# Head-to-Head Comparison of [$^{68}$Ga]Ga-P16-093 and [$^{68}$Ga]Ga-PSMA-617 in Dynamic PET/CT Evaluation of the Same Group of Recurrent Prostate Cancer Patients

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## Abstract

**Purpose:** This study was prospectively designed to evaluate the early dynamic organ distribution and tumor detection ability of [$^{68}$Ga]Ga-P16-093, which was compared with [$^{68}$Ga]Ga-PSMA-617 in the same group of recurrent prostate cancer patients.

**Methods:** Twenty patients with recurrent prostate cancer were enrolled. In two consecutive days, each patient underwent a 60-min dynamic PET/CT scan after intravenous administration of 148–185 MBq (4–5 mCi) [$^{68}$Ga]Ga-P16-093 and [$^{68}$Ga]Ga-PSMA-617, respectively. Following a low-dose CT scan, serial dynamic PET scans were performed from head to proximate thigh at 9 time points (30 sec/bed at 4, 7, 10, 13 and 16 min, 1 min/bed at 20, 30 and 45 min, and 2 min/bed at 60 min). Standardized uptake values were measured for semi-quantitative comparison.

**Results:** [$^{68}$Ga]Ga-P16-093 PET/CT revealed a significantly higher tumor uptake at 4 min (SUVmax 7.88 ± 5.26 *vs.* 6.01 ± 3.88, P < 0.001), less blood pool retention at 4 min (SUVmean 5.12 ± 1.16 *vs.* 6.14 ± 0.98, P < 0.001) and lower bladder accumulation at 60 min (SUVmean 31.33 ± 27.47 *vs.* 48.74 ± 34.01, P = 0.042) than [$^{68}$Ga]Ga-PSMA-617 scan. Significantly higher [$^{68}$Ga]Ga-P16-093 uptakes were also observed in the parotid gland, liver, spleen and kidney. Besides, [$^{68}$Ga]Ga-P16-093 exhibited a better detection ability than [$^{68}$Ga]Ga-PSMA-617 (366 *vs.* 321, P = 0.009).

**Conclusions:** [$^{68}$Ga]Ga-P16-093 showed advantages over [$^{68}$Ga]Ga-PSMA-617 with higher tumor uptakes, tumor-to-blood pool ratio and detection ability, less blood pool and bladder accumulation in recurrent prostate cancer patients.

**Trial registration** [$^{68}$Ga]Ga-P16-093 and [$^{68}$Ga]Ga-PSMA-617 PET/CT Imaging in the Same Group of Prostate Cancer Patients (NCT04796467, Registered 12 March 2021, retrospectively registered)

**URL of registry** https://clinicaltrials.gov/ct2/show/NCT04796467


## Introduction

Prostate cancer (PCa) is one of the most common male malignancy and a leading cause of death [1]. Early diagnosis and accurate staging are of paramount significances to the treatment and prognosis of PCa, yet there are persistent major challenges for all detection modalities. Blood prostate specific antigen (PSA) test, digital rectal examination (DRE), and transrectal ultrasound (TRUS) are classic methods to monitor PCa, which are also the most common approaches for clinical screening of PCa by far. Abnormal DRE is an indication for biopsy, but as an independent variable, it's reported that PSA value is a better predictor of PCa than either DRE or TRUS [2]. Nonetheless, all the above methods have unsurmountable limitations in tumor exact localization, staging of disease, distinguishing between chronic prostatitis and PCa and so on. Over the past years, multi-parametric MR imaging (mpMRI) has proven to be a valuable imaging tool to avoid unnecessary prostate biopsies, which can better confirm the integrity of the prostate capsule and tumor invasion into tissues and organs around the prostate, through T1, T2-weighted images, DWI, DCE, and other functional sequences [3]. However, mpMRI also exhibited some drawbacks as its specificity for high-grade PCa is only moderate (37%) and limited tumor staging, which are critical for clinical decision-making [4, 5].

In the past few years, PET imaging on prostate cancer patients has been a revolutionary advance due to the development of multitudinous radiopharmaceuticals. Prostate specific membrane antigen (PSMA), as known as folate hydrolase I or glutamate carboxypeptidase II, is regarded as the best-established target antigen in PCa, as it is highly and specifically expressed on the cells of prostatic adenocarcinoma. Besides, the level of PSMA expression on PCa cells further increases with tumor dedifferentiation and in metastatic castration-resistant prostate cancer (mCRPC) [6–9]. In the current decade, PSMA-targeted PET/CT has proven to be an extremely promising imaging modality with high sensitivity and specificity in detecting PCa and its metastases, even at a very low serum PSA level [10–12]. Currently, quite a few of radiolabeled PSMA probes have been developed, including [$^{68}$Ga]Ga-PSMA-11 and [$^{68}$Ga]Ga-PSMA-617, which are the most widely used as imaging agents. [$^{68}$Ga]Ga-P16-093, a modified radiotracer based on [$^{68}$Ga]Ga-PSMA-11, targets cellular PSMA with the urea fragment of a conjugate that employs the HBED-CC chelator for labeling with $^{68}$Ga(III) [13, 14]. The HBED-based chelating ligand binds the $^{68}Ga^{3+}$ ion with high affinity ($K_a$ nearly $10^{39}$) in a pseudo-octahedral $N_2O_4$ coordination sphere by its two phenolate O, two amino-acetate carboxylate O, and two amino N donor atoms [14–18], as shown in Fig. 1. Mark A. Green et.al [14] had demonstrated that both [$^{68}$Ga]Ga-P16-093 and [$^{68}$Ga]Ga-PSMA-11 performed equally well and showed high accuracy in detection of the PCa patients with biochemical recurrence (BCR). Moreover, [$^{68}$Ga]Ga-P16-093 also revealed less urinary excretion than [$^{68}$Ga]Ga-PSMA-11, which may achieve a better detection ability for tumor lesions close to the urinary bladder.

Herein, with the purpose of broadening the existing knowledge on [$^{68}$Ga]Ga-P16-093 PET/CT in diagnosis and staging of PCa, we conducted this study to evaluate the early kinetics and compare the detection ability of [$^{68}$Ga]Ga-P16-093 with [$^{68}$Ga]Ga-PSMA-617 in the same group of

recurrent PCa patients by means of multiparametric PET/CT consisting of a combination of a dynamic and whole-body PET/CT protocol.

## Materials And Methods

This matched-pair study was approved by the Institutional Review Board of Peking Union Medical College Hospital and registered at clinicaltrials.gov (NCT04796467). Written informed consent was obtained from all subjects. Patients with recurrent prostate cancer were prospectively recruited to this study.

# Synthesis of [$^{68}$Ga]Ga-P16-093 and [$^{68}$Ga]Ga-PSMA-617

The P16-093 molecule was synthesized as previously described [13]. $^{68}GaCl_3$ was eluted from a $^{68}Ge/^{68}Ga$ generator produced by Eckert & Ziegler using 5 mL of 0.1 M ultrapure hydrochloride acid. The eluted $^{68}GaCl_3$ solution was added to a reaction vial, which contained P16-093 (15μg) and NaOAc•$3H_2O$ (68 mg) as a lyophilized powder. The reaction mixture was heated for 5 min at 95℃. Subsequently, the final product was diluted with saline and sterilized by filtered through a 0.2-μm sterile vented PVDF filter into a sterile septum-capped vial.

Preparation of PSMA-617 and $^{68}$Ga labeling was performed as described previously [19].

The quality control of the labeled product was conducted by ITLC assessment. Final radiochemical purities over 95% for both [$^{68}$Ga]Ga-P16-093 and [$^{68}$Ga]Ga-PSMA-617 were accepted for intravenous injection.

# PET/CT Imaging acquisition and analysis

In two consecutive days, patients were instructed to drink 500 mL of water within 2 hours prior to acquisition and to void immediately before the start of scan. Each patient underwent a 60-min dynamic PET/CT (dPET/CT) acquisition by using a Biograph 64 Truepoint TrueV system (Siemens Medical Solutions, Erlangen, Germany) after intravenous injection of 148–185 MBq (4–5 mCi) of [$^{68}$Ga]Ga-P16-093 and [$^{68}$Ga]Ga-PSMA-617, respectively. The dPET/CT scan started with a low-dose CT scan (120 kV, 35 mA, 512 × 512 matrix, 3mm layer, and 70 cm field of view) for attenuation correction and anatomical localization from head to proximate thigh. Then PET scan of each patient was performed at 9 time points (30 sec/bed at 4, 7, 10, 13, 16 min, 1 min/bed at 20, 30, 45 min, and 2 min/bed at 60 min), with the arms placed on the sides of body.

The mean standardized uptake value (SUVmean) of selected normal tissues were established by placing 3D volumes of interest (VOIs) on the right side of the parotid gland, blood pool (at the arcus aortae level), the right liver lobe, the spleen, the left kidney and the bladder, respectively. As for prostate cancer lesions, [$^{68}$Ga]Ga-P16-093and [$^{68}$Ga]Ga-PSMA-617 scans was interpreted independently by 2 experienced nuclear medicine physicians blinded to all relevant clinical statistics, any focal accumulation that was higher than surrounding background activity and didn't match for physiologic tracer uptake was interpreted as PCa lesion. The maximum standardized uptake value (SUVmax) in each segment of the PCa lesion was measured using a 1–2 cm spheric volume of interest.

# Statistical Analysis

All statistical analyses were performed using SPSS (version 26.0; IBM Corp, for Windows [Microsoft]). All quantitative data were expressed as mean ± standard deviation (SD). For comparison of uptake values, two-sided paired t-test and Spearman correlation coefficient analysis were used. The results were considered significant when $P < 0.05$.

## Results

# Characteristics of enrolled patients

A total of 20 patients with recurrent PCa after therapies were enrolled into the study from October 2020 to May 2021, including 6 cases of BCR and 14 cases of mCRPC, the average age of them was 67.8 ± 6.6 years (range 56–83, median 68.5), with a mean Gleason score of 8.5 ± 1.1 (range 7–10, median 9) and a mean PSA level of 36.5 ± 42.0 ng/ml (range 0.2-138.3, median 19.5 ng/ml). The patients' characteristics are summarized in Table 1. There were no adverse events and clinically evident pharmacological reactions associated with the injection of [$^{68}$Ga]Ga-P16-093 and [$^{68}$Ga]Ga-PSMA-617.

# Radionuclide distribution of normal tissues

We calculated the SUV values of specific tissues, in which PSMA ligands showed normally high uptakes (parotid gland, blood pool, liver, spleen, kidney and bladder). The distribution of the two tracers in body was similar in several aspects, but there were also clearly observable differences (Fig. 2). Firstly, time-activity curves (TACs) derived from dPET/CT demonstrated that [$^{68}$Ga]Ga-P16-093 was cleared faster from

blood pool than [$^{68}$Ga]Ga-PSMA-617. It is determined that [$^{68}$Ga]Ga-P16-093 had a lower initial activity and a more pronounced clearance than [$^{68}$Ga]Ga-PSMA-617 from 4 min to 60 min (two-sided paired t tests, SUVmean 5.12 ± 1.16 *vs.* 6.14 ± 0.98 at 4 min, P < 0.001). Secondly, [$^{68}$Ga]Ga-P16-093 displayed a more distinct activity in kidneys than [$^{68}$Ga]Ga-PSMA-617 over time (two-sided paired t tests, SUVmean 8.88 ± 1.79 *vs.* 7.51 ± 1.39 at 4 min, P < 0.001); Bladder accumulation was consistently lower for [$^{68}$Ga]Ga-P16-093 than [$^{68}$Ga]Ga-PSMA-617, with the difference being statistically significant not until the 60 minute (two-sided paired t tests, SUVmean 31.33 ± 27.47 *vs.* 48.74 ± 34.01 at 60 min, P = 0.042). Thirdly, the liver and spleen also showed physiological uptakes of both two radiopharmaceuticals and the SUV values of [$^{68}$Ga]Ga-P16-093 were significantly higher than [$^{68}$Ga]Ga-PSMA-617 (two-sided paired t tests, liver: SUVmean 5.74 ± 1.11 *vs.* 4.38 ± 0.80 at 4 min, P < 0.001; spleen: SUVmean 5.62 ± 1.07 *vs.* 4.18 ± 0.71 at 4 min, P < 0.001). However, their metabolic profiles were different. [$^{68}$Ga]Ga-P16-093 PET/CT exhibited a gradually upward trend of SUVmean in liver and spleen over time, but [$^{68}$Ga]Ga-PSMA-617 PET/CT showed a stable, lower tracer accumulation. Finally, the SUVmean of parotid gland occurred marked increases in the respective VOIs overtime and [$^{68}$Ga]Ga-P16-093 PET/CT revealed a significantly higher uptake than [$^{68}$Ga]Ga-PSMA-617 PET/CT (two-sided paired t tests, SUVmean 3.68 ± 1.02 *vs.* 2.95 ± 0.81 at 4 min, P < 0.001). Figure 3 (**a-f**) exhibited the resulting TACs based on the mean values and the standard deviation of all evaluated data derived from blood pool, bladder, kidney, parotid gland, liver and spleen, respectively.

## Uptake values of tumor lesions and detection ability

According to dynamic imaging series, tracer uptakes of PCa lesions started at a very early time point, visible positive at the 4 min, with intensity continually increasing until the end of the dPET/CT. [$^{68}$Ga]Ga-P16-093 PET/CT also demonstrated consistently higher tumor uptakes of nearly all tumor lesions than [$^{68}$Ga]Ga-PSMA-617 PET/CT (two-sided paired t tests, SUVmax 7.88 ± 5.26 *vs.* 6.01 ± 3.88 at 4 min, P < 0.001; SUVmax 18.85 ± 14.02 *vs.* 14.27 ± 11.59 at 60 min, P < 0.001). The difference in the uptake of the two tracers, both in BCR and mCRPC patients, was not correlated with patients' age, PSA value, Gleason score (Spearman correlation coefficient analysis). Figure 3 (**g**) showed the TAC of tumor lesions. We have also calculated the tumor-to-blood pool ratio (TBR), which revealed a statistically higher ratio for [$^{68}$Ga]Ga-P16-093 than [$^{68}$Ga]Ga-PSMA-617 from 4 min to 60 min (two-sided paired t test, 1.58 ± 1.11 vs. 0.96 ± 0.57 at 4 min, P < 0.001; 13.16 ± 10.41 *vs.* 5.39 ± 3.37 at 60 min, P < 0.001,), even the TBR of [$^{68}$Ga]Ga-P16-093 PET/CT at 20 min was significantly higher than that of [$^{68}$Ga]Ga-PSMA-617 PET/CT at 60 min (two-sided paired t test, 7.43 ± 5.85 *vs.* 5.39 ± 3.37, P = 0.002), as shown in Fig. 3 (**h**).

Among these patients, 18 of 20 patients (90.0%) were PET positive. Overall, 366 and 321 focal lesions were identified on [$^{68}$Ga]Ga-P16-093 PET/CT and [$^{68}$Ga]Ga-PSMA-617 PET/CT, respectively. The difference was statistically significant (two-sided paired t tests, 366 *vs.* 321, P = 0.009, as shown in Table 2 and Fig. 4–5).

Table 1
The characteristics of patients

| No. | Patient classification | Age (years) | Gleason Score | PSA (ng/ml) | [$^{68}$Ga]Ga-P16-093 (MBq) | [$^{68}$Ga]Ga-PSMA-617 (MBq) |
|---|---|---|---|---|---|---|
| 1 | BCR | 70 | 4 + 4 | 1.1 | 159.5 | 166.1 |
| 2 | BCR | 71 | 4 + 3 | 1.0 | 177.6 | 170.2 |
| 3 | BCR | 71 | 5 + 5 | 1.9 | 166.5 | 166.5 |
| 4 | BCR | 72 | 4 + 4 | 0.2 | 177.6 | 173.9 |
| 5 | BCR | 78 | 4 + 5 | 1.3 | 155.8 | 162.4 |
| 6 | BCR | 64 | 4 + 3 | 2.0 | 166.5 | 170.2 |
| 7 | mCRPC | 69 | 3 + 4 | 7.0 | 159.1 | 159.1 |
| 8 | mCRPC | 66 | 4 + 4 | 9.3 | 166.8 | 162.5 |
| 9 | mCRPC | 83 | 3 + 4 | 7.3 | 166.5 | 159.1 |
| 10 | mCRPC | 66 | 5 + 5 | 52.0 | 173.9 | 181.3 |
| 11 | mCRPC | 68 | 4 + 5 | 89.5 | 162.8 | 170.2 |
| 12 | mCRPC | 72 | 5 + 5 | 33.8 | 159.1 | 166.5 |
| 13 | mCRPC | 72 | 5 + 4 | 53.7 | 170.2 | 162.8 |
| 14 | mCRPC | 57 | 5 + 4 | 32.6 | 155.4 | 159.1 |
| 15 | mCRPC | 56 | 4 + 3 | 65.0 | 161.5 | 159.1 |
| 16 | mCRPC | 71 | 5 + 4 | 96.2 | 177.6 | 170.2 |
| 17 | mCRPC | 63 | 4 + 5 | 29.6 | 155.4 | 162.8 |
| 18 | mCRPC | 64 | 5 + 4 | 4.6 | 170.2 | 166.5 |
| 19 | mCRPC | 59 | 4 + 5 | 103.4 | 159.1 | 151.7 |
| 20 | mCRPC | 63 | 5 + 4 | 138.3 | 173.9 | 170.2 |

*BCR* biochemical recurrence; *mCRPC* metastatic castration-resistant prostate cancer

Table 2

Number and SUVmax of positive lesions identified by [$^{68}$Ga]Ga-P16-093 versus [$^{68}$Ga]Ga-PSMA-617 in recurrent PCa patients

| No. | Patient classification | [$^{68}$Ga]Ga-P16-093 | | | | [$^{68}$Ga]Ga-PSMA-617 | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Intraprostatic lesions | LN metastases | Osseous metastases | SUVmax | Intraprostatic lesions | LN metastases | Osseous metastases | SUVmax |
| 1 | BCR | 0 | 1 | 0 | 19.0 | 0 | 1 | 0 | 13.8 |
| 2 | BCR | 0 | 0 | 6 | 6.5 | 0 | 0 | 6 | 4.8 |
| 3 | BCR | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 4 | BCR | 0 | 1 | 1 | 8.5 | 0 | 0 | 1 | 6.6 |
| 5 | BCR | 0 | 2 | 1 | 19.4 | 0 | 1 | 1 | 12.7 |
| 6 | BCR | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7 | mCRPC | 1 | 0 | 39 | 12.8 | 1 | 0 | 32 | 7.1 |
| 8 | mCRPC | 0 | 0 | 32 | 40.3 | 0 | 0 | 30 | 20.5 |
| 9 | mCRPC | 0 | 0 | 12 | 12.3 | 0 | 0 | 12 | 10.4 |
| 10 | mCRPC | 0 | 0 | 36 | 58.1 | 0 | 0 | 31 | 33.6 |
| 11 | mCRPC | 0 | 0 | 18 | 47.1 | 0 | 0 | 19 | 43.4 |
| 12 | mCRPC | 0 | 0 | 29 | 21.6 | 0 | 0 | 24 | 14.2 |
| 13 | mCRPC | 1 | 0 | 64 | 29.1 | 1 | 0 | 51 | 15.2 |
| 14 | mCRPC | 0 | 0 | 13 | 6.3 | 0 | 0 | 13 | 5.7 |
| 15 | mCRPC | 0 | 7 | 5 | 47.7 | 0 | 6 | 4 | 46.6 |
| 16 | mCRPC | 1 | 1 | 0 | 15.1 | 1 | 1 | 0 | 8.3 |
| 17 | mCRPC | 0 | 0 | 33 | 26.6 | 0 | 0 | 27 | 20.8 |
| 18 | mCRPC | 1 | 3 | 23 | 13.8 | 1 | 3 | 23 | 12.3 |
| 19 | mCRPC | 0 | 0 | 31 | 14.7 | 0 | 0 | 27 | 10.6 |
| 20 | mCRPC | 0 | 0 | 4 | 14.2 | 0 | 0 | 4 | 11.0 |

*BCR* biochemical recurrence; *mCRPC* metastatic castration-resistant prostate cancer

## Discussion

The clinical application of PET imaging with the $^{68}$Ga-labeled PSMA radioligands, such as [$^{68}$Ga]Ga-PSMA-11 and [$^{68}$Ga]Ga-PSMA-617, has been regarded as a revolutionary breakthrough in the diagnosis of PCa [20]. In the past few years, PSMA-targeting radiotracers has been structurally modified with the goal to achieve improved specificity and sensitivity for clinical applications [21].

In our study, [$^{68}$Ga]Ga-P16-093 PET/CT exhibited remarkably higher SUV values of tumor lesions and TBR, better tumor detection ability, as well as lower blood pool and bladder accumulation than those observed by [$^{68}$Ga]Ga-PSMA-617 scan. Importantly, we performed this research by comparing the two agents in the same patients, rather than conducting group analysis. And both PET/CT scans were randomly performed in two successive days. Obviously, given the nature of PCa progression, there was no significant variation in PCa lesions within such a short period of time. So, findings of this prospective head-to-head comparison study are credible.

As expected, the biodistribution patterns in normal tissues of [$^{68}$Ga]Ga-P16-093 were similar to [$^{68}$Ga]Ga-PSMA-617 and other small molecular weight PSMA-targeting radiotracers [22–25]. But there were substantial differences between [$^{68}$Ga]Ga-P16-093 and [$^{68}$Ga]Ga-PSMA-617. We will emphasize and discuss the results of this study in detail to further confirm the advantages of [$^{68}$Ga]Ga-P16-093 over [$^{68}$Ga]Ga-PSMA-617 as the following.

First and foremost, [$^{68}$Ga]Ga-P16-093 showed statistically significant higher tracer uptakes (higher SUVmax) and a superior satisfactory detection ability of tumor lesions than [$^{68}$Ga]Ga-PSMA-617. Particularly for the recurrent PCa patients, NCCN guidelines recommend that confirming metastases was a key factor for PCa patients with BCR and CRPC, as this determined their therapeutic schedules [26]. Nevertheless, accurate detection of lesion is still challenging due to its slowly progressive disease occurring and multiple treatment options. There were a number of prospective and retrospective studies using different imaging agents to compare the detection ability of biochemical recurrent and progressive PCa patients, with the purpose of finding a more appropriate imaging modality [27–31]. In our study, the better detection ability of tumor lesions by [$^{68}$Ga]Ga-P16-093 is a significant advantage over [$^{68}$Ga]Ga-PSMA-617, which might benefit the subsequent management of patients.

Secondly, [$^{68}$Ga]Ga-P16-093 exhibited increased blood clearance rate than [$^{68}$Ga]Ga-PSMA-617, which is also an important aspect to enhance the detection ability. In this study, the positive finding of [$^{68}$Ga]Ga-P16-093 in mediastinal lymph nodes compared with [$^{68}$Ga]Ga-PSMA-617 (Fig. 4) had well demonstrated this superiority. Furthermore, [$^{68}$Ga]Ga-P16-093 showed lower bladder accumulation in comparation with [$^{68}$Ga]Ga-PSMA-617, which was also of paramount importance in the diagnosis of recurrent prostate cancer. Low bladder activity was beneficial to identify localized lesions in close anatomical relation to the urinary bladder as recurrence PCa was most frequently associated with pelvic lymph node, which was previously demonstrated in a prospective study [32]. Although there were no lesions found around the bladder in our study, this showed a special advantage of [$^{68}$Ga]Ga-P16-093 over [$^{68}$Ga]Ga-PSMA-617 for detection of lesions in the pelvic area. However, it should be noted that the kidneys was still the critical organ, since the slightly higher radioactive retention for [$^{68}$Ga]Ga-P16-093 than [$^{68}$Ga]Ga-PSMA-617, which was consistent with previous research [14].

Thirdly, the main difference between the two drugs was that [$^{68}$Ga]Ga-P16-093 demonstrated higher hepatobiliary excretion and parotid gland cumulated activity value than [$^{68}$Ga]Ga-PSMA-617, as shown in the MIP images and TACs, which were statistically significant as exhibited in the Results (Fig. 3). This is a phenomenon worthy of attention, in general, we prefer a lower uptake in the liver so as not to affect the detection of liver metastases. High liver uptake could, however, be a less significant factor for using [$^{68}$Ga]Ga-P16-093 imaging in PCa, because it is uncommon to have liver metastasis in these patients.

As for our dPET/CT studies, we also observed that quite a few of PCa lesions presented with visible contrast at 4 min after the injection of imaging agents. Whereas, the blood pool background accumulation was relatively high at this time point, it was not the optimal time point of imaging. Although previous studies have demonstrated that early dynamic scan in PET/CT can reliably identify pathologic tracer uptake in PC lesions from physiologic accumulation in the urinary bladder [33, 34]. Our early dynamic PET/CT acquisition did not detect more PCa lesions, which indicated that early dynamic imaging may be of little use due to the shortcomings of technically demanding and time-consuming [35]. Of course, further analyses are needed to confirm this result. EANM and SNMMI procedure guideline suggested a 60-min interval (range 50–100 min) was appropriate for uptake time [36]. In our study, the images at 20 min on [$^{68}$Ga]Ga-P16-093 PET/CT exhibited roughly equivalent tracer uptakes of tumor lesions and higher TBR to that at 60 min on [$^{68}$Ga]Ga-PSMA-617 PET/CT. We propose that [$^{68}$Ga]Ga-P16-093 PET/CT allows a more flexible imaging time, which greatly increases the practicability and alleviate concerns with regard to necessary coordination of patient activities. So, we suggest that a 20–60 min interval for uptake time for [$^{68}$Ga]Ga-P16-093 PET/CT scan may be appropriate.

There were some limitations in our study. Firstly, the studied cohort was relatively small. Nevertheless, it was surprising that there were statistically significant differences in many aspects, such as tumor uptake, detection ability, in this small sample. The second limitation was the lack of histological confirmation of both the [$^{68}$Ga]Ga-P16-093 and [$^{68}$Ga]Ga-PSMA-617 avid focal lesions in cases of recurrent PCa. Whereas, quite a few studies had confirmed the high correlation between immunohistochemical findings and PSMA PET/CT imaging in PCa [28, 37]. Therefore, the results of PET/CT are reliable and consistent with pathological examination.

In the past ten years, precision medicine based on PSMA-targeting theranostic agents has created a dramatic shift in the practice of nuclear medicine. Significant impact of PSMA PET imaging in diagnosis and management of prostate cancer at different stages is well-recognized [20, 38]. Recently, [$^{68}$Ga]Ga-PSMA-11 [39, 40] and [$^{18}$F]PYL (Pylarify; piflufolastat F 18) [41] have received approval by Food and Drug Administration (FDA), and PSMA PET imaging is now becoming an important part of standard clinical practice for diagnosis and treatment of prostate cancers all over the world. [$^{68}$Ga]Ga-PSMA-11 and [$^{68}$Ga]Ga-PSMA-617 are two of the most widely used $^{68}$Ga-labeled imaging agents for the diagnosis of prostate cancer. Based on numerous advantages of [$^{68}$Ga]Ga-P16-093, described herein, it could be an excellent alternative agent, which can be prepared readily in high yield and purity at local hospitals. In the past three years, [$^{68}$Ga]Ga-P16-093 was under clinical studies in the Indiana University and University of Pennsylvania (IND #133222). We hope that [$^{68}$Ga]Ga-P16-093, if it is successfully tested and approved by the local authority, could serve the un-met clinical need worldwide.

## Conclusions

[$^{68}$Ga]Ga-P16-093 is a promising PSMA targeting imaging agent in detecting PCa lesions. Compared with [$^{68}$Ga]Ga-PSMA-617, [$^{68}$Ga]Ga-P16-093 shows several advantages, including faster blood clearance and lower bladder background, higher tumor uptakes, TBR and detection ability, which can identify PCa lesions with improved efficiency. These findings warrant further investigation in a larger number cohort of PCa patients.

## Declarations

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**Ethics approval**: Ethical approval was obtained from the Institute Review Board of Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, and this study was conducted in accordance with the principles of the Declaration of Helsinki.

**Availability of data and material**: Not applicable.

**Consent to participate**: Informed consent was obtained from all participants included in the study.

**Conflict of interest:** None to declare.

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## Figures

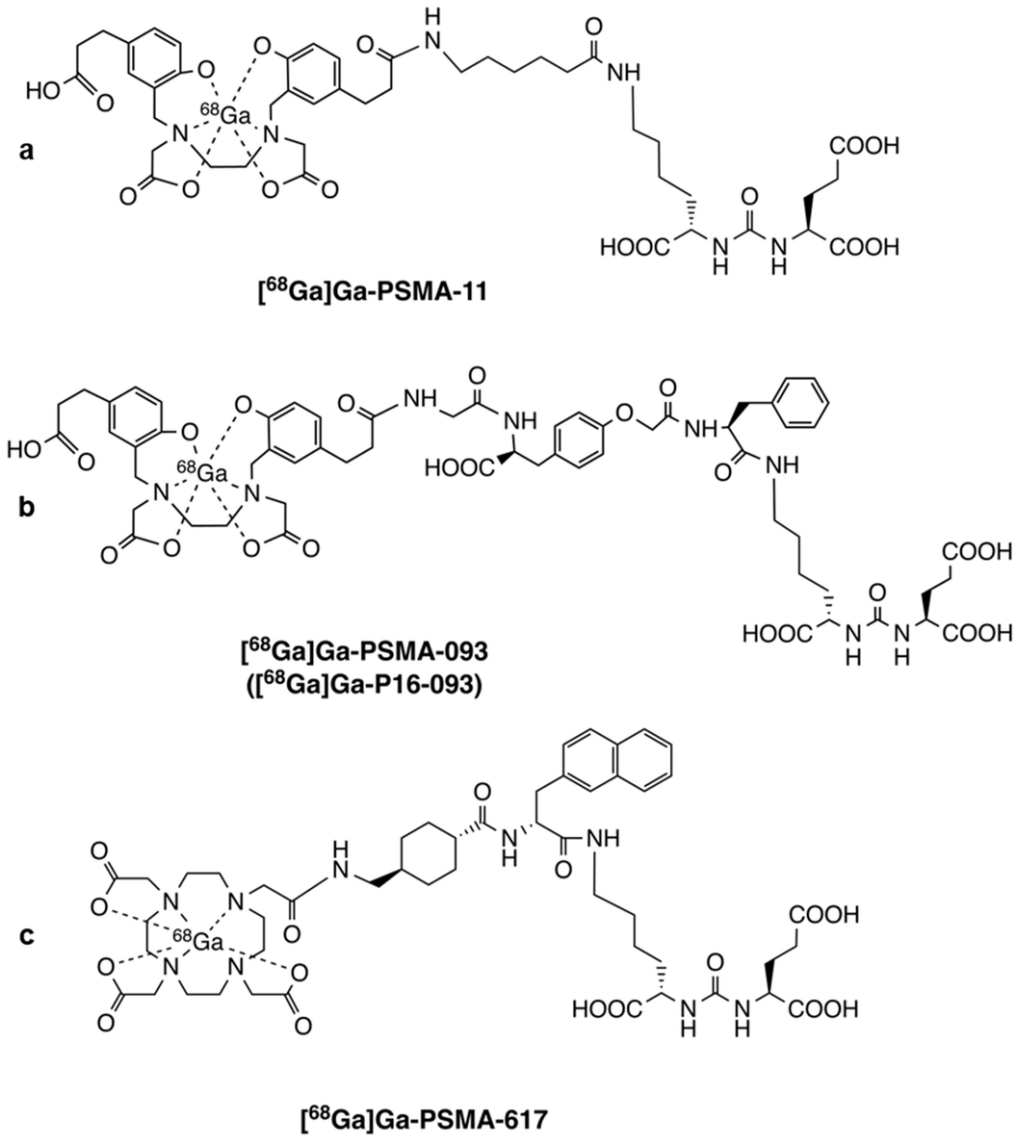


Figure 1

Structural formula of the [68Ga]Ga-PSMA-11 (a), [68Ga]Ga-P16-093 (b) and [68Ga]Ga-PSMA-617 (c) radiopharmaceuticals

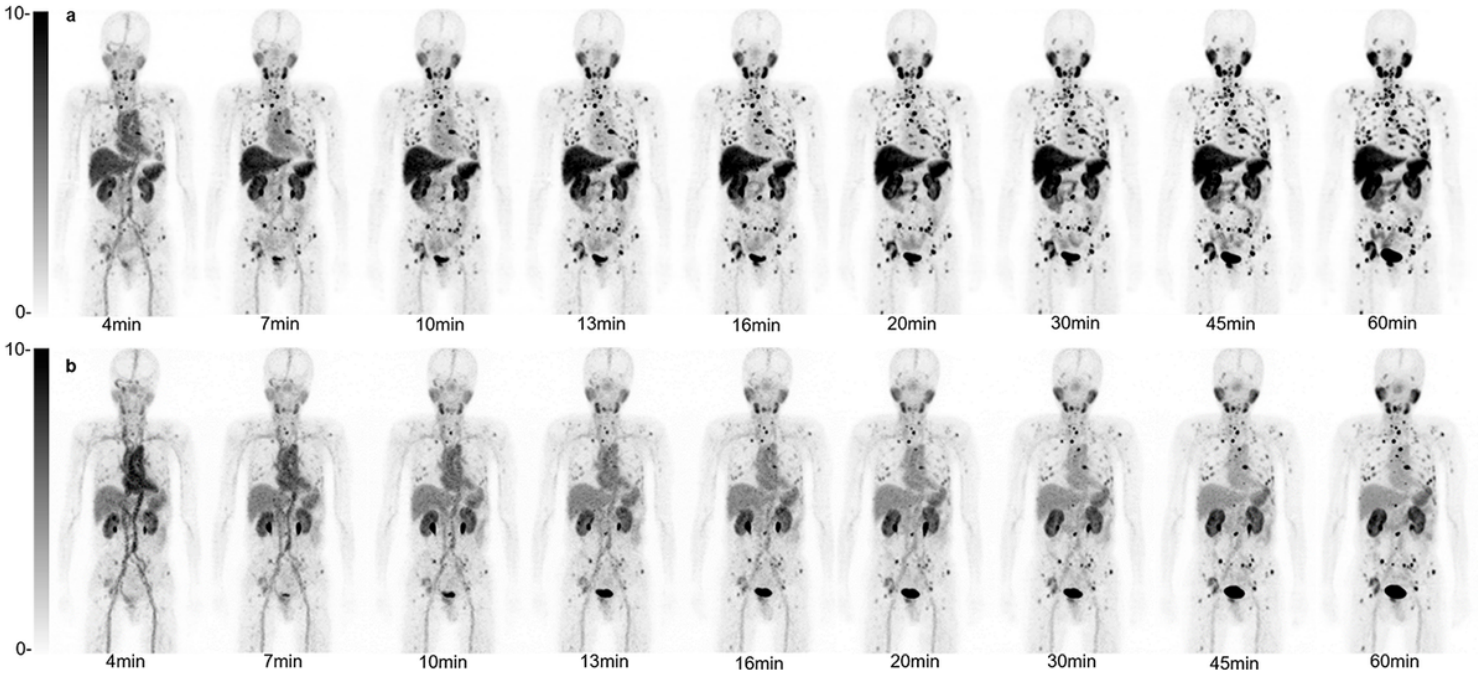


Figure 2

Series Maximum Intensity Projection (MIP) images based on dPET/CT of [68Ga]Ga-P16-093 (a) and [68Ga]Ga-PSMA-617 (b).

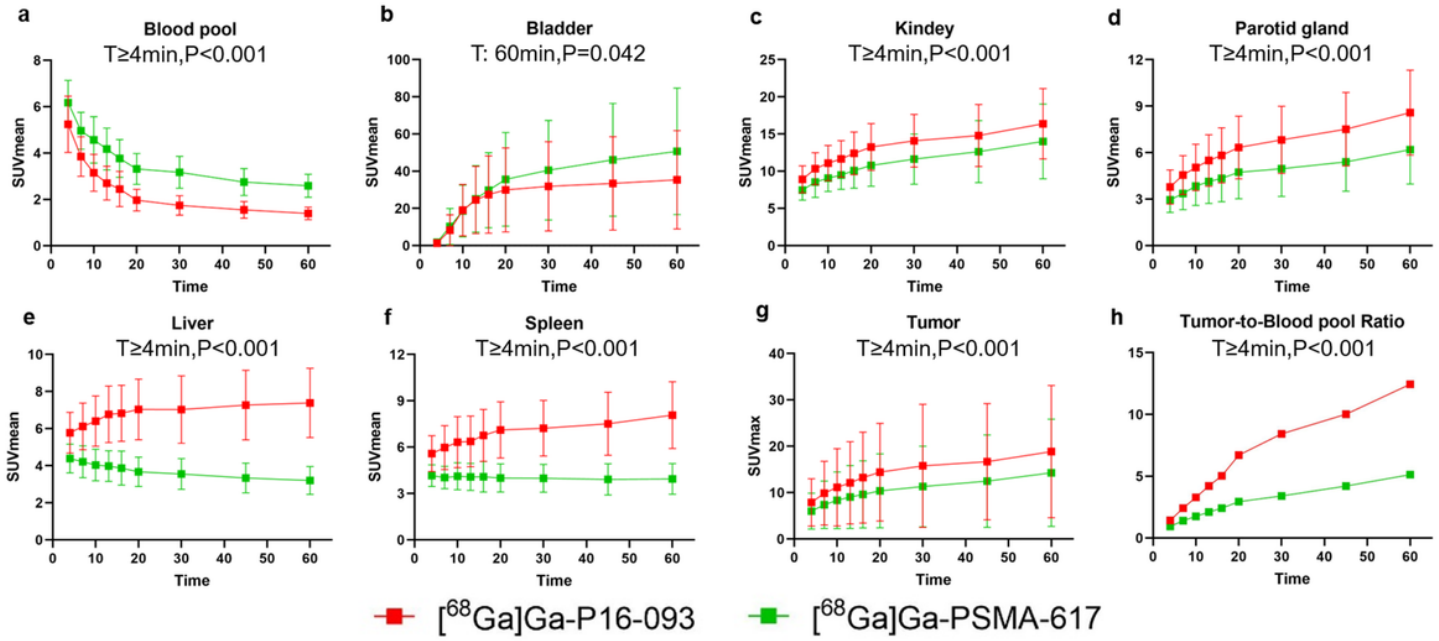


Figure 3

Time-activity curves (TACs) derived from 20 dPET/CT scans. The TACs represented the SUVmean and their SD of all evaluated VOIs based on physiologic tissues, including the blood pool (a), bladder (b), kidney (c), parotid gland (d), liver (e) and spleen (f), as well as the SUVmax and their SD of evaluated VOIs corresponding to the PCa-associated lesions (g). The curves demonstrated statistically less blood pool, bladder retention, higher tumor uptake and TBR (h) on [68Ga]Ga-P16-093 PET/CT. Besides, higher [68Ga]Ga-P16-093 uptakes were also shown in the kidney, parotid gland, liver and spleen.

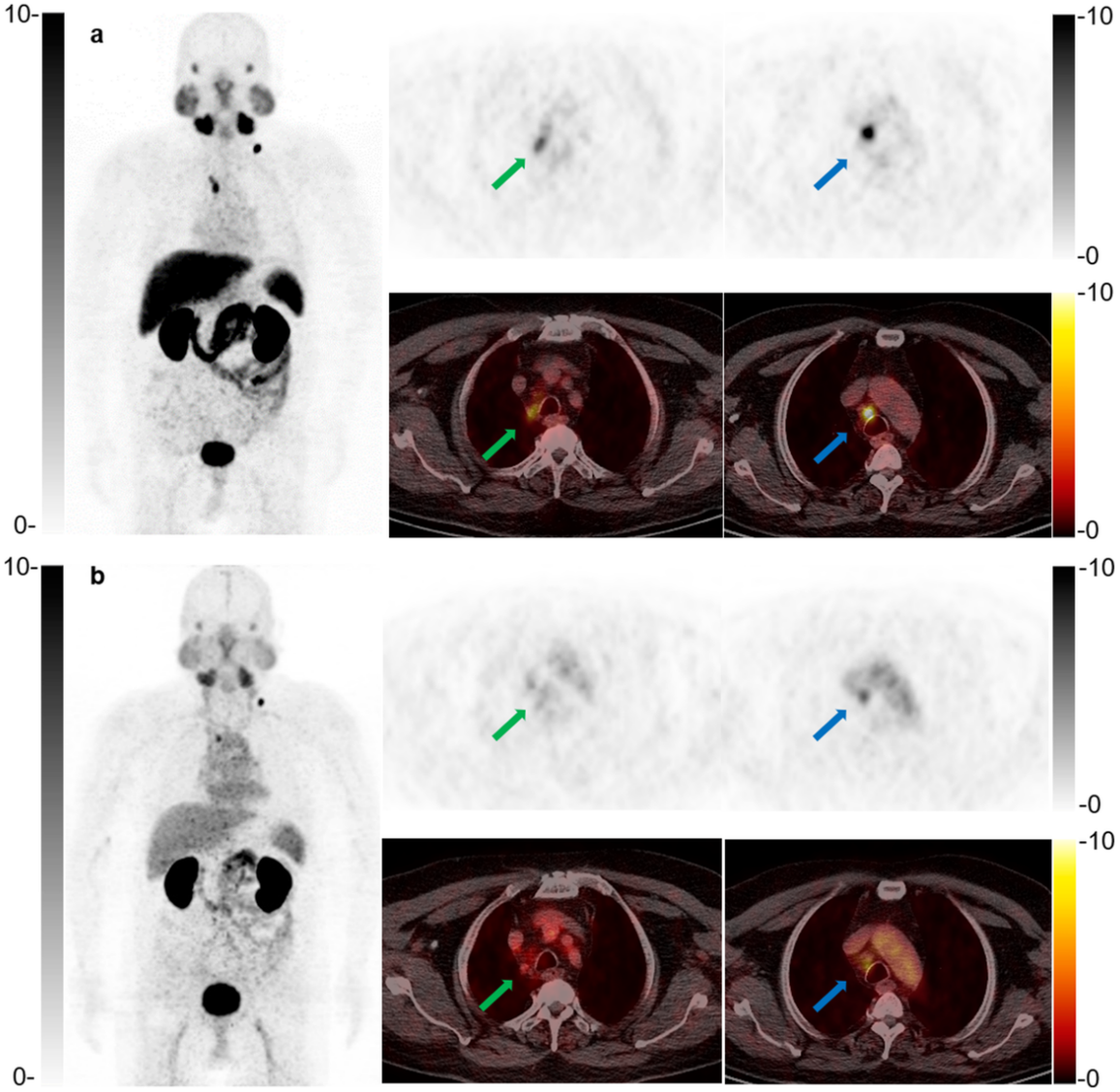


**Figure 4**

A 69-year-old PCa patient with BCR (PSA 1.17ng/ml). Whole-body MIP image as well as axial [68Ga]Ga-P16-093 PET/CT (a) showed increased tracer uptakes of lymph nodes in mediastinal 2R region (green arrow, SUVmax 7.2) and 4R region (blue arrow, SUVmax 12.1), which was ambiguous for lymph node in mediastinal 2R region (green arrow, SUVmax 2.9) on [68Ga]Ga-PSMA-617 PET/CT (b) due to higher radiotracer accumulation in the mediastinum and the blood pool, and tracer accumulation of lymph node in mediastinal 4R region was distinct (blue arrow, SUVmax 7.8).

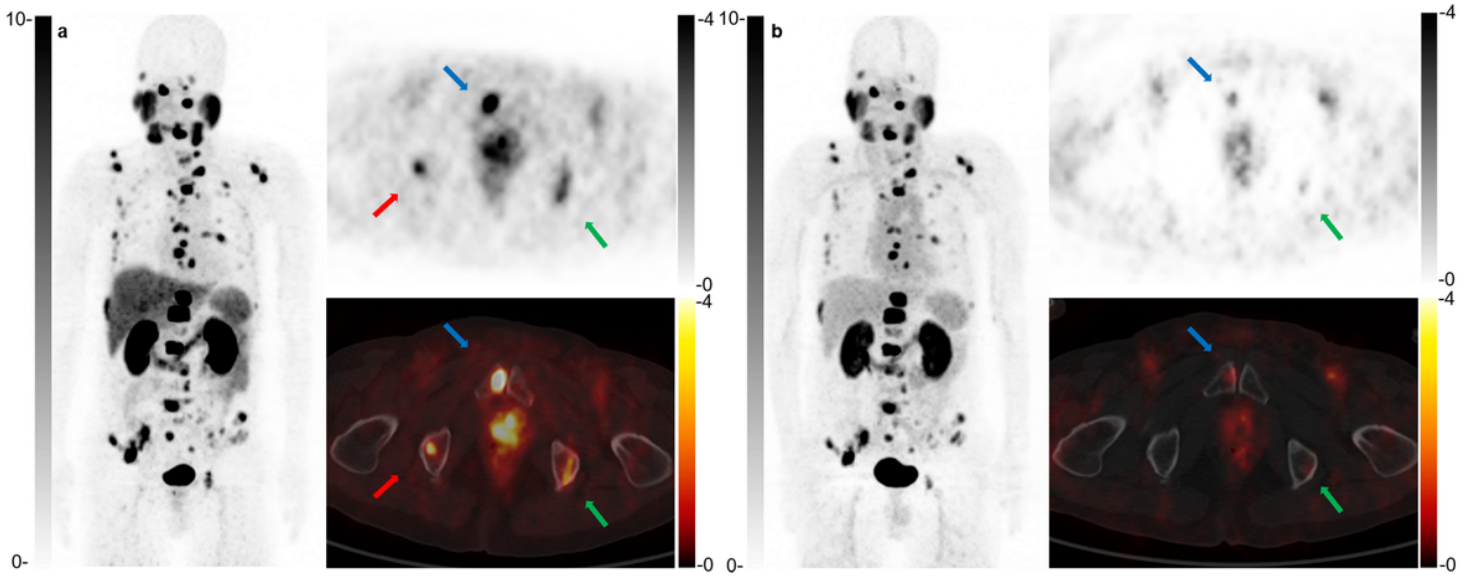


**Figure 5**

A 66-year-old PCa patient with mCRPC (PSA 52.00 ng/ml). [68Ga]Ga-P16-093 PET/CT (a) showed distinctive three PSMA-avid lesions of the right pubis and bilateral ischia (blue arrow, SUVmax 7.6 for the right pubis lesion), but only the right pubis lesion and left ischium lesion (blue arrow, SUVmax 1.5 for the right pubis lesion) were moderately detected on [68Ga]Ga-PSMA-617 PET/CT (b).