Comparison of $^{68}$Ga-PSMA PET/CT with fluoride PET/CT for detection of bone metastatic disease in prostate cancer

Naresh Regula1*, Vasileios Kostaras2, Silvia Johansson2, Carlos Trampal1, Elin Lindström1,2, Mark Lubberink1,3, Victor Iyer1, Irina Velikyan1 and Jens Sörensen1,4

Abstract

Background: $^{18}$F-NaF positron emission tomography/computed tomography (fluoride PET/CT) is considered the most sensitive technique to detect bone metastasis in prostate cancer (PCa). $^{68}$Ga-PSMA-11 (PSMA) PET/CT is increasingly used for staging of PCa. This study primarily aimed to compare the diagnostic performance of fluoride PET/CT and gallium-based PSMA PET/CT in identifying bone metastasis followed by a comparison of PSMA PET/CT with contrast-enhanced CT (CE-CT) in identifying soft tissue lesions as a secondary objective.

Methods: Twenty-eight PCa patients with high suspicion of disseminated disease following curative treatment were prospectively evaluated. PET/CT examinations using fluoride and PSMA were performed. All suspicious bone lesions were counted, and the tracer uptake was measured as standardized uptake values (SUV) for both tracers. In patients with multiple findings, ten bone lesions with highest SUV$_{max}$ were selected from which identical lesions from both scans were considered for direct comparison of SUV$_{max}$. Soft tissue findings of local and lymph node lesions from CE-CT were compared with PSMA PET/CT.

Results: Both scans were negative for bone lesions in 7 patients (25%). Of 699 lesions consistent with skeletal metastasis in 21 patients on fluoride PET/CT, PSMA PET/CT identified 579 lesions (83%). In 69 identical bone lesions fluoride PET/CT showed significantly higher uptake (mean SUV$_{max}$: 73.1 ± 36.8) compared to PSMA PET/CT (34.5 ± 31.4; $p < 0.001$). Compared to CE-CT, PSMA PET/CT showed better diagnostic performance in locating local (96% vs 61%, $p = 0.004$) and lymph node (94% vs 46%, $p < 0.001$) metastasis.

Conclusion: In this prospective comparative study, PSMA PET/CT detected the majority of bone lesions that were positive on fluoride PET/CT. Further, this study indicates better diagnostic performance of PSMA PET/CT to locate soft tissue lesions compared to CE-CT.

Keywords: PSMA, Fluoride, Prostate cancer, PET/CT
Background

In prostate cancer (PCa) patients, spread to the skeletal system is common with progressive disease and approximately 80% of patients show bone metastasis in advanced stages (Herrera and Berthold 2015; Hernandez et al. 2018). Bone provides an environment rich in factors that facilitate survival and stimulate growth of metastatic tumour cells. Interaction of tumour cells with local bone matrix leads to an osseous response dominated by excess osteoblastic activity (Fornetti et al. 2018; Buenrostro et al. 2016; Wang et al. 2020; Quiroz-Munoz et al. 2019), resulting in formation of predominantly osteoblastic bone lesions most commonly located in axial skeleton.

The presence of bone metastasis has a profound impact on patient prognosis with a shorter cancer specific mortality-free survival of 24 months (Gandaglia et al. 2015). Thus, accurate early detection of bone spread throughout PCa disease progression is important to reduce potential complications and to provide optimal treatment. This challenge is further amplified by the continuous development of new imaging techniques. Through a range of imaging techniques currently available to detect bone lesions, the choice of selection for the clinicians is complex. Further, the chosen imaging modality must be able to accurately visualize the site of bone metastasis.

Bone scintigraphy (BS) with \(^{99m}\text{Tc}\)-methylene diphosphonate (MDP) is used in the diagnostic workup of PCa patients with bone lesions. BS is a relatively inexpensive technique with the advantage of broad availability and a large body of validation. On BS, MDP is incorporated into the hydroxyapatite matrix of bone in proportion to osteoblastic activity and allows the visualization of bone lesions. The tumour volume on a BS can be quantified with bone scan index (BSI) (Ulmert et al. 2012; Nakajima et al. 2017), an independent prognostic biomarker of survival (Ali et al. 2020; Wiyanto et al. 2017; Armstrong et al. 2018; Miyoshi et al. 2017). Currently, conventional BS is still considered the international standard and recommended in the guidelines for management of PCa patients with bone metastasis (Cornford et al. 2017; Mottet et al. 2017). However, BS has several limitations such as poor anatomical correlation, low sensitivity and specificity. As per European Association of Urology (EAU) guidelines BS should not be recommended in biochemical relapse patients with PSA below 10 ng/mL due to high probability for negative findings (Cornford et al. 2017; Mottet et al. 2017). Further, BS is often complemented by diagnostic grade contrast-enhanced CT (CE-CT) to rule out false positive uptake in focal degenerative bone disease, evaluate fracture risk and diagnose soft tissue metastasis.

Prior to use of \(^{99m}\text{Tc}\)-MDP, \(^{18}\text{F}\)-sodium fluoride (NaF) with a similar uptake mechanism was approved for bone imaging but the relatively short half-life and high energy of \(^{18}\text{F}\) limited its use with gamma cameras at that time. However, the growing popularity of PET/CT with improved detection prompted the resurgence of fluoride PET/CT. Further, more rapid blood clearance, high bone-to-background ratio and shorter examination time favoured the use of fluoride PET/CT over BS. Several studies have shown superiority of fluoride PET/CT compared to BS in terms of sensitivity and specificity (Beheshti et al. 2016; Langsteger et al. 2016; Cook et al. 2016).

With respect to other PET tracers, accuracy of \(^{18}\text{F}\)- or \(^{11}\text{C}\)-choline PET/CT in detection of bone lesions was identical but with higher specificity compared to fluoride PET/CT (Beheshti et al. 2016; Wondergem et al. 2013). Further, choline PET/CT showed
promising results for the early detection of bone metastasis (Beheshti et al. 2016). A systematic review from 2016 concluded that fluoride-based, acetate-based and choline-based PET/CT are the most sensitive and adequate imaging techniques (Wibmer et al. 2016). In recent years, $^{68}$Ga-PSMA-11, targeting prostate-specific membrane antigen (PSMA), was successfully introduced into clinical practice (Afshar-Oromieh et al. 2015, 2013). Results from comparative studies showed that PSMA PET/CT outperformed commonly used tracers in localizing lesions in PCa recurrent patients (Diao Wei and Lio 2019; Calais et al. 2019; Afshar-Oromieh et al. 2014).

At our institution fluoride PET/CT is commonly recommended over BS to identify bone metastasis in PCa patients at primary staging of high-risk cancer, at biochemical relapse. PSMA PET/CT was recently introduced at our hospital with the intention to use PSMA PET/CT as the primary tool for restaging of PCa. To enable PSMA PET/CT for clinical routine, both scans need to be compared and validated. Therefore, the primary aim of this study was to compare and evaluate diagnostic performance of fluoride PET/CT and PSMA PET/CT in identifying bone metastasis in PCa relapse patients. Further, comparison of PSMA PET/CT and CE-CT to detect soft tissue lesions was set as a secondary objective.

**Methods**

**Patient characteristics**

Twenty-eight patients were internally referred for PET imaging with high suspicion of widespread disease. The inclusion criteria for this prospective study were: histologically confirmed adenocarcinoma of the prostate, primary treatment followed by secondary and/or third-line therapy, and rising PSA levels with high likelihood of suspicious cancer spread prior to the PET examinations. Three patients had curative first-line therapy, five patients were given second-line treatment following first-line therapy and in 20 patients additional third-line therapy was offered prior to PET scan. In this prospective study both PSMA and fluoride PET/CT scans were acquired within 1 week in 27 subjects and in one subject the time interval was 15 days. All relevant clinical data including PSA at time of scan, PSA doubling time (PSADT), PSA velocity (PSAVel), Gleason score (GS) and age were recorded. The study was approved by the regional ethics review board (Dnr. 2017/190). Written informed consent was obtained from all research subjects.

**Production of $^{68}$Ga-PSMA-11 and $^{18}$F-NaF**

$^{68}$Ga-PSMA-11 ($^{68}$Ga-PSMA-11: $^{68}$Ga-Glu-NH-CO-NH-Lys(Ahx)-HBED-CC (ABX, Germany) was synthesized on a fully automated synthesis platform (Modular-lab, PharmTracer; Eckert & Ziegler, Eurotope, Berlin, Germany) using dedicated disposable cassettes (C4-Ga68-PSMA, Eckert & Ziegler, Germany) (Eder et al. 2012) in accordance with good manufacturing practice (GMP) guidelines. Pharmaceutical grade $^{68}$Ge/$^{68}$Ga generator (GalliaPharm, 50 mCi, Eckert&Ziegler, Germany) was used to produce gallium-68. The product was formulated in saline containing less than 10% of ethanol and sterile filtered (0.22 µm).

$^{18}$F-NaF was produced on in-house built automated system on a cyclotron (17 MeV, Scanditronix) from $\text{H}_2^{18}\text{O}$ and was trapped on the QMA-cartridge that then was washed...
with sterile water. The product was eluted with sterile physiological phosphate buffer saline and passed through a sterile 0.22 µm filter.

**PET/CT imaging protocol**

All PET/CT examinations were performed on a Discovery MI PET/CT system (GE Healthcare, Waukesha, WI) with a spatial resolution of 4 mm at the centre of the field of view and 2 min acquisition per bed position. After obtaining a CT transmission scan (140 kV, 40–80 mA) without contrast medium, emission scans from mid-thigh to skull base were acquired. PET scans were acquired 63 ± 5 min (range 59–75 min) after intravenous administration of 1.6 ± 0.5 MBq/kg (range 0.8–2.7 MBq/kg) of PSMA and 64 ± 12 min (range 47–97 min) after intravenous administration of 3.1 ± 0.3 MBq/kg (range 2.4–3.8 MBq/kg) of fluoride. A CE-CT scan was performed immediately after fluoride PET.

PSMA PET images were reconstructed using a block-sequential regularized expectation maximization (BSREM) (Q.Clear; GE Healthcare) method with β-value 900 (Lindström et al. 2019). Ordered subsets expectation maximization (OSEM) (VPFX-S; GE Healthcare) method with 3 iterations, 16 subsets and a 5-mm Gaussian post-processing filter was used for Fluoride PET image reconstruction.

**Image analysis**

Hermes Hybrid Viewer version 2.0.0 (Hermes Medical Solutions AB, Stockholm, Sweden) was used for PET/CT image analysis. All bone lesions with focal uptake above the background activity of normal bone and high suspicion for malignancy were identified on both PSMA and fluoride PET/CT scans. Degenerative bone lesions, bone fractures and other lesions with non-specific uptake were ruled out and excluded based on findings from CE-CT and inter-observer agreement. Along with bone metastases, soft tissue lesions were also counted on PSMA PET/CT. Two observers (V.I. and N.R.) independently reviewed CE-CT findings for identification of metastatic bone lesions, and one of the observers (V.I.) was completely blinded to PET information.

Tracer uptake in positive lesions was measured as standardized uptake values (SUV). SUV was defined as a ratio of radioactivity concentration in region of interest (Bq/mL) and injected dose (Bq) divided by body weight (g). Maximum and mean SUV (SUV\(\text{max}\), SUV\(\text{mean}\)) and tumour volume (TV) were calculated by placing a volume of interest (VOI) over pathological lesions having a fixed isocontour threshold (Fluoride: threshold of 50% SUV\(\text{max}\); PSMA: threshold of 40% SUV\(\text{max}\)) for all lesions. Total tumour volume (TTV = sum of TV of all lesions) and total lesion activity (TLA = sum of SUV\(\text{max}\)*TV of all lesions) were calculated for all positive bone lesions on fluoride and PSMA PET/CT. Due to higher reproducibility, SUV\(\text{max}\) was chosen for comparison. In patients having multiple bone lesions, ten bone lesions with highest SUV\(\text{max}\) were selected from which identical bone lesions on both PET scans were considered for direct comparison of SUV\(\text{max}\) among the two scans.

**Statistical analysis**

Data were presented as mean ± SD. Wilcoxon signed-rank test was used for comparison of SUV\(\text{max}\) of bone lesions. McNemar test was used to compare the number of lesions
on PSMA and fluoride PET/CT scans. Inter reader agreement on reviewing CT findings was evaluated using kappa coefficient. \(\text{SUV}_{\text{max}}\) from both PET scans were normalized using log transformation and the correlation among them was examined using univariate analysis.

**Results**

Patient characteristics are summarized in Table 1. Average age of the patients was 70.4±7.4 years (range 55–82, median 70) with a mean PSA level of 205±688 ng/mL (range 2.2–3456, median 23) at time of diagnosis. Mean PSA measured at time of the first scan was 51±93 ng/mL (range 0.7–341, median 7.6).

No adverse reactions were observed in any of the patients after administration of fluoride and PSMA. Both scans were negative for bone metastases in 7 patients (25%). However, PSMA PET/CT detected at least one positive finding of local and/or lymph node metastases in all 7 subjects. Mean PSA at time of scan in patients with positive

| Patient no. | Age (years) | ISUP GG | PSA at diagnosis | PSA at scan | Fluoride (MBq) | PSMA (MBq) | Time diff. (days) |
|-------------|-------------|---------|------------------|-------------|----------------|-------------|------------------|
| 1           | 62          | 2       | 2.2              | 29          | 264            | 182         | 7                |
| 2           | 65          | 3       | 71               | 4.4         | 256            | 142         | 2                |
| 3           | 78          | –       | 38               | 0.7         | 194            | 175         | 5                |
| 4           | 62          | 1       | 8.7              | 9.5         | 337            | 196         | 5                |
| 5           | 82          | –       | 3456             | 276         | 231            | 150         | 2                |
| 6           | 80          | 4       | 200              | 1.9         | 227            | 163         | 2                |
| 7           | 73          | 1       | 9                | 341         | 258            | 144         | 2                |
| 8           | 73          | 5       | 6.9              | 2           | 307            | 164         | 7                |
| 9           | 78          | 5       | 26               | 8           | 239            | 149         | 7                |
| 10          | 75          | 3       | 7.1              | 42          | 260            | 123         | 7                |
| 11          | 69          | 4       | 7.2              | 4           | 256            | 162         | 7                |
| 12          | 76          | 3       | 7.1              | 5.8         | 256            | 152         | 7                |
| 13          | 64          | 5       | 112              | 171         | 268            | 123         | 7                |
| 14          | 65          | 5       | 9                | 2.3         | 257            | 186         | 15               |
| 15          | 62          | 5       | 28               | 32          | 322            | 183         | 7                |
| 16          | 67          | 5       | 30               | 20          | 293            | 114         | 7                |
| 17          | 76          | 5       | 950              | 7.2         | 333            | 196         | 7                |
| 18          | 79          | 1       | 18               | 211         | 292            | 132         | 7                |
| 19          | 65          | 4       | 69               | 25          | 263            | 102         | 7                |
| 20          | 80          | 2       | 9                | 4.3         | 230            | 91          | 7                |
| 21          | 82          | 2       | 80               | 177         | 299            | 138         | 7                |
| 22          | 66          | 3       | –                | 6.7         | 295            | 175         | 7                |
| 23          | 69          | 2       | –                | 4           | 309            | 121         | 7                |
| 24          | 61          | 2       | 128              | 19          | 280            | 101         | 7                |
| 25          | 55          | 3       | 5.4              | 4.7         | 422            | 120         | 7                |
| 26          | 74          | 1       | 20               | 9.4         | 269            | 115         | 7                |
| 27          | 70          | 3       | 27               | 2.7         | 246            | 86          | 5                |
| 28          | 64          | 3       | 16               | 1.9         | 300            | 83          | 5                |
bone lesions on PET scans (64.4 ± 103.5 ng/mL) was significantly elevated, compared to patients with negative bone findings (10.0 ± 14.3 ng/mL; \( p = 0.03 \)).

Bone lesions were categorized into axial (spine, ribs, sternum and skull) and appendicular (upper and lower limbs and pelvis) skeletal lesions. The pattern of detected bone lesions is shown in Fig. 1. Both scans identified bone metastases limited to axial skeleton in five patients (18%). Patients with both axial and appendicular skeletal lesions on fluoride and PSMA PET/CT scans were 16 (57%) and 15 (54%), respectively. Positive bone lesions in appendicular skeleton alone were seen with PSMA PET/CT in one subject.

In 21 of 28 included patients, 699 lesions consistent with bone lesions were detected with fluoride PET/CT. In contrast, PSMA PET/CT identified 579 bone lesions (83% of positive fluoride PET/CT lesions, \( p < 0.001 \)) considered positive for bone metastasis. All bone lesions detected on PSMA PET/CT were also seen on fluoride PET/CT. Stratification of the patients based on number of lesions is shown in Fig. 2. Fluoride PET/CT showed less than 10 lesions in 10 patients, up to 30 lesions in three subjects and more than 30 lesions in eight patients. Whereas, PSMA PET/CT detected less than 10 lesions in 10 patients, up to 30 lesions in five subjects and more than 30 lesions in six patients. Bone metastases up to five lesions were considered as oligometastatic bone disease, fluoride PET/CT identified this in six patients whereas nine patients were detected on PSMA PET/CT. Along with bone lesions, PSMA PET/CT identified local relapse in the prostatic fossa in 7 patients and 36 positive lymph node lesions in 9 patients. Four subjects showed both positive local relapse and lymph node lesions (\( n = 15 \)).

Sixty-nine identical bone lesions in 21 patients with tracer uptake on both scans were included for a quantitative comparison. Mean \( \text{SUV}_{\text{max}} \) was significantly higher on fluoride PET/CT compared to PSMA PET/CT (73 ± 37 vs 35 ± 31; \( p < 0.001 \)). TTV from bone lesions on PSMA PET/CT strongly correlated with fluoride PET/CT TTV (\( r = 0.9, p < 0.001 \)).

![Fig. 1 Pattern of detected bone lesions on both fluoride and PSMA PET. Seven patients showed negative findings and five subjects showed positive bone metastases in the axial skeleton on both scans. Bone lesions with axial and appendicular skeleton were detected in 16 patients on fluoride PET and 15 subjects on PSMA PET. In one patient bone lesions in appendicular skeleton were detected only on PSMA PET](image-url)
Reviewing of CE-CT scans showed widespread disease (>30 lesions) in three patients and were excluded. In the remaining 25 patients, the total number of bone lesions detected by the observers in CE-CT were 120 (V.I.) and 136 (N.R.), respectively. Substantial agreement was observed between the readers (89%, Cohen’s k = 0.72) in locating bone lesions.

Findings from one blinded observer (V.I.) were considered for comparison of soft tissue lesions with PSMA PET/CT. In 12 of 28 patients, local relapse in the prostatic fossa was found, of which 11 lesions were detected with PSMA PET/CT, whereas CE-CT showed only one lesion (Fig. 3). A total of 50 lymph node lesions suspicious for cancerous lesions in 20 patients were detected using CE-CT or PSMA PET/CT (Fig. 3). Twenty-seven of 50 lymph nodes were only seen on PSMA PET/CT, whereas CE-CT alone was positive for 3 lymph nodes. Both CE-CT and PSMA PET/CT detected 20 lymph node lesions in 13 patients.

All patients had clinical follow-up and additional imaging scans at different time points were available in 21 subjects (CT in 9, fluoride PET/CT in 4, PSMA PET/CT in 4, BS in 2, WB-MRI in one and ultrasound in one subjects). Follow-up scans were not available in seven patients. Among the four subjects with PSMA PET/CT at follow-up several bone lesions with initially fluoride+/PSMA- findings were PSMA-positive at follow-up. A few instances of PSMA+/fluoride- lesions were seen in subjects with widespread bone disease, but none of these lesions could be adequately evaluated by follow-up imaging.
Discussion

This was a prospective study in PCa patients with suspected bone metastases to evaluate the performance of PSMA PET/CT compared to fluoride PET/CT. The results suggested that PSMA PET/CT was able to detect most of the bone lesions (83%) that were positive on fluoride PET/CT.

The usefulness of PSMA PET/CT has primarily been investigated with a focus on localizing biochemical relapse of PCa (Afshar-Oromieh et al. 2015, 2014; Eiber et al. 2015). A number of studies (summarized in Additional file 1: Table S1) have investigated the diagnostic accuracy of PSMA PET/CT regarding bone metastasis compared to BS (Pyka et al. 2016; Janssen et al. 2018). In addition, several studies compared the diagnostic performance of several clinically available imaging modalities in localizing bone spread in PCa patients (Dyrberg et al. 2019; Fonager et al. 2017; Jambor et al. 2016; Lengana et al. 2018; Poulsen et al. 2014; Zacho et al. 2018a, b; Zacho et al. 2020; Madsen et al. 2020; Harmon et al. 2018). These studies showed better diagnostic performance of fluoride PET/CT and PSMA PET/CT compared to other modalities such as BS, SPECT/CT, WB-MRI and choline PET/CT (see Additional file 1: Table S1 for details). Further, PSMA PET/CT showed additional value with improved specificity but with an
overlapping sensitivity in comparison to fluoride PET/CT. The results from this study on comparison of PSMA PET/CT with fluoride PET/CT were also in line with these studies.

One important finding from this study is a higher detection rate of fluoride PET/CT compared to PSMA PET/CT (699 vs 579 bone lesions). In comparison to our study, a retrospective study with a smaller dataset (n = 16) conducted by Uprimny et al. also documented higher detection rate of fluoride PET/CT (Uprimny et al. 2018). In that study, the authors observed low uptake of PSMA in osteosclerotic lesions similar to Eiber et al. (2015), stated as the possible explanation for low detection rate of bone lesions on PSMA PET/CT. In concordance, we also noticed overall low intensity of PSMA uptake in sclerotic bone lesions (Fig. 4). However, PSMA PET had an influential role with its ability to detect soft tissue PCa spread. In seven patients without bone disease on both PET scans, the presence of lymph node lesions on PSMA PET/CT changed the treatment decision (Fig. 5). We used $^{68}$Ga-PSMA-11 in this study, but the superior sensitivity of $^{18}$F-fluoride for bone lesions has been documented for other PSMA-based radiopharmaceuticals (Fourquet et al. 2021). Findings from a comparative study using all comparative imaging data for PET radiotracers in recurrent PCa confirmed the superiority of the three most commonly used PSMA radiotracers ($^{68}$Ga-PSMA-11, $^{18}$F-PSMA-1007 and $^{18}$F-DCFPyL) with a large overlap between $^{68}$Ga and $^{18}$F-labelled PSMA-radiotracers with regard to patient-level detection rates (Alberts et al. 2021). Further, a direct comparison between $^{68}$Ga-PSMA-11, $^{18}$F-PSMA-1007 in terms of clinical performance and cost efficacy showed

![Fig. 4](image-url)
non-significantly higher PET positivity rate but significantly greater rates of uncertain findings for $^{18}$F-PSMA-1007, whereas as cost efficacy analysis based on available health economic data favoured $^{68}$Ga-PSMA-11 in majority jurisdictions (three of four) (Alberts et al. 2021b). Though logistical and clinical advantages of low urinary excretion seems to favour the use of $^{18}$F-fluoride-based radiotracers over $^{68}$Ga-based PSMA-tracers, further studies are needed to advocate this with certain.

Determining the presence of oligometastatic bone lesions, the potential targets for metastatic-directed therapies are clinically relevant as they can be irradiated. In the six patients who were identified with oligometastatic bone lesions with both PSMA and fluoride PET/CT, one patient showed additional non-osseous lesions on PSMA PET/CT, altering the treatment plan. The remaining five subjects received radiation therapy. Three additional patients were identified with oligometastatic bone status on PSMA PET/CT but had more than five lesions on fluoride PET/CT. In addition to bone lesions, PSMA PET/CT also showed either local relapse or lymph node lesions in these patients which influenced the treatment management. However, this cohort is not large enough to determine the added value of PSMA PET/CT treatment decisions related to oligometastatic disease.

The choice of imaging techniques for restaging of PCa at a given centre depends on local parameters such as cost-effectiveness, accessibility and expertise. Many hospitals around the world still use BS along with an abdominal CE-CT scan as standard-of-care in the diagnostic workup. Although CE-CT has limited sensitivity (Yang et al. 2011), findings particularly of skeletal lesions from CE-CT together with bone scan findings has clinical implication in many hospitals where access to PET/CT imaging is limited. Hence, comparison of CE-CT findings with PSMA PET/CT is relevant to confirm the better diagnostic performance of the latter. Fluoride PET/CT is generally considered superior to $^{99m}$Tc-MDP-BS and $^{99m}$Tc-MDP-SPECT/CT for detection of bone metastasis (Poulsen et al. 2014; Bortot et al. 2012; Iagaru et al. 2012). In further
support, few studies evaluated the impact of fluoride PET/CT on patient prognosis (Hillner et al. 2018; Gareen et al. 2018). At our hospital, fluoride PET/CT has been recommended over BS in PCa restaging to locate early signs of bone disease and is generally performed with CE-CT to detect soft tissue lesions.

Using follow-up scanning we could show that some lesions are detected earlier with fluoride PET/CT than with PSMA PET/CT. In none of these cases did the higher sensitivity of fluoride PET/CT lead to therapy changes and the measured tumour burden was similar for both tracers. However, equivocal skeletal findings on fluoride PET/CT are relatively common and contribute to false positive cases (Fonager et al. 2017; Poulsen et al. 2014), which might require additional diagnostic procedures. In this study, we also found equivocal bones lesions on PSMA PET/CT, but the overall perception is that this is a lesser problem with PSMA than with fluoride PET/CT. In addition, PSMA PET/CT provided additional information in detecting local recurrences and lymph node metastases, thus influencing the management, as seen in 7 subjects in our current study.

Based on this study and the vast literature already published, ⁶⁸Ga-PSMA PET/CT is a highly relevant first-line imaging modality in recurrent PCa. However, fluoride PET/CT had a significantly higher detection rate for bone metastases and could be a relevant complement to PSMA PET in certain scenarios. PSMA-expression might be reduced or absent in dedifferentiated PCa and a discrepancy between PSA levels and PSMA PET findings should potentially trigger additional imaging with higher sensitivity in biochemical relapses after treatments with curative intent (McGeorge et al. 2021). PSMA PET/CT followed by fluoride PET/CE-CT might also be a relevant combination for ruling out PSMA-negative lesions before treatment with PSMA-targeted radionuclide therapies.

This study has several limitations. It was based on a small group of patients with high suspicion for widespread disease involving bone, introducing some bias. A standard reference, preferably histological reports, to confirm the discrepant findings of PET imaging is missing. However, accessing bone for biopsy collection is neither ethically nor practically possible in all lesions. Follow-up scans with optimal imaging modalities were not available in all patients.

**Conclusions**

In this prospective comparative study, fluoride PET/CT identified significantly more bone lesions compared to PSMA PET/CT. However, better diagnostic performance of PSMA PET/CT to locate soft tissue lesions compared to CE-CT favours the use of PSMA PET/CT as the more relevant molecular imaging method for restaging of PCa recurrence.

**Supplementary Information**

The online version contains supplementary material available at https://doi.org/10.1186/s41824-022-00127-4.

**Acknowledgements**

This work was supported by Swedish Cancer Society (CAN2016/835). The authors wish to express a sincere thanks to the Uppsala PET Centre staff for their dedicated efforts.
Authors’ contributions
NR, SJ, VK and JS conceptualized and designed the study. SJ and VK recruited the subjects. NR drafted the text and performed statistical analysis. NR, CT, VI and JS performed PET image analysis. ML and EL designed and validated PET reconstructions. JS supervised and financed the project. IV and JS contributed feedback during the entire writing process. All authors read and approved the final manuscript.

Funding
Open access funding provided by Uppsala University. Swedish cancer society (CAN2016/835) funded this study.

Availability of data and materials
The datasets used and/or analysed during this study are available from the corresponding author on reasonable request.

Declarations

Ethical approval and consent to participate
All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee with the principles of the 1964 Declaration of Helsinki and its later amendments. Ethical approval for this prospective study was obtained from the Regional ethical review board (Dnr. 2017/190). Informed consent was obtained from all individual participants included in the study.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Author details
1Division of Radiology and Nuclear Medicine, Department of Surgical Sciences, Uppsala University, Uppsala, Sweden. 2Division of Oncology, Department of Immunology, Genetics and Pathology, Uppsala University Hospital, Uppsala, Sweden. 3Department of Medical Physics, Uppsala University Hospital, Uppsala, Sweden. 4Department of Medical Imaging, Uppsala University Hospital, Uppsala, Sweden.

Received: 27 October 2021   Accepted: 1 February 2022

Published online: 01 March 2022

References
Afshar-Oromieh A, Malcher A, Eder M, Eisenhut M, Linhart HG, Hadaschik BA et al (2013) PET imaging with a [68Ga]gallium-labelled PSMA ligand for the diagnosis of prostate cancer: biodistribution in humans and first evaluation of tumour lesions. Eur J Nucl Med Mol Imaging 40(4):486–495
Afshar-Oromieh A, Zechmann CM, Malcher A, Eder M, Eisenhut M, Linhart HG et al (2014) Comparison of PET imaging with a [68Ga]-labelled PSMA ligand and [18F]-choline-based PET/CT for the diagnosis of recurrent prostate cancer. Eur J Nucl Med Mol Imaging 41(1):11–20
Afshar-Oromieh A, Avtzi E, Giesel FL, Holland-Letz T, Linhart HG, Eder M et al (2015) The diagnostic value of PET/CT imaging with the 68Ga-labelled PSMA ligand HBED-CC in the diagnosis of recurrent prostate cancer. Eur J Nucl Med Mol Imaging 42(2):197–209
Alberts IL, Seide SE, Mingels C, Bohn KP, Shi K, Zacho HD et al (2021a) Comparing the diagnostic performance of radiotracers in recurrent prostate cancer: a systematic review and network meta-analysis. Eur J Nucl Med Mol Imaging 48(9):2978–2989
Alberts I, Mingels C, Zacho HD, Lanz S, Schöder H, Rominger A et al. Comparing the clinical performance and cost efficacy of [68Ga]Ga-PSMA-11 and [18F]PSMA-1007 in the diagnosis of recurrent prostate cancer: a Markov chain decision analysis. Eur J Nucl Med Mol Imaging. 2021b.
Ali A, Hoyle AP, Parker CC, Brawley CD, Cook A, Amos C et al (2020) The automated bone scan index as a predictor of response to prostate radiotherapy in men with newly diagnosed metastatic prostate cancer: an exploratory analysis of STAMPEDE’s ‘M1|RT comparison’: Eur Urol Oncol 3(4):412–419
Armstrong AJ, Anand A, Edenbrandt L, Bondesson E, Bjartell A, Wildmark A et al (2018) Phase 3 assessment of the automated bone scan index as a prognostic imaging biomarker of overall survival in men with metastatic castration-resistant prostate cancer: a secondary analysis of a randomized clinical trial. JAMA Oncol 4(7):944–951
Beheshi M, Rezaee A, Geinitz H, Loidl W, Pirich C, Langsteger W (2016) Evaluation of prostate cancer bone metastases with 18F-NaF and 18F-fluorocholine PET/CT. J Nucl Med 57(Supplement 3):S55-605
Bortot DC, Amorim BJ, Oki GC, Gapski SB, Santos AO, Lima MCL et al (2012) 18F-Fluoride PET/CT is highly effective for excluding bone metastases even in patients with equivocal bone scintigraphy. Eur J Nucl Med Mol Imaging 39(11):1730–1736
Buenrostro D, Muicrone PL, Owens P, Sterling JA (2016) The bone microenvironment: a fertile soil for tumor growth. Curr Osteoporos Rep 14(4):151–158
Calais J, Ceci F, Eiber M, Hope TA, Hofman MS, Rischsperger C et al (2019) 18F-Fluciclovine PET-CT and 68Ga-PSMA-11 PET-CT in patients with early biochemical recurrence after prostatectomy: a prospective, single-centre, single-arm, comparative imaging trial. Lancet Oncol 20(9):1286–1294
Cook GJR, Azad G, Padhani AR (2016) Bone imaging in prostate cancer: the evolving roles of nuclear medicine and radiology. Clin Transl Imaging 4(8):439–447
Conford P, Bellmunt J, Bolla M, Biers E, De Santis M, Gross T et al (2017) EAU-ESTRO-SIOG guidelines on prostate cancer. Part II: treatment of relapsing, metastatic, and castration-resistant prostate cancer. Eur Urol 71(4):630–642

Diao Wei ZZ, Liao X (2019) Recent advances in prostate-specific membrane antigen–based radiopharmaceuticals. Curr Top Med Chem 19(1):33–56

Dyberg E, Hendel HW, Huynh TV, Løgager TB, Madsen C et al (2019) 68Ga-PSMA-PET/CT in comparison with 18F-fluoride–PET/CT and whole-body MRI for the detection of bone metastases in patients with prostate cancer: a prospective diagnostic accuracy study. Eur Radiol 29(3):1221–1230

Eder M, Schafer M, Bauder-Wüst U, Hull W-E, Wängler C, Mier W et al (2012) 68Ga-complex lipophilicity and the targeting property of a urea-based PSMA inhibitor for PET imaging. Biocongem Chem 23(4):688–697

Eiber M, Maurer T, Sourvatzoglou M, Beer AJ, Ruffani A, Haller B et al (2015) Evaluation of hybrid 68Ga-PSMA ligand PET/CT in 248 patients with biochemical recurrence after radical prostatectomy. J Nucl Med 56(5):668–674

Fonager RF, Zacho HD, Langkilde NC, Fledelius E, Ejlersen JA, Haarmark C et al (2017) Diagnostic test accuracy study of 18F-sodium fluoride PET/CT, 99mTc-labelled diphosphonate SPECT/CT, and planar bone scintigraphy for diagnosis of bone metastases in newly diagnosed, high-risk prostate cancer. Am J Nucl Med Mol Imaging 7(5):218–227

Fornetti J, Welm AL, Stewart SA (2018) Understanding the bone in cancer metastasis. J Bone Miner Res 33(12):2099–2113

Fourquet A, Rosenberg A, Mena E, Shih JJ, Turkbey B, Blam M et al. A comparison of 18F-DCFPyL, 18F-NaF and 18F-FDG PET/CT in a prospective cohort of men with metastatic prostate cancer. J Nucl Med. 2021:jnumed.121.262371

Gandaglia G, Karakiewicz PI, Briganti A, Passoni NM, Schiffmann J, Trudeau V et al (2015) Impact of the site of metastases on survival in patients with metastatic prostate cancer. Eur Urol 68(2):325–334

Gareen IF, Hillier BE, Hanna L, Makiniemi R, Duan F, Shields AF et al (2018) Hospice admission and survival after (18)F-fluoride PET performed for evaluation of osseous metastatic disease in the national oncologic PET registry. J Nucl Med 59(3):427–433

Harmon SA, Bergvall E, Mena E, Shih JH, Adler S, McKinney Y et al (2018) A prospective comparison of 18F-sodium fluoride PET/CT and PSMA-PET/CT in metastatic prostate cancer. J Nucl Med 59(4):1665–1671

Hernandez RK, Wade SW, Reich A, Prolli M, Liede A, Lyman GH (2018) Incidence of bone metastases in patients with solid tumors: analysis of oncology electronic medical records in the United States. BMC Cancer 18(1):44

Herrera FGTT, Berthold DR (2015) Bone cancer: Primary bone cancers and metastases, 2nd edn. Elsevier, San Diego

Hillier BE, Hanna L, Makiniemi R, Duan F, Shields AF, Subramaniam RM et al (2018) Intended versus untreated inference after (18)F-fluoride PET performed for evaluation of osseous metastatic disease in the national oncologic PET registry. J Nucl Med 59(3):421–426

Iagaru A, Mittra E, Dick DV, Gambhir SS (2012) Prospective evaluation of 99mTc MDP scintigraphy, 18F NaF PET/CT, and 18F FDG PET/CT for detection of skeletal metastases. Mol Imaging Biol 14(2):252–259

Jambor I, Kuisma A, Ramadan S, Huovinen R, Sandell M, Kajander S et al (2016) Prospective evaluation of planar bone scintigraphy, SPECT/PECT/CT, 18F-NaF PET/CT and whole body 1.5T MRI, including DWI, for the detection of bone metastases in high risk breast and prostate cancer patients: SKELETA clinical trial. Acta Oncol 55(1):39–67

Janssen JC, Meilhner S, Woythal N, Prasad V, Brenner W, Diederichs G et al. A comparison of 18F-DCFBC PET/CT and 99mTc-DPD-SPECT/CT for the detection of bone metastases in prostate cancer patients: additional value of morphologic information from low dose CT. Eur Radiol 28(2):610–619

Langsteger W, Rezaee A, Pirch C, Beheshti M (2016) 18F-NaF-PET/CT and 99mTc-MDP bone scintigraphy in the detection of bone metastases in prostate cancer. Semin Nucl Med 46(6):491–501

Lengana T, Lawal IO, Bohsomanen TG, Popoola GO, Mokoala KMG, Moshokoa E et al (2018) 68Ga-PSMA PET/CT replacing bone scan in the initial staging of skeletal metastasis in prostate cancer: a fait accompli? Clin Genitourin Cancer 16(5):392–401

Lindström E, Velikyan I, Regula N, Ahluseinalkhudhur A, Sundin A, Sörensen J et al (2019) Diagnostic test accuracy of bone scan index in men with metastatic castration-resistant prostate cancer treated with enzalutamide or abiraterone acetate. Clin Genitourin Cancer 15(4):472–478

Madsen C, Østergren P, Haarmark C (2020) The value of 68Ga-PSMA PET/CT following equivocal 18F-NaF PET/CT in prostate cancer patients. Diagnostics 10(6):352

McGeorge S, Kwok M, Jiang A, Emmett L, Pattison DA, Thomas PA et al (2021) Dual-tracer positron-emission tomography using prostate-specific membrane antigen and fluorideoxysugars for staging of prostate cancer: a systematic review. Adv Urol 2021:1544208

Miyoshi Y, Uemura K, Kawahara T, Yoneyama S, Hattori Y, Teranishi J-I et al (2017) Prognostic value of automated bone scan index in men with metastatic castration-resistant prostate cancer treated with enzalutamide or abiraterone acetate. Clin Genitourin Cancer 15(4):472–478

Mottet N, Bellmunt J, Bolla M, Biers E, Cumberbatch MG, De Santis M et al (2017) EAU-ESTRO-SIOG guidelines on prostate cancer. Part I: screening, diagnosis, and local treatment with curative intent. Eur Urol 71(4):618–629

Nakajima K, Edembrandt L, Mizikami O (2017) Bone scan index: a new biomarker of bone metastasis in patients with prostate cancer. Int J Urol 24(9):668–673

Poulsen MH, Petersen H, Hjellund-Carlsen PF, Jakobsen JS, Gerke O, Karstoft J et al (2014) Spine metastases in prostate cancer: comparison of technetium-99m-MDP whole-body bone scintigraphy, [18F]choline positron emission tomography(PET)/computed tomography (CT) and [18F]NaF PET/CT. BJU Int 114(6):818–823

Pyka T, Okamoto S, Dahlbender M, Tauber R, Retz M, Heck M et al (2016) Comparison of bone scintigraphy and 68Ga-PSMA PET for skeletal staging in prostate cancer. Eur J Nucl Med Mol Imaging 43(12):2114–2121

Quirce-Munoz M, Izadmehr S, Arumugam D, Wong B, Kirchsenbaum A, Levine AC (2019) Mechanisms of osteoblastic bone metastasis in prostate cancer: role of prostatic acid phosphatase. J Endocr Soc 3(3):655–664

Ulmt M, Kabotche R, Fox JJ, Savage C, Evans MJ, Lilja H et al (2012) A novel automated platform for quantifying the extent of skeletal tumour involvement in prostate cancer patients using the bone scan index. Eur Urol 62(1):78–84

Uprinmy C, Sviydzenka A, Fritz J, Kroiss AS, Nilica B, Decristoforo C et al (2018) Comparison of 68Ga-PSMA–11 PET/CT with [18F]NaF PET/CT in the evaluation of bone metastases in metastatic prostate cancer patients prior to radionuclide therapy. Eur J Nucl Med Mol Imaging 45(11):1873–1883
Wang M, Xia F, Wei Y, Wei X (2020) Molecular mechanisms and clinical management of cancer bone metastasis. Bone Res 8:30
Wibmer AG, Burger IA, Sala E, Hricak H, Weber WA, Vargas HA (2016) Molecular imaging of prostate cancer. Radiographics 36(1):142–159
Wiyanto J, Shintawati R, Darmawan B, Hidayat B, Kartamihardja AHS (2017) Automated bone scan index as predictors of survival in prostate cancer. World J Nucl Med 16(4):266–270
Wonderegem M, van der Zant FM, van der Ploeg T, Knol RJ (2013) A literature review of 18F-fluoride PET/CT and 18F-choline or 11C-choline PET/CT for detection of bone metastases in patients with prostate cancer. Nucl Med Commun 34(10):935–945
Yang HL, Liu T, Wang XM, Xu Y, Deng SM (2011) Diagnosis of bone metastases: a meta-analysis comparing 18FDG PET, CT, MRI and bone scintigraphy. Eur Radiol 21(12):2604–2617
Zacho HD, Nielsen JB, Dettmann K, Haberkorn U, Langkilde NC, Jensen JB et al (2018a) 68Ga-PSMA PET/CT in patients with biochemical recurrence of prostate cancer: a prospective, 2-center study. Clin Nucl Med 43(8):579–585
Zacho HD, Nielsen JB, Afshar-Oromieh A, Haberkorn U, deSouza N, De Paepe K et al (2018b) Prospective comparison of 68Ga-PSMA PET/CT, 18F-sodium fluoride PET/CT and diffusion weighted-MRI at for the detection of bone metastases in biochemically recurrent prostate cancer. Eur J Nucl Med Mol Imaging 45(11):1884–1897
Zacho HD, Ravn S, Afshar-Oromieh A, Fledelius J, Ejlersen JA, Petersen LJ (2020) Added value of 68Ga-PSMA PET/CT for the detection of bone metastases in patients with newly diagnosed prostate cancer and a previous (99m)Tc bone scintigraphy. EJNMMI Res 10(1):31

Publisher’s Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.