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ORIGINAL ARTICLE

Performance of ^{18}F-fluciclovine PET/MR in the evaluation of osseous metastases from castration-resistant prostate cancer

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Abstract

Purpose ^{18}F-Fluciclovine is indicated for evaluation of suspected prostate cancer (PCa) biochemical recurrence. There are few studies investigating fluciclovine with PET/MR and none evaluated osseous metastases. Our aim was to assess the performance of ^{18}F-fluciclovine PET/MR (fluciclovine-PET/MR) for detecting osseous metastases in patients with castration-resistant prostate cancer (CRPC). We also investigated possible correlations between SUVmax and ADCmean.

Methods We evaluated 8 patients with CRPC metastatic to bones, some before and some after radium therapy, who underwent 13 fluciclovine-PET/MR studies. We analyzed the performance of radionuclide bone scan (RBS), MR alone, fluciclovine-PET alone, and fluciclovine-PET/MR in detecting osseous metastases. Lesion size, characteristics (early sclerotic, late sclerotic, mixed, lytic), SUVmax, and ADCmean were assessed. The reference standard was a combination of clinical information and correlation with both prior and follow-up imaging.

Results Of 347 metastatic bony lesions in 13 studies, 238/347 (68%) were detected by fluciclovine-PET alone, 286/347 (82%) by RBS, 344/347 (99%) by MR alone, and 347/347 (100%) by fluciclovine-PET/MR. Fluciclovine-PET/MR and MR had the best performance ($p < 0.001$). There was no statistically significant difference between fluciclovine-PET/MR and MR alone ($p = 0.25$). Fluciclovine-PET had a lower detection rate especially with late sclerotic lesions ($p < 0.001$). There was a moderate inverse correlation between lesion SUVmax and ADCmean ($r = -0.49$; $p < 0.001$).

Conclusions This study suggests that fluciclovine-PET/MR and MR have high sensitivity for detecting osseous metastases in CRPC. Fluciclovine-PET alone underperformed in detecting late sclerotic lesions. The inverse correlation between SUVmax and ADCmean suggests a possible relationship between tumor metabolism and cellularity.

Keywords PET/MR · Fluciclovine · Prostate cancer · Osseous metastases

Introduction

Prostate cancer (PCa) is the most frequently diagnosed cancer and the second leading cause of cancer-related mortality in men [1]. When PCa progresses despite first-line androgen deprivation therapy (e.g., GnRH agonist), it is termed "castration-resistant prostate cancer (CRPC)." Bones are the most common site for metastases in

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CRPC and can cause pain, fractures, impaired quality of life, and death [2].

Currently, radionuclide bone scan (RBS) is the most commonly utilized imaging modality to detect osseous metastases in PCa, despite suboptimal sensitivity and specificity (79% and 82% respectively) [3, 4]. Given suboptimal performance characteristics of standard-of-care imaging, many positron emission tomography (PET) radiopharmaceuticals have been evaluated for this purpose. Among the specific PET tracers for PCa, one of the most used worldwide is the prostate-specific membrane antigen (PSMA) labeled with gallium-68 (^{68}Ga-PSMA). PSMA is a trans-membrane protein expressed on dysplastic prostate cells and its expression is increased in prostate cancer cells compared with normal cells [5]. In the USA, the most used prostate-specific tracer available is the ^{18}F-fluorocyclobutane-1-carboxylic acid (^{18}F-FACBC or ^{18}F-fluciclovine), which is a synthetic amino acid analog approved by the FDA for the evaluation of biochemical PCa recurrence, with increased uptake in several neoplasms in which amino acid transport and metabolism are upregulated [6]. Most researches with both tracers, ^{68}Ga-PSMA and ^{18}F-fluciclovine, have focused on PET/CT [7, 8].

PET combined with magnetic resonance (PET/MR) imaging has been recently approved for clinical usage, allowing for synchronous acquisition of PET and MR data from the same body region. The combination of high PET sensitivity and superior anatomical detail and functional information provided by MR could result in better diagnostic performance than other imaging modalities, including stand-alone PET and MR. Moreover, PET/MR allows concomitant measurement of several quantitative biomarkers including standard uptake value (SUV) from PET, which gives an estimate of metabolic activity, and the apparent diffusion coefficient (ADC) from MR, which is correlated with cellular density. SUV has been extensively studied with other radiopharmaceuticals, especially fluorodeoxyglucose (FDG), where it bears important implications regarding prognosis, treatment planning, and response evaluation [9].

To the best of our knowledge, this is the first study specifically evaluating ^{18}F-fluciclovine PET/MR (fluciclovine-PET/MR) in detecting osseous metastases in CRPC. The main aim of our study was to assess the performance of fluciclovine-PET/MR for detecting osseous metastases in CRPC. We also explored possible correlations between SUVmax and ADCmean in these lesions.

Methods

We prospectively evaluated the performance of fluciclovine-PET/MR in men affected by bone metastatic CRPC at our institution. This study was approved by our local Institutional Review Board (Dana Farber/Harvard Cancer Center IRB, protocol 14-375). All participants provided written informed consent.

Patient selection

We included men with CRPC metastatic to the bones who were being considered for treatment or recently treated with standard-of-care radium-223 therapy. Each participant underwent fluciclovine-PET/MR and RBS. All participants underwent fluciclovine-PET/MR and RBS between March 2017 and January 2019.

Fluciclovine-PET/MR acquisition

Three hundred seventy megabecquerel (10 mCi) of ^{18}F-fluciclovine was injected while the patients were already in the PET/MR gantry (Biograph mMR, Siemens Healthcare, Erlangen, Germany). Imaging acquisition was performed from the upper thighs to the base of the neck; three or four 12-channel body coils, depending on the height of the patients, were combined using total imaging matrix technology to form a single multichannel whole-body coil to encompass the area of interest.

PET image acquisition lasted 3 min/bed position and the protocol included early acquisition sequences, starting 5 min after injection, and late acquisition sequences starting at 20 min. WB attenuation correction maps were obtained both during early and late acquisitions with a FDA-approved Dixon-based segmentation method.

WB coronal high-resolution T1-weighted two-point Dixon images were obtained during the early acquisition; WB axial diffusion-weighted (DWI) and WB coronal short-time inversion recovery (STIR) images were acquired during the late acquisition. For the entire fluciclovine-PET/MR exam, acquisition time was around 60 min with the early phase completed within 20 min from injection.

Radionuclide bone scan

All patients had a technetium-99m (^{99m}Tc) methylene diphosphonate radionuclide bone scan (RBS) within a mean of 18.6 days (range 0–43 days) from the fluciclovine-PET/MR. One patient had a RBS performed before a same-day fluciclovine-PET/MR.

Imaging analysis

A dedicated workstation (Syngo.via; Siemens Healthcare, Erlangen, Germany) was used for fusion, analysis, and evaluation of the fluciclovine-PET/MR images. A picture archiving and communication system (PACS, Impax, Agfa Healthcare, Mortsel, Belgium) and Syngo.via were used to analyze the CT, MR, and RBS images.

Fluciclovine-PET/MR images were evaluated in consensus reading by one nuclear medicine physician (with 20 years of experience) and two radiologists (with 20 and 5 years of experience).

Reference standard

Pathology was not available as reference standard. Imaging, including both prior standard-of-care imaging and follow-up standard-of-care imaging, along with clinical information, constituted our standard of reference.

Lesions were considered metastases if increased in size or intensity on follow-up images, reduced in size or intensity on follow-up studies after oncologic treatment, or were new or increased in size or in intensity compared with prior studies.

Lesion count analysis

Fluciclovine-PET/MR was analyzed in three different sets: MR alone (all sequences), fluciclovine-PET alone, fluciclovine-PET/MR together (all sequences).

Imaging sets were presented randomly at least 4 weeks apart, to reduce recall bias, and interpreted separately.

Findings were classified as suspicious for metastases or probably benign according to the following criteria:

On RBS, findings considered suspicious for metastases were focal areas of uptake with a random distribution. Areas of uptake localized around the joints or vertically distributed along the ribs were classified as probably benign.

On the fluciclovine-PET images, PET findings were analyzed according to recently published recommendations [8]; any focal uptake clearly visualized on maximum intensity projection (MIP) images was considered suspicious. Mild to moderate diffuse and homogeneous uptake in the axial skeleton was considered physiological bone marrow uptake.

On MR, a lesion was considered suspicious for metastasis if there was focal hyperintensity or a rim of hyperintensity encircling a central hypointense core on STIR images, and/or focal diffusion restriction on DWI/ADC maps, and/or focal hypointensity on T1-weighted images without further drop of signal in the out of phase images.

On fluciclovine-PET/MR, a lesion was considered suspicious for metastasis when fulfilling the above criteria for PET and/or MR.

Since some patients had innumerable lesions, we analyzed up to 50 of the most avid and/or largest lesions per exam. There was not a minimum size cutoff for this analysis.

Lesion size and characteristic analysis

The maximum diameter of each counted lesion was measured on STIR or T1-weighted images. This was performed in up to 50 lesions per study.

Lesions were characterized as early sclerotic, late sclerotic, lytic, or mixed based on the closest available CT scan. In the case a lesion was not visible on CT, then its MR features were used for such a classification:

1. Early sclerotic: ground glass sclerosis on CT or mild hypointense center surrounded by a peripheral hyperintense halo on STIR, hypointense on T1-weighted images;
2. Late sclerotic: densely sclerotic on CT or markedly hypointense with minimal or no surrounding hyperintense halo on STIR, hypointense on T1-weighted images;
3. Lytic: lytic on CT or markedly hyperintense on STIR, hypointense on T1-weighted images;
4. Mixed (lytic/sclerotic): heterogeneous lesions with mixed features of sclerotic and lytic lesions from above criteria.

SUV and ADC analysis

Maximum SUV (SUVmax) and mean ADC (ADCmean) of the 15 most fluciclovine avid lesions per study, with a diameter of at least 2 cm, were measured. The 2-cm size threshold was chosen to minimize partial volume effect when measuring the ADC. A volume of interest (VOI) was drawn on the PET images including the entire lesion in order to automatically calculate the SUVmax. A region of interest (ROI) was drawn on the 2D ADC maps including at least three-quarters of each lesion in order to calculate the ADCmean.

Statistical analysis

For statistical analysis, the following tests were used:

The detection rate of fluciclovine-PET/MR, MR alone, fluciclovine-PET alone, and RBS was assessed using McNemar's test with continuity correction. Pearson's chi-square test with Yates' continuity correction was used to test for effect of lesion characteristics on detection rate. The logistic regression test was used to test for effect of lesion size. Pearson's correlations were calculated at the level of individual lesions as well as averaged over subjects to correlate SUVmax and ADCmean. For all analysis, we performed a lesion-based analysis and a p value of 0.05 was chosen for statistical significance.

Results

Patients

Thirteen studies from 8 male patients with CRPC metastatic to the bones were included. All patients underwent fluciclovine-PET/MR between March 2017 and January 2019. Five patients underwent two studies at different time points, 1 to

2 months apart (mean = 1.8 months); four of these patients underwent systemic oncologic treatment with standard-of-care radium-223 between the two time points (range 6–29 days before the second PET/MR, average 21.75 days, standard deviation ± 10.6), and one patient had the second PET/MR 5 days before radium-223 therapy.

The mean age was 74.4 years (range 62–88 years) and mean PSA level was 62.3 ng/mL (range 0.9–207.4 ng/mL) (Table 1).

Prior imaging, in the form of CT plus RBS plus MR, was available as standard of reference for 8/13 studies, and in the form of CT plus RBS for 5/13. Follow-up imaging was represented by MR only in 2/13, RBS plus CT plus MR in 4/13, RBS plus CT in 5/13, and MR plus RBS in 1/13. In one study, since no follow-up imaging was available, we had to rely only on prior imaging as standard of reference.

Lesion count analysis

A total of 347 metastatic lesions were counted on these 13 studies. Six out of these 13 studies (46%) had less than 5 lesions; 7/13 studies (54%) had 26 to 50 lesions.

Fluciclovine-PET alone detected 238/347 lesions (68%), RBS detected 286/347 (82%), MR alone detected 344/347 (99%), and fluciclovine-PET/MR detected 347/347 (100%). False negative rates were 32% for fluciclovine-PET alone, 18% for RBS, 1% for MR, and none for fluciclovine-PET/MR. Fluciclovine-PET alone had the lowest detection rate compared with all the other modalities (fluciclovine-PET/MR, MR alone, and RBS) ($p < 0.001$). Fluciclovine-PET/MR and MR alone had the best performance without a significant statistical difference between them ($p = 0.25$). Table 1 summarizes the lesion count results in each study. Figure 1 shows metastases to the pelvic bones detected with all imaging modalities.

In 7/13 studies (54%), fluciclovine-PET alone detected fewer lesions than the other modalities (cases 1, 5, 6, 7, 8, 10, and 11); among these studies, in 3/13 (23%), fluciclovine-PET alone did not detect any lesion (cases 5, 10, and 11). In 4/13 (31%), the number of lesions was the same on all imaging (fluciclovine-PET alone, MR alone, fluciclovine-PET/MR, and RBS). In 2/13 studies (15%), from the same patient (cases 12 and 13), fluciclovine-PET alone showed 3 lesions not visible on MR due to spinal metallic hardware leading to ferromagnetic artifacts that made the MR interpretation difficult. PET alone analysis in these subjects was made on the non-attenuated corrected images in order to avoid artifacts introduced by the metallic devices.

PET/MR did not yield any false positive results; on the other hand, RBS mis-interpreted post traumatic changes in a rib as metastasis (case 5). This case was correctly interpreted by the other modalities.

On PET images, a physiological diffuse and quite homogeneous bone marrow uptake, more evident in the spine, was found in the majority of patients (8/13, 61%) (Fig. 2).

Table 1 Patient data and lesion count results in each study

Cases no.	Clinical characteristics		Number of osseous lesions				
Fluciclovine-PET/MR reading sets							
	Age	PSA	MR alone	Fluciclovine-PET alone	Fluciclovine-PET/MR	RBS	Total osseous metastases
1	78	9.53	26	8	26	14	26
2	64	9.5	4	4	4	4	4
3	69	59.9	50	50	50	50	50
4		56.32	50	50	50	50	50
5	84	207.4	3	0	3	2 (1 FN)	3
6	62	89.52	47	12	47	24	47
7		124.3	50	25	50	35	50
8	88	45.1	50	32	50	50	50
9		174.1	50	50	50	50	50
10	80	1.08	4	0	4	3	4
11		0.9	4	0	4	3	4
12	70	15.2	2	3	4	1	4
13		16.68	4	4	5	1	5
Total lesions detected			344 (99%)	238 (68%)	347 (100%)	286 (82%)	347
False negative			3 (1%)	109 (32%)	0 (0%)	61 (18%)	

RBS radionuclide bone scintigraphy, *FN* false negative

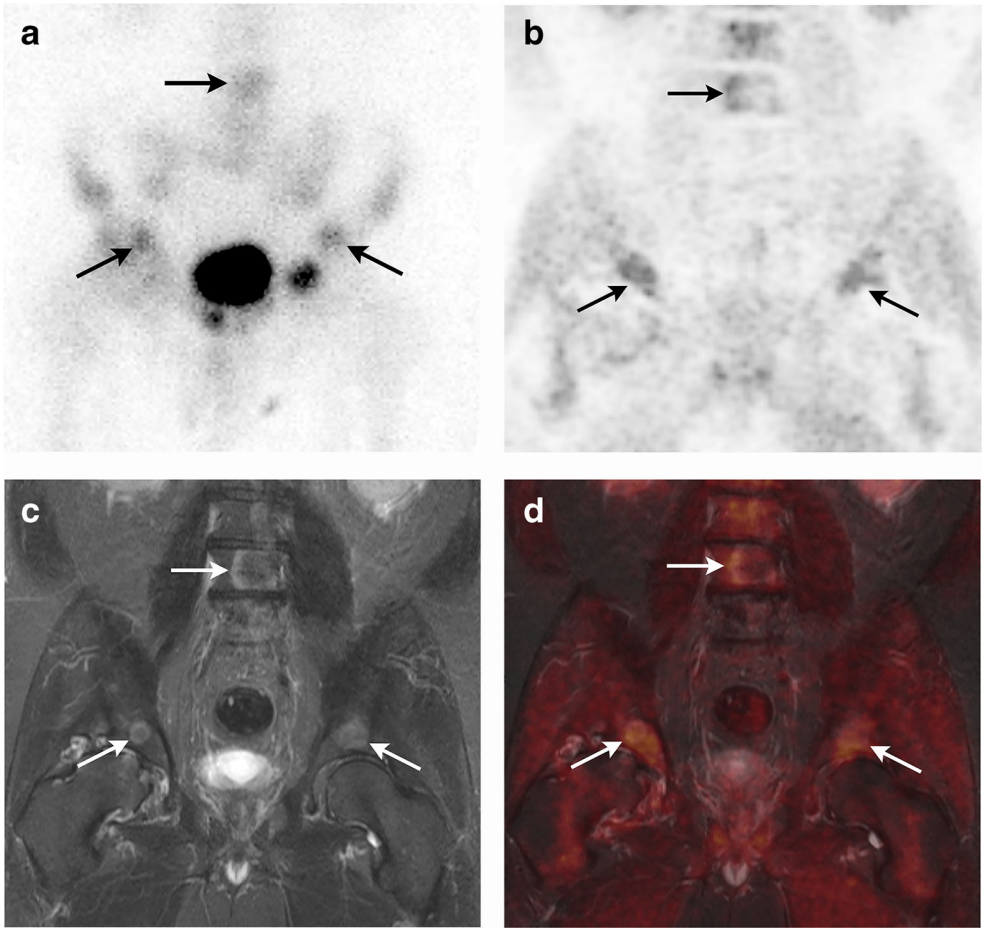

Fig. 1 A 62-year-old man, PSA = 89.52 ng/mL (case 6). RBS (**a**), fluciclovine-PET (**b**), STIR from MR (**c**), and fluciclovine-PET/MR (**d**). Metastases (arrows) to the pelvic bones detected with all imaging modalities. Notice how the fluciclovine-PET uptake is mild in comparison with uptake on RBS and clarity of lesion visualization on MR

Lesion characteristic analysis

Imaging characteristics of 344/347 lesions were analyzed. This was impossible to perform in 3/347 lesions that were visible only on fluciclovine-PET but invisible on MR and on most recent CT, due to artifacts caused by metallic spinal fixation hardware.

Mean lesion size was 22.4 mm (range 6–86 mm) and the lesions were characterized as follows: 187 early sclerotic

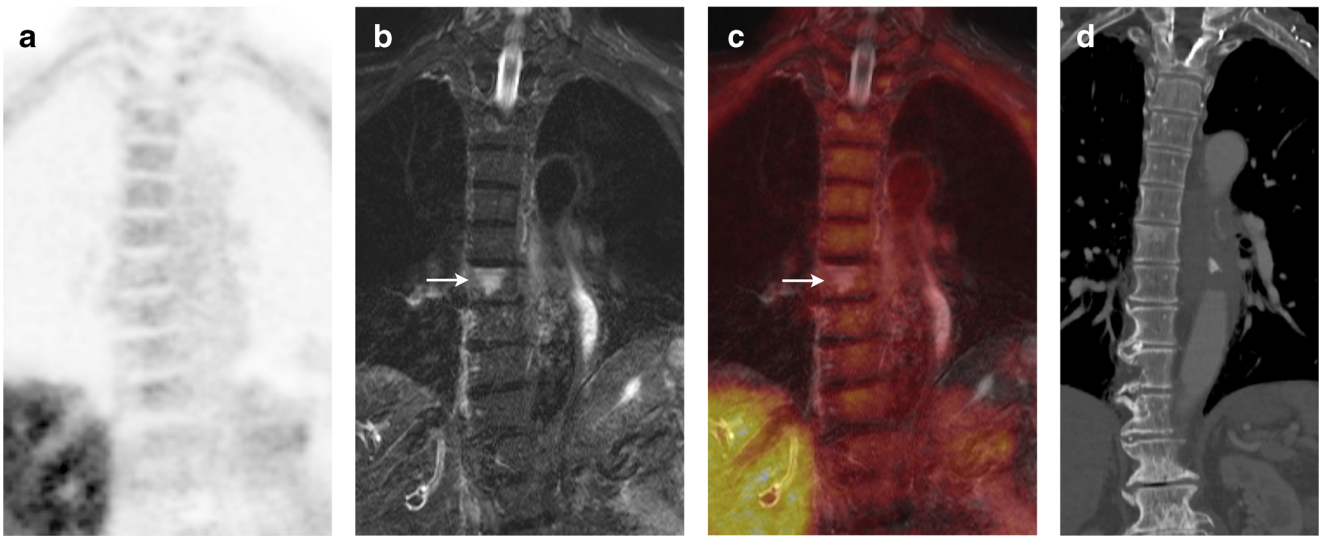

Fig. 2 Fluciclovine-PET/MR physiological uptake throughout the bone marrow may mask detection of metastases. Fluciclovine-PET (**a**), STIR from MR (**b**), fluciclovine-PET/MR (**c**), and corresponding CT (**d**). Diffuse physiologic bone marrow fluciclovine uptake as seen in (**a**) may reduce the visibility of osseous metastases (arrow in (**b**))

(54%); 112 late sclerotic (33%); 34 mixed (10%); and 11 lytic (3%).

The detection rate of fluciclovine-PET alone according to lesion characteristics was 163/187 (87%) for early sclerotic; 25/112 (22%) for late sclerotic; 34/34 (100%) for mixed; and 10/11 (91%) for lytic lesions. The lesion detection in the late sclerotic subgroup was significantly lower than that of the other subgroups ($p < 0.001$) (Fig. 3). The best detection rate was seen in the lytic and mixed subgroups, and this difference in performance, when compared with the late sclerotic subgroup, was statistically significant ($p < 0.001$). It did not reach statistical significance against the early sclerotic subgroup ($p = 0.055$).

The detection rate of RBS in relation to lesion subgroups was as follows: 172/187 (92%) early sclerotic; 71/112 (63%) late sclerotic; 34/34 (100%) mixed; and 10/11 (91%) lytic. The worst performance of RBS also occurred in the late sclerotic lesions and this was statistically significant compared with other lesions ($p < 0.001$). When comparing the other three lesion types, early sclerotic, mixed, and lytic, the differences in detection rates were not statistically significant ($p = 0.21$).

RBS detected significantly more lesions than fluciclovine-PET alone especially in the late sclerotic (63% vs 21%, $p < 0.001$) and early sclerotic subgroups (92% vs 87%, $p = 0.04$). There was no statistically significant difference in detection rate of lytic and mixed lesions between fluciclovine-PET alone and RBS.

When possible influence of lesion size on detectability was explored, lesion size did not influence the performance of fluciclovine-PET alone and RBS ($p = 0.26$ and $p = 0.06$, respectively).

However, when size and characteristics of metastases were analyzed together, size was found to influence the detection of sclerotic lesions:

- Fluciclovine-PET alone: for late sclerotic lesions, the bigger the lesion, the lower the detection rate; meanwhile for early sclerotic lesions, the bigger the lesion, the higher the detection rate ($p < 0.001$);
- RBS: the bigger the lesion, the higher the detection rate for both late sclerotic and early sclerotic lesions ($p = 0.002$).

The size versus characteristics analysis was not possible for fluciclovine-PET/MR and MR alone, as fluciclovine-PET/MR detected all lesions and MR detected almost all lesions.

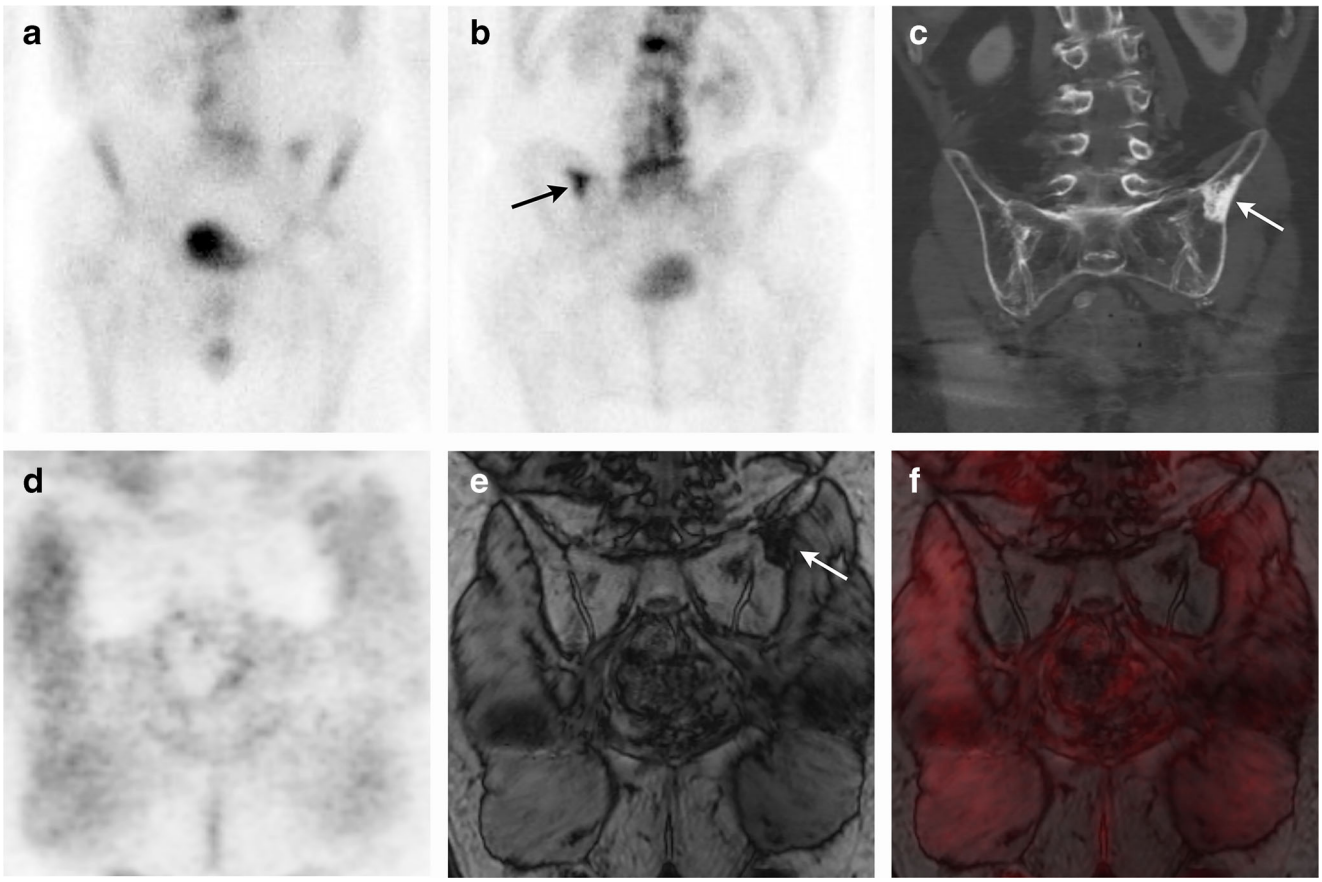

Fig. 3 An 84-year-old male PSA = 207.4 ng/mL (case 5). Fluciclovine-PET (**a**), T1w from MR (**b**), fluciclovine-PET/MR (**c**), and RBS (**d**). A late sclerotic bony metastasis (arrow) in the left iliac wing is not appreciated on fluciclovine-PET but detected by MR, fluciclovine-PET/MR, and RBS

Similarly, this analysis was not possible to be performed for the mixed and lytic lesions on fluciclovine-PET alone and RBS since these modalities detected almost all these lesions.

SUVmax and ADCmean analysis

Forty-eight lesions met the criteria for the quantitative SUVmax and ADCmean analysis. Mean lesion size was 3.23 ± 1.03 cm (range 2.01–6.28 cm); mean SUVmax was 5.09 (SD ± 1.91), and mean ADCmean was 804.22 × 10^{-3} mm^2/s (SD ± 250.1).

Pearson's correlation coefficient yielded a moderate inverse correlation between SUVmax and ADCmean ($r = -0.49$) that was statistically significant ($p < 0.001$). The analysis was also performed taking into account the correlation among subjects and the result did not change ($r = -0.51$). Figure 4 displays the correlation scatter plot.

Discussion

To the best of our knowledge, this is the first study to analyze the performance of fluciclovine-PET/MR for the detection of bone metastases in osseous metastatic CRPC. We demonstrated that fluciclovine-PET/MR had excellent performance for osseous metastasis detection in patients with CRPC. Fluciclovine-PET/MR performed better than fluciclovine-PET alone and RBS but was equivalent to MR alone.

In the settings of bone metastases from PCa, ^{68}Ga-PSMA and ^{18}F-fluoride have shown the best performances, and might outperform whole-body MR [3, 10, 11]. In a meta-analysis that included 24 studies, PSMA-PET/CT revealed a pooled sensitivity of 0.97 versus 0.87, 0.96, 0.91, and 0.86 for choline-PET/CT, fluoride-PET/CT, MR, and RBS, respectively, while the pooled specificity values were 1.00, 0.99, 0.97, 0.96, and 0.95, respectively [10].

There are very few studies evaluating fluciclovine-PET/MR in PCa patients in any clinical setting. Most have focused on primary cancer detection [12, 13] or lymph node staging [14]. Fluciclovine-PET was previously demonstrated to add important information to MR analysis by improving primary detection and characterization of high-risk PCa in one study [12] but failed to outperform MR in primary lesion detection in another study [13]. For lymph node staging, fluciclovine-PET/MR had a high specificity but low sensitivity [14]. On the other hand, PET/MR with ^{68}Ga-PSMA was studied in the setting of bone metastases in one study, comparing PET/MR with PET/CT and showing an equivalent accuracy [15]. In other studies, ^{68}Ga-PSMA PET/MR was able to detect bone metastases even at low serum prostate-specific antigen levels (PSA < 0.2 ng/mL) [16] and was able to define four bone metastases which were indeterminate on PET/CT [17].

In our study, fluciclovine-PET alone showed an overall 32% false negative rate and underperformed particularly in late sclerotic lesions (21%). There are no published dedicated clinical studies performed to assess skeletal lesions with fluciclovine-PET [18]. However, in a review, the authors

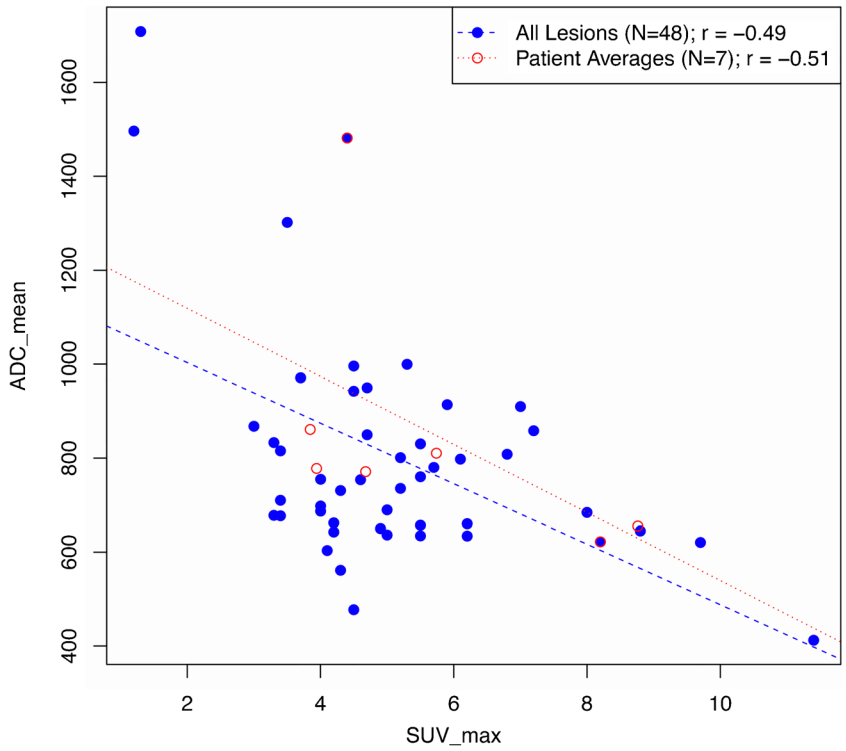

Fig. 4 Scatter plot comparing SUVmax vs ADCmean ($n = 48$ lesions)

comment that, in their practical experience, fluciclovine demonstrates intense uptake in lytic prostate cancer lesions, moderate [15] uptake within mixed lesions, and may not accumulate in densely sclerotic lesions [6]. One recent pre-clinical study reported thematically similar findings for fluciclovine in bone metastases from PCa using rat models. In that study, fluciclovine accumulated in lytic and early-stage sclerotic lesions and only vaguely accumulated in mature osteoblastic lesions [19]. This is in agreement with our clinical results. Moreover, we also observed that in late sclerotic lesions, the bigger the lesion, the lower the detection rate. We hypothesize that interspersion of PCa cells in a large volume of sclerosis might have made the uptake subtler and/or that the dense sclerosis might have reduced perfusion and access to fluciclovine. In fact, densely sclerotic lesions have fewer cells and extensive calcification [19]. In agreement with our data, a study with ^{68}Ga-PSMA in PCa patients observed a reduced SUVmax in osteoblastic lesions compared with lytic lesions and this difference was statistically significant [20].

Another factor that might contribute to the reduced detection of late osteoblastic lesions is the high incidence (61%) of diffuse, almost homogeneous physiologic fluciclovine uptake in the bone marrow. This background uptake may be of similar magnitude as the low fluciclovine uptake of sclerotic lesions and therefore mask their detection. This physiological bone marrow uptake was reported in a multicenter trial that recruited 611 patients [6]. The authors mentioned that this physiological uptake can be moderate and somewhat heterogeneous or patchy, and might make the evaluation of bone marrow metastases challenging. This uptake might have been observed more frequently in our patient group that included only CRPC who had undergone and failed previous systemic therapies. In comparison, we observed a higher overall sensitivity of RBS for osseous metastases compared with fluciclovine PET. We believe high sensitivity of RBS for sclerotic osseous lesions is explained by increase in bone turnover at the site of active and treated osseous metastases, where, as mentioned above, fluciclovine-PET inherently has low sensitivity due to scant tumor cellularity and high background bone marrow uptake. This observation reinforces the importance of interpreting the fluciclovine-PET images along with the corresponding MR or CT anatomical images.

We observed a significant moderate inverse correlation between SUVmax and ADCmean. An inverse correlation between SUV and ADC was first observed with ^{18}F-FDG in other tumors, such as rectal cancer [21]. In PCa specifically, this correlation was also demonstrated with ^{18}F-choline, which targets PCa cells that have increased phosphorylcholine levels and elevated turnover of phosphatidylcholine [22]. The authors analyzed 32 osseous metastases and found a moderate inverse correlation between SUVmax and ADCmean during ^{18}F-choline PET/MR scans. Finding a similar inverse correlation between SUVmax and ADCmean in our study, using a different radiopharmaceutical that targets amino acid metabolism instead of membrane turnover (fluciclovine instead of choline), further suggests the possibility of an association between metabolic cellular activity and tumor cellularity in bone metastases from PCa. SUVmax has been extensively studied with ^{18}F-FDG and it bears important implications regarding prognosis, treatment planning, and response evaluation [9]. ADC is a functional parameter from MR that also has clinical implications such as potentially discriminating aggressive from non-clinically significant untreated prostatic cancers [23]; moreover, it has been shown to be capable of predicting treatment response in other tumors [24]. The real value of SUVmax with fluciclovine in PCa has not yet been explored and its potential management implications are unknown.

There are several notable limitations of our study. First, we used the FDA-approved Dixon-based segmentation method to account for attenuation correction in PET. The relatively high attenuation of osseous structures is ignored with this approach, potentially leading to under-estimation of PET data, as compared with PET/CT [25]. One study analyzed SUV values obtained by same-day prostate-specific membrane antigen (^{68}Ga-PSMA) PET/CT and PET/MR and showed a linear correlation between SUVmax values from PET/CT and PET/MR. However, the values from PET/MR were on average 20% lower than those from PET/CT, likely due to the differences in attenuation correction methods [26]. It is likely that similar attenuation correction issues with SUVmax underestimation affected our study. Second, in our preliminary study, our patient sample size was low ($n = 8$ patients with 13 studies) and featured exclusively men with CRPC metastatic to bone but without known visceral or bulky nodal disease. Importantly, our lesion sample size ($n = 347$ lesions) was adequate. Third, the performance of fluciclovine-PET alone might have been detrimentally affected by the small size of some of the lesions. However, this is a known limitation of PET, not restricted to the specific tracer we used or the population we recruited. Finally, our study does not feature non-imaging gold-standard assessment (e.g., biopsy pathology) since it would have been impossible and non-ethical to biopsy all the lesions. Instead, we used consolidated and clinically accepted imaging criteria.

We recruited a specific population composed exclusively of men with CRPC metastatic to bones who had progressed despite first-line androgen deprivation therapy. More specifically, all patients were receiving ongoing androgen deprivation therapy with a GnRH agonist at the time of the PET/MR. All of them had received one prior secondary hormonal manipulation with either (1) the antiandrogen enzalutamide or (2) the androgen biosynthesis inhibitor abiraterone with prednisone.

This might have selected a specific cancer biology that stands in contrast to patients who have not been treated with systemic therapy. Our results therefore may not be

generalizable to all patients with PCa. Moreover, although the study readers were not aware of the number and location of the osseous metastases, they were aware that all patients had osseous metastases.

In conclusion, the present study suggests that fluciclovine-PET/MR and MR alone have a high sensitivity in detecting osseous metastases from CRPC. Fluciclovine-PET/MR does not seem to add significant information to MR alone for lesion detection in these patients. The underperformance of fluciclovine-PET was notably driven by difficulty detecting late sclerotic lesions. SUVmax and ADCmean obtained from fluciclovine-PET/MR had a moderate inverse correlation, suggesting a relation between tumor metabolism and tumor cellularity even in osseous metastases.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study was approved by our local Institutional Review Board and all patients signed written, informed consent.

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