often overestimated, and an intra-individual correction including normal tissues (e.g. liver tissue) is at least from a clinical point of view not always necessary.

**Conclusion**

The detectability of both the primary tumor and the metastases in lymph nodes and bone in PSMA PET decreased early after onset of ADT. Metabolic parameters as PSMA-TV and TL-PSMA are more suitable for inter- and intra-individual comparison than SUVmax, and SUVmean. Even when leaving the local tumor outside, PSMA-PET acquired after initiation of ADT (> 4 – 6 weeks) led to an underestimation of the miTNM Stage in a significant proportion of patients.

However, there is a greater potential in a post-ADT (T2) PET than widely supposed as these fewer lesions might be those that cannot be controlled by ADT alone and thus might require different treatment strategies, e.g. molecular image guided local ablative therapy. Furthermore, prospective research is necessary to evaluate the potential benefit of that approach.

**Declarations**

**Funding:** Open Access Funding by the Publication Fund of the TU Dresden.

**Conflicts of interest/Competing interests (include appropriate disclosures):** No conflicts of interest occurred.

**Ethics approval:** The institutional review board of the local ethics committee at our medical faculty approved this analysis. (BO-EK-249062-020).

**Consent to participate (include appropriate statements) and for publication:** Written informed consent was obtained from all patients for the clinically indicated examination and the consecutive scientific analysis of their clinical and imaging data. Consent for publication is not required as long as information is anonymized and the submission does not include images that may identify the person.

**Availability of data and material (data transparency):** Anonymized data can be offered upon request.

**Author's contribution:**

All authors contributed to the study conception and design. Material preparation, data collection and analysis including statistics were performed by Sebastian Hoberück, Steffen Löck, Robert Winzer, Klaus Zöphel, and Dieter Fedders. The first draft of the manuscript was written by Sebastian Hoberück and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

**References**

1. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. *CA Cancer J Clin*. 2014;64:9-29.
2. Corfield J, Perera M, Bolton D, Lawrentschuk N. 68Ga-prostate specific membrane antigen (PSMA) positron emission tomography (PET) for primary staging of high-risk prostate cancer: a systematic review. *World J Urol*. 2018;36:519-527.
3. Han S, Woo S, Kim YJ, Suh CH. Impact of 68 Ga-PSMA PET on the Management of Patients with Prostate Cancer: A Systematic Review and Meta-analysis. *Eur Urol*. 2018;74:179-190.
4. von Eyben FE, Picchio M, von Eyben R, Rhee H, Bauman G. 68Ga-Labeled Prostate-specific Membrane Antigen Ligand Positron Emission Tomography/Computed Tomography for Prostate Cancer: A Systematic Review and Meta-analysis. *Eur Urol Focus*. November 2016.
5. Hofman MS, Lawrentschuk N, Francis RJ, et al. Prostate-specific membrane antigen PET-CT in patients with high-risk prostate cancer before curative-intent surgery or radiotherapy (proPSMA): a prospective, randomised, multicentre study. *Lancet (London, England)*. 2020;395:1208-1216.
6. Parker CC, James ND, Brawley CD, et al. Radiotherapy to the primary tumour for newly diagnosed, metastatic prostate cancer (STAMPEDE): a randomised controlled phase 3 trial. *Lancet*. 2018;392:2353-2366.
7. Burdett S, Boevé LM, Ingleby FC, et al. Prostate Radiotherapy for Metastatic Hormone-sensitive Prostate Cancer: A STOPCAP Systematic Review and Meta-analysis. *Eur Urol*. 2019;76:115-124.
8. Rosenthal SA, Hu C, Sartor O, et al. Effect of Chemotherapy With Docetaxel With Androgen Suppression and Radiotherapy for Localized High-Risk Prostate Cancer: The Randomized Phase III NRG Oncology RTOG 0521 Trial. *J Clin Oncol*. 2019;37:1159-1168.
9. Fizazi K, Faire L, Lesaunier F, et al. Androgen deprivation therapy plus docetaxel and estramustine versus androgen deprivation therapy alone for high-risk localised prostate cancer (GETUG 12): A phase 3 randomised controlled trial. *Lancet Oncol*. 2015;16:787-794.
10. James ND, De Bono JS, Spears MR, et al. Abiraterone for prostate cancer not previously treated with hormone therapy. *N Engl J Med*. 2017;377:338-351.
11. Davis ID, Martin AJ, Stockler MR, et al. Enzalutamide with standard first-line therapy in metastatic prostate cancer. *N Engl J Med*. 2019;381:121-131.
12. Chi KN, Agarwal N, Bjartell A, et al. Apalutamide for metastatic, castration-sensitive prostate cancer. *N Engl J Med*. 2019;381:13-24.
13. Vaz S, Hadaschik B, Gabriel M, Herrmann K, Eiber M, Costa D. Influence of androgen deprivation therapy on PSMA expression and PSMA-ligand PET imaging of prostate cancer patients. *Eur J Nucl Med Mol Imaging*. 2020;47:9-15.
14. Watt F, Martorana A, Brookes DE, et al. A tissue-specific enhancer of the prostate-specific membrane antigen gene, FOLH1. Genomics. 2001;73:243-254.

15. Murga JD, Moorji SM, Han AQ, Magargal WW, DiPippo VA, Olson WC. Synergistic co-targeting of prostate-specific membrane antigen and androgen receptor in prostate cancer. Prostate. 2015;75:242-54.

16. Evans MJ, Smith-Jones PM, Wongvipat J, et al. Noninvasive measurement of androgen receptor signaling with a positron-emitting radiopharmaceutical that targets prostate-specific membrane antigen. Proc Natl Acad Sci. 2011;108:9578-9582.

17. Aggarwal R, Wei X, Kim W, et al. Heterogeneous Flare in Prostate-specific Membrane Antigen Positron Emission Tomography Tracer Uptake with Initiation of Androgen Pathway Blockade in Metastatic Prostate Cancer. Eur Urol Oncol. 2018;1:78-82.

18. Emmett L, Yin C, Crumbaker M, et al. Rapid modulation of PSMA expression by androgen deprivation: Serial 68Ga-PSMA-11 PET in men with hormonensitive and castrate-resistant prostate cancer commencing androgen blockade. J Nucl Med. 2019;60:950-954.

19. Vallabhajosula S, Jhanwar Y, Tagawa S, et al. 99mTc-MIP-1404 Planar and SPECT scan: Imaging biomarker of androgen receptor (AR) signaling and prostate specific membrane antigen (PSMA) expression. J Nucl Med. 2016;57:1541-1541.

20. Zacho HD, Petersen LJ. Bone Flare to Androgen Deprivation Therapy in Metastatic, Hormone-Sensitive Prostate Cancer on 68Ga-Prostate-Specific Membrane Antigen PET/CT. Clin Nucl Med. 2018;43:e404-e406.

21. Afshar-Oromieh A, Debus N, Uhrig M, et al. Impact of long-term androgen deprivation therapy on PSMA ligand PET/CT in patients with castration-sensitive prostate cancer. Eur J Nucl Med Mol Imaging. 2018;45:2045-2054.

22. Gupta P, Murthy V, Agarwal A, Maitre M, Mhatre N, Rangarajan V. 68Ga-prostate-specific membrane antigen PETCT-based response to androgen deprivation therapy in patients with prostate cancer. Nucl Med Commun. 2019;40:1283-1288.

23. Schmuck S, von Klot CA, Henkenberens C, et al. Initial Experience with Volumetric 68Ga-PSMA I&T PET/CT for Assessment of Whole-Body Tumor Burden as a Quantitative Imaging Biomarker in Patients with Prostate Cancer. J Nucl Med. 2017;58:1962-1968.

24. Eiber M, Herrmann K, Calais J, et al. Prostate Cancer Molecular Imaging Standardized Evaluation (PROMISE): Proposed mITNM Classification for the Interpretation of PSMA-Ligand PET/CT. J Nucl Med. 2018;59:469-478.

25. Eiber M, Neels O, Müller M, et al. Novel Preclinical and Radiopharmaceutical Aspects of [68Ga]Ga-PSMA-HBED-CC: A New PET Tracer for Imaging of Prostate Cancer. Pharmaceuticals. 2014;7:779-796.

26. Fanti S, Minozzi S, Morigi JJ, et al. Development of standardized image interpretation for 68Ga-PSMA PET/CT to detect prostate cancer recurrent lesions. Eur J Nucl Med Mol Imaging. 2017;44:1622-1635.

27. Eiber M, Herrmann K, Calais J, et al. Prostate Cancer Molecular Imaging Standardized Evaluation (PROMISE): Proposed mITNM Classification for the Interpretation of PSMA-Ligand PET/CT. J Nucl Med. 2018;59:469-478.

28. Larson SM, Erdi Y, Akhurst T, et al. Tumor Treatment Response Based on Visual and Quantitative Changes in Global Tumor Glycolysis Using PET-FDG Imaging. The Visual Response Score and the Change in Total Lesion Glycolysis. Clin Positron Imaging. 1999;2:159-171.

29. Gravis G, Boher JM, Joly F, et al. Androgen Deprivation Therapy (ADT) Plus Docetaxel Versus ADT Alone in Metastatic Non castrate Prostate Cancer: Impact of Metastatic Burden and Long-term Survival Analysis of the Randomized Phase 3 GETUG-AFU15 Trial. Eur Urol. 2016;70:256-262.

30. Liu T, Wu Ly, Fulton MD, Johnson JM, Berkman CE. Prolonged androgen deprivation leads to downregulation of androgen receptor and prostate-specific membrane antigen in prostate cancer cells. Int J Oncol. 2012;41:2087-2092.

31. Lohaus F, Zöphel K, Löck S, et al. Can Local Ablative Radiotherapy Revert Castration-resistant Prostate Cancer to an Earlier Stage of Disease? Eur Urol. 2019;75:548-551.

32. Afshar-Oromieh A, Holland-Letz T, Giesel FL, et al. Diagnostic performance of 68Ga-PSMA-11 (HBED-CC) PET/CT in patients with recurrent prostate cancer: evaluation in 1007 patients. Eur J Nucl Med Imaging. 2017;44:1258-1268.

33. Afshar-Oromieh A, Avtzi E, Giesel FL, et al. The diagnostic value of PET/CT imaging with the (68)Ga-labeled PSMA ligand HBED-CC in the diagnosis of recurrent prostate cancer. Eur J Nucl Med Imaging. 2015;42:197-209.
Table 1

Patients characteristics; * two of these were new in T2

| Characteristics                                      | Results               |
|------------------------------------------------------|-----------------------|
| Age [years], median, mean, range                      | 73, 70, 57–80         |
| Time between ADT initiation and second 68Ga-PSMA-PET [days], median, mean, range | 156, 160, 61–289     |
| PSA value at 68Ga-PSMA-PET (T1), median, mean, range [ng/ml] | 29.1, 39.9, 2.5–107.0 |
| PSA value at 68Ga-PSMA-PET (T2), median, mean range [ng/ml] | 0.69, 1.18, 0.05–4.91 |

Lesions T1 vs. T2
- Prostate tumor [n: patients; n: lesions]
- Lymph node metastases [n: patients; n: lesions]
- Bone metastases [n: patients; n: lesions]
- Sum [n: lesions]

Table 2

Patient-based characteristics. GSC = Gleason Score, ADT: androgen deprivation therapy; CTx: Chemotherapy / in all cases Docetaxel; B: Bicalutamide; L: Leuprorelin; Max: maximal androgen blockade, *Patient 8 underwent TUR-P in the meantime.

| Pat. | Age | T1 | T2 | GSC | ADT | ADT [days] | CTx | Initial PSA [ng/ml] | PSA after ADT [ng/ml] [% of T1] |
|------|-----|----|----|-----|-----|------------|-----|---------------------|----------------------------------|
| 1    | 60  | MR | CT2 | 4+3 | B   | 219        | 6 Cycles | 80                  | 0.41                             |
| 2    | 64  | CT1| CT2 | 5+4 | L   | 289        | 6 Cycles | 5.9                 | 0.15                             |
| 3    | 59  | CT1| CT1 | 5+4 | Max | 279        | 6 Cycles | 2.49                | 0.27                             |
| 4    | 74  | CT1| CT2 | 4+4 | Max | 149        | X            | 29.14                | 0.69                             |
| 5    | 57  | MR | CT2 | 4+3 | Max | 218        | X            | 45.4                 | 0.71                             |
| 6    | 74  | MR | MR  | 4+4 | Max | 61         | X            | 57.5                 | 1.42                             |
| 7    | 73  | MR | MR  | 4+5 | Max | 98         | X            | 14.06                | 0.1                              |
| 8    | 74  | CT1| MR  | 4+3 | Max | 115        | X            | 25.8                 | 0.05*                            |
| 9    | 79  | MR | CT1 | 4+5 | Max | 156        | X            | 42.06                | 1.9                              |
| 10   | 79  | MR | CT1 | 4+4 | Max | 116        | X            | 17.97                | 1.52                             |
| 11   | 76  | CT1| CT1 | 4+3 | Max | 118        | X            | 100.4                | 1.93                             |
| 12   | 65  | MR | CT1 | 4+5 | Max | 155        | X            | 91.5                 | 0.09                             |
| 13   | 59  | CT1| CT1 | 4+4 | Max | 81         | X            | 32.9                 | 3.08                             |
| 14   | 66  | CT1| CT1 | 4+4 | Max | 168        | 6 Cycles | 107                  | 0.21                             |
| 15   | 74  | CT1| CT1 | 4+4 | Max | 174        | X            | 16.17                | 0.93                             |
| 16   | 80  | CT1| CT1 | 4+5 | Max | 253        | X            | 12.07                | 0.45                             |
| 17   | 66  | CT1| CT1 | 3+4 | Max | 205        | 4 Cycles | 31.5                 | 0.05                             |
| 18   | 70  | CT1| CT1 | 4+4 | Max | 109        | X            | 21                   | 4.91                             |
| 19   | 81  | CT2| CT2 | 4+3 | Max | 102        | X            | 26.13                | 3.53                             |
Table 3
Patient based analysis of detectable lesions prior (T1) and during ADT (T2); * = both examinations on same device; *= new manifestation under ADT

| Pat. | Prostatic lesions [n] | Lymph node metastases [n] | Bone metastases [n] | Max mIPSMAScore | Summed mIPSMAScore | PSMA-TV | TL-PSMA |
|------|-----------------------|--------------------------|---------------------|-----------------|--------------------|---------|---------|
|      | T1 T2 T1 T2         | T1 T2 T1 T2             | T1 T2 T1 T2        | T1 T2 T1 T2     | T1 T2 T1 T2        | T1 T2   | T1 T2   |
| 1    | 1 1 1 7             | 1 2 2 3                | 3 2 3 2            | 23 6            | 25.98 1.17         | 533.80 | 31.45   |
| 2    | 2 2 1 4             | 1 4 3 3                | 21 7              | 112.29 3.14     | 1355.46 58.82      |         |         |
| 3    | 1 1 1 7             | 0 5 2* 2*             | 2 2              | 21 4            | 57.61 7.27         | 326.76 | 29.25   |
| 4    | 1 1 1 10            | 7 1 0 3              | 27 18            | 48.30 4.66      | 1304.34 205.85     |         |         |
| 5    | 1 1 1 1             | 1 2 1 2              | 5 4             | 6.90 2.63       | 44.10 41.73        |         |         |
| 6    | 1 1 1 2             | 1 1 1 2              | 8 6             | 24.77 8.70      | 276.52 79.63       |         |         |
| 7    | 1 1 1 6             | 0 0 0 3              | 15 2             | 17.59 2.94      | 216.78 24.75       |         |         |
| 8    | 1 0 0 0             | 3 1 2 0              | 6 0             | 14.99 3.50      | 154.94 4.55        |         |         |
| 9    | 1 1 1 1             | 0 0 2 1              | 3 1             | 8.00 3.55       | 46.92 15.76        |         |         |
| 10   | 1 1 1 0             | 0 1 1 2              | 4 4             | 5.44 2.89       | 62.93 31.48        |         |         |
| 11   | 1 1 1 5             | 0 0 3 2              | 16 6             | 23.78 9.41      | 972.02 90.27       |         |         |
| 12   | 1 0 1 0             | 0 0 3 0              | 8 0             | 22.78 .00       | 475.38 .00         |         |         |
| 13   | 1 1 1 0             | 0 1 1 2              | 4 3             | 11.06 22.86     | 56.80 152.14       |         |         |
| 14   | 1 1 1 1             | 1 0 1 2              | 6 2             | 21.54 9.16      | 513.79 33.42       |         |         |
| 15   | 1 1 1 0             | 0 0 3 2              | 5 2             | 28.72 4.87      | 1652.99 45.10      |         |         |
| 16   | 1 1 1 0             | 0 0 3 2              | 4 3             | 13.78 8.75      | 178.49 54.15       |         |         |
| 17   | 1 1 0 0             | 0 0 0 8              | 8 0             | 25.10 .00       | 102.18 .00         |         |         |
| 18   | 1 1 1 3             | 2 0 3 3              | 8 5             | 29.05 17.42     | 562.41 287.53      |         |         |
| 19   | 2 0 0 0             | 1 1 3 1              | 6 1             | 0.83 0.38       | 8.57 3.44          |         |         |
|      | ∑ 21 15 54 18       | 27 12 47 33           | 198 75          | 498.51 116.47   | 8845.18 1189.33    |         |         |

Table 4
Lesion based quantification parameters in T1 and T2.

| Parameter     | Prostatic lesions T1[mean; CI] | Prostatic lesions T2[mean; CI] | p   | Lymphatic lesions T1[mean; CI] | Lymphatic lesions T2[mean; CI] | p   | Bone lesions T1 [mean; CI] | Bone lesions T2 [mean; CI] | p   | All lesions T1[mean; CI] | All lesions T2[mean; CI] | p   |
|---------------|--------------------------------|--------------------------------|-----|-------------------------------|-------------------------------|-----|-----------------------|-----------------------|-----|-----------------------|-----------------------|-----|
| Score         | 2.24; 1.95–2.52                 | 1.38; 0.92–1.85                | 0.001 | 1.98; 1.89–2.16               | 0.57; 0.32–0.83               | < 0.001 | 1.52; 1.26–1.78         | 0.48; 0.22–0.74         | < 0.001 | 1.9; 1.77–2.04         | 0.71; 0.53–0.90         | < 0.001 |
| SUVmax        | 28.47; 18.27–38.67              | 13.69; 7.71–19.68              | 0.004 | 19.71; 14.87–24.55            | 7.95; 2.41–13.50              | < 0.001 | 12.84; 8.27–17.41       | 3.48; 1.30–5.65          | < 0.001 | 19.56; 16.04–23.08      | 7.86; 4.69–11.04        | < 0.001 |
| SUVmean       | 17.35; 11.21–23.49              | 7.97; 4.53–11.42               | 0.003 | 12.90; 9.68–16.11             | 4.95; 1.55–8.36               | < 0.001 | 8.36; 5.37–11.36        | 2.20; 0.80–3.61          | < 0.001 | 12.53; 10.29–14.78      | 4.80; 2.86–6.73         | < 0.001 |
| PSMA_TV [ml]  | 13.18; 9.32–17.04               | 3.60; 1.55–5.65                | < 0.001 | 3.10; 1.44–4.75               | 0.23; 0.07–0.39               | < 0.001 | 1.88; 1.24–2.52         | 0.98; 0.23–1.75          | < 0.001 | 4.79; 1.91–2.78         | 1.12; 0.61–1.63         | < 0.001 |
| TL_PSMA [ml]  | 281.73; 114.36–449.10           | 35.89; 8.25–63.54              | < 0.001 | 42.94; 20.27–65.62            | 4.66; 0–10.75                 | < 0.001 | 21.03; 4.49–34.57       | 6.33; 0–13.65            | < 0.001 | 85.05; 46.10–124.00     | 11.44; 4.63–18.25       | < 0.001 |
Table 5
Correlation between the miPSMA expression score and the other obtained metabolic parameters. Q: quotient of T2/T1; LN: Liver normalisation [Value divided through hepatic SUVmean]

| T2/T1-quotient (Q) of miPSMA Score | T2/T1 | T2/T1 | T2/T1 | T2/T1 | T2/T1 | T2/T1 | T2/T1 | T2/T1 |
|-----------------------------------|-------|-------|-------|-------|-------|-------|-------|-------|
|                                   | SUVmax| LN_SUVmax| SUVmean| SUVmean| PSMA_TV| TL_PSMA| TL_PSMA_LN| Layer  |
| All lesions                       |       |       |       |       |       |       |       |       |
| Correlation coefficient           | 0.973 | 0.971 | 0.974 | 0.972 | 0.847 | 0.918 | 0.911 | 0.161 |
| p-value                           | < 0.001 | < 0.001 | < 0.001 | < 0.001 | < 0.001 | < 0.001 | < 0.001 | 0.105 |
| Primary tumor                     |       |       |       |       |       |       |       |       |
| Correlation coefficient           | 0.883 | 0.899 | 0.900 | 0.899 | 0.557 | 0.703 | 0.685 | 0.244 |
| p-value                           | < 0.001 | < 0.001 | < 0.001 | < 0.001 | 0.009 | < 0.001 | 0.001 | 0.287 |
| Lymph nodes metastases            |       |       |       |       |       |       |       |       |
| Correlation coefficient           | 0.991 | 0.990 | 0.991 | 0.996 | 0.922 | 0.969 | 0.962 | 0.123 |
| p-value                           | < 0.001 | < 0.001 | < 0.001 | < 0.001 | 0.011 | < 0.001 | 0.376 | < 0.01 |
| Bone metastases                   |       |       |       |       |       |       |       |       |
| Correlation coefficient           | 0.945 | 0.951 | 0.945 | 0.951 | 0.873 | 0.917 | 0.917 | 0.132 |
| p-value                           | < 0.001 | < 0.001 | < 0.001 | < 0.001 | < 0.001 | < 0.001 | < 0.001 | 0.510 |

Table 6
Lesion based comparison of values at T2 and T1 - All differences are significant with a p < 0.01; LQ: Liver normalization [value divided through hepatic SUVmean]. * Two bone metastases were newly occurred at T2 and thus have higher values at T2 in all surrogate parameters.

| Value in T2 ≤ T1 | Score | SUVmax | SUVmax_LN | SUVmean | SUVmean_LN | PSMA_TV | TL_PSMA | TL_PSMA_LN |
|------------------|-------|--------|-----------|---------|------------|---------|---------|------------|
| Prostatic lesions [n = 21] |       | 20/21  | 16/21     | 18/21   | 15/21      | 20/21   | 19/21   | 19/21      |
| Lymphonodal lesions [n = 54] |       | 51/54  | 46/54     | 47/54   | 48/54      | 53/54   | 53/54   | 54/54      |
| Bone lesions [n = 29] |       | 27/29  | 26/29     | 25/29   | 25/29      | 26/29   | 23/29   | 25/29      |
| All lesions [n = 104] |       | 98/104 | 89/104    | 90/104  | 89/104     | 96/104  | 97/104  | 99/104     |

Table 7
Patient-based correlation between PSMA-derived tumor volumes and PSA values at different time points. *: p < 0.05; **: p < 0.001

| All patients(n = 19) | miPSMA Score | PSMA_TV | TL_PSMA | PSMA_TV | TL_PSMA | PSMA_TV | TL_PSMA | PSMA_TV | TL_PSMA | PSMA_TV | TL_PSMA |
|----------------------|--------------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|
|                      | All lesions  | All lesions | All lesions | All lesions | All lesions | All lesions | All lesions | All lesions | All lesions | All lesions | All lesions |
| Parameter time point | T1 | T1 | T1 | T1 | T1 | T1 | T1 | T1 | T1 | T1 | T1 | T1 |
| T1 PSA Correlation coefficient | -0.005 | -0.211 | -0.060 | -0.114 | 0.002 | -0.019 | 0.090 | -0.186 | -0.211 |       |       |
| Parameter time point | T2 | T2 | T2 | T2 | T2 | T2 | T2 | T2 | T2 | T2 | T2 | T2 |
| T2 PSA Correlation coefficient | 0.325 | 0.449 | 0.523* | 0.451 | 0.446 | 0.191 | 0.197 | 0.037 | 0.137 |       |       |
| Parameter time point | T2/T1 | T2/T1 | T2/T1 | T2/T1 | T2/T1 | T2/T1 | T2/T1 | T2/T1 | T2/T1 | T2/T1 | T2/T1 | T2/T1 |
| T2 PSA Correlation coefficient | 0.609** | 0.729** | 0.763** | 0.531* | 0.532* | 0.483 | 0.464 | 0.304 | 0.034 |       |       |
| Parameter time point | T2/T1 PSA | T2/T1 PSA | T2/T1 PSA | T2/T1 PSA | T2/T1 PSA | T2/T1 PSA | T2/T1 PSA | T2/T1 PSA | T2/T1 PSA |       |       |
| T2/T1 PSA Correlation coefficient | 0.464* | 0.385 | 0.578** | 0.631** | 0.404 | 0.486* | 0.002 | 0.075 | 0.304 |       |       |
## Table 8
Lesion based correlation of PSA-values and PSMA-parameters of different time points. LN: Intraindividual liver correction [Value divided through hepatic SUVmean] *: p < 0.05; **: p < 0.001

| All lesions (n = 104) | Score | SUVmax | SUVmax_LN | SUVmean | SUVmean_LN | PSMA_TV | TL_PSMA_TV | TL_PSMA_LN |
|-----------------------|-------|--------|-----------|---------|------------|---------|------------|------------|
| Parameter time point  |       |        |           |         |            |         |            |            |
| T1 PSA                |       |        |           |         |            |         |            |            |
| Correlation coefficient | 0.188 | 0.259**| 0.250*    | 0.281** | 0.265**    | -0.113  | 0.057      | 0.042      |
| Parameter time point  |       |        |           |         |            |         |            |            |
| T2 PSA                |       |        |           |         |            |         |            |            |
| Correlation coefficient | 0.431**| 0.431**| 0.424**   | 0.435** | 0.431**    | 0.405** | 0.416**    | 0.411**    |
| Parameter time point  |       |        |           |         |            |         |            |            |
| T2/T1 PSA             |       |        |           |         |            |         |            |            |
| Correlation coefficient | 0.161 | 0.146  | 0.151     | 0.153   | 0.157      | 0.105   | 0.158      | 0.160      |
| T2 PSA                |       |        |           |         |            |         |            |            |
| Correlation coefficient | 0.450**| 0.443**| 0.447**   | 0.443** | 0.451**    | 0.457** | 0.481**    | 0.488**    |

## Figures

**Figure 1**

MIPs and fused PSMA-PET/CT of Patient #3. The MIPs show a clearer demarcation of the prostatic tumor as well as the complete regression of lymphonodal metastases. While two new osseous metastases occurred the lower one is indicated by the blue arrow.
Figure 2
MIPs and fused PET/MRI at T1 and PET/CT at T2. There is no pathologic PSMA expression neither in the prostate nor in the metastatic sites (arrows in the fused image at T1) at T2.