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Non-specific PSMA-1007 bone uptake evaluated through PSMA-11 PET, bone scan and MRI triple validation in patients with biochemical recurrence of prostate cancer

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ABSTRACT

Introduction

18F-PSMA-1007 PET is used in the management of patients with prostate cancer. However, recent reports indicate a high rate of non-specific bone uptake (NSBU) with 18F-PSMA-1007, which may lead to false positive diagnosis. NSBU have not been evaluated thoroughly. Here, we evaluate the frequency of NSBU and bone metastases separately for 18F-PSMA-1007 and 68Ga-PSMA-11 in biochemical recurrence (interindividual comparison). Additionally, we investigate NSBU seen in 18F-PSMA-1007 through follow up examinations (intraindividual comparison) using 68Ga-PSMA-11 PET, bone scintigraphy and MRI.

Methods

First, all patients (*n*=383) who had 68Ga-PSMA-11 PET between January 2020 and December 2020 and all patients (*n*=409) who had 18F-PSMA-1007 PET between January 2020 and November 2021 due to biochemical recurrence were included for an interindividual comparison of bone metastases and NSBU rate. In a second approach, we regarded all patients with NSBU in 18F-PSMA-1007, characterized by focal bone uptake with SUV_{max}>4 and PSA≤5 ng/ml, who had an additional 68Ga-PSMA-11 PET (*n*=17) (interindividual comparison). Of these, 12 patients also had bone scintigraphy and wbMRI within a 1–5-week interval. Bone uptake seen on 18F-PSMA-1007 but not on any of the other four modalities (CT, MRI (n=1), bone scan and 68Ga-PSMA-11 PET) was recorded as false positive.

Results

Patients scanned with 18F-PSMA-1007 PET had a significantly higher rate of NSBU compared with 68Ga-PSMA-11 (140 vs. 64; p<0.001); however, the rate of bone metastases was not significantly different (72 vs. 64; p=0.7). In the intraindividual comparison group, workup by CT, MRI, bone scan and 68Ga-PSMA-11 PET resulted in a positive predictive value for 18F-PSMA-1007 focal bone uptake (mean SUV_{max} 6.1±2.9) per patient and per lesion of 8.3 % and 3.6 %, respectively.

Conclusion

In patients with PSA≤5 ng/mL and SUV>4 at biochemical recurrence, most 18F-PSMA-1007 focal bone uptake are likely to be false positive and therefore due to NSBU. In case of low clinical likelihood of metastatic disease, 18F-PSMA-1007 bone uptake without morphologic surrogate should be assessed carefully with regard to localization and clinical context. However, the rate of bone metastases was not higher with 18F-PSMA-1007 in the clinical routine, indicating that experienced reporting physicians adjust for NSBU findings.

INTRODUCTION

Up to 60% of prostate cancer patients develop biochemical recurrence (BCR) after initial radiotherapy or radical prostatectomy in 10 years of follow-up (*1*). Local salvage therapy and complete metastatic ablation of oligometastatic prostate cancer may provide a curative pathway and an alternative to initiation of palliative androgen deprivation therapy (*2*). Therefore, to determine location and extent of recurrent PC is of the utmost importance for directing salvage therapy.

The recent European Association of Urology Prostate Cancer guideline recommended that, Prostate Specific Membrane Antigen (PSMA) Positron Emission Tomography (PET) should be offered to BCR patients with a persistent prostate-specific antigen (PSA) level > 0.2 ng/mL if the results will influence subsequent treatment decisions (*3*). PSMA-PET readers need proper training, as each PSMA ligand features distinct characteristics (*4*,*5*).

More recently, ^{68}Ga-labelled PSMA-ligands are increasingly replaced by 18F labeled compounds offering mostly technical and logistic advantages including lower positron energy, improved spatial resolution, longer half-life, high yield production in cyclotrons, large batch production thereby enabling long-distance distribution and potential cost savings (*4*). Moreover, 18F-PSMA-1007 exhibits blood clearance through the liver that leads to only minimal urinary excretion, yielding potential advantages for pelvic tumor assessment (*6*,*7*). However, unspecific bone uptake (UBU) on 18F- PSMA-1007 PET, reported in a considerable fraction of patients, may lead to false positive findings as metastasis; this in turn may result in over-staging, leading to inadequate therapy (*4*,*8*,*9*). However, despite large observational data, UBU have not been correlated systematically by other imaging, including 68Ga-PSMA-11 PET/CT, MRI and bone scan.

Therefore, the aim of this study was twofold. First, we evaluated the rate of unspecific bone uptake and bone metastases reported in clinical reads separately for 18F-PSMA-1007 and 68Ga-PSMA-11 PETs to estimate the relevance of UBUs (inter-individual group). Second, we present a single center experience

with 18F-PSMA-1007 UBU in 17 patients, who underwent follow up examinations to clarify the nature of the bone uptake. In those patients, we evaluated ~~[^{18}F]~~18F-PSMA-1007 UBUs intra-individually with bone scan, 68Ga-PSMA-11 PET and MRI.

MATERIAL AND METHODS

Patient Characteristics

Patient characteristics are shown in Table 1 and Supplemental Table 1. All patients were recruited at the Department of Nuclear Medicine of the University Hospital Essen. The analysis was performed retrospectively and the need for study-specific written consent was waived (Ethics approval number 22-10694-BO and 21-9865-BO). Briefly, two patient cohorts were investigated: First, the rate of unspecific bone uptake and bone metastases in all patients scanned with 68Ga-PSMA-11 in the last year prior to the introduction of 18F-PSMA-1007 was compared to the respective rates in all patients scanned with 18F-PSMA-1007 in the first year of its use in our Department (interindividual comparison group). Additionally, patients who received a 18F-PSMA-1007 and underwent 68Ga-PSMA-11 due to 18F-PSMA-1007 UBU clinical workup were included (intraindividual group).

Inclusion Criteria of the Interindividual Comparison Group

All patients who received a 68Ga-PSMA-11 PET between January 2020 until December 2020 and all patients who received a 18F-PSMA-1007 PET between January 2020 until November 2021 were regarded for the interindividual comparison group. Of these, 383 and 409 patients were referred to PET due to BCR or persistence and further analyzed with regard to the rate of unspecific bone uptake and bone metastases. For this group of patients, bone-related imaging findings were retrospectively extracted from our archives regardless of the finding's SUVmax and regardless of pre-imaging prostate specific antigen (PSA) values in case of:

1. Histologically proven prostate cancer and
2. Biochemical recurrence or PSA persistence without any known metastases.

The incidence of UBU and bone metastases on 18F-F-PSMA-1007 and 68Ga-PSMA were compared in different pre-image PSA level groups (PSA < 1 ng/ml vs 1-5 ng/ml vs > 5 ng/ml).

Inclusion Criteria of the Intraindividual Comparison Group

The SUV_{max} of UBU was reported among different studies with similar image acquisition and the measurements were ranging between 3.6-21.1 (*4,10*). Therefore, in this study, UBU was defined as focally increased [^{18}F]PSMA-1007 uptake in the bone with a SUVmax higher than 4 and clear visualization in the Maximum Intensity Projection (MIP) images without CT correlate (no lytic or osteoplastic reaction). Patients with 18F-PSMA-1007 PET UBU were offered additional workup in case of:

1. Histologically proven prostate cancer
2. Biochemical recurrence of prostate cancer
3. PSA levels at the time of imaging ≤5 ng/mL
4. No known distant metastases.

Patients underwent additional clinical whole-body 68Ga-PSMA-11 PET/MRI and bone scan (together with SPECT/CT). Patient datasets were analyzed retrospectively.

Imaging and Image Interpretation of the Intraindividual Comparison Group

Tracer precursors (PSMA-11 and PSMA-1007) were obtained from ABX advanced biochemical compounds (ABX GmbH, Radeberg, Germany). 18F-PSMA-1007 and 68Ga-PSMA-11 were synthesized on site using a kit-based approach on automated platforms with comprehensive pH, radiochemical, chemical, radionuclide purity control tests.

111 ± 20 minutes after i.v. injection of 350.6 ± 61.8 MBq-18F-PSMA-1007, PET/CT was obtained between the base of the skull and mid-thighs with the patient in a supine position. A Biograph Vision and Biograph mCT were used for image acquisition (all: Siemens Healthineers, Erlangen, Germany). Full-dose CT was acquired for attenuation correction (210 mAs, 120 keV, 512 × 512 matrix, 128x0.6 mm slice thickness). PET emission data were attenuation corrected by help of the CT data and iteratively reconstructed (Vision: 4 iterations, 5 subsets, voxel size 3.3x3.3x3 mm^3, Gauss filtering: 4 mm; mCT 3

iterations, 21 subsets, voxel size: 4.07x4.07x3 mm^3, Gauss filtering: 4 mm) with time-of-flight information and point-spread function correction (HD PET).

[~~^{68}Ga~~]68Ga-PSMA-11 PET/MR (n=14) or PET/CT (n=3) were used to acquire co-registrated images. The mean injected dose and mean imaging delay was 133.3 ± 81.2 MBq and 67 ± 14 minutes, respectively. PET/MRI examination was obtained with integrated 3.0-Tesla Biograph mMR scanner (Siemens Healthineers) simultaneous PET and 3D-Dixon-VIBE sequences for MRI-based scatter correction were performed, followed by a standardized whole-body MRI protocol. The following MR sequences of choice were acquired: high-resolution T2- weighted fast spin-echo sequences (axial, coronal, and sagittal planes), diffusion-weighted sequences (b values, b = 0, 500, 1000 s/mm2), and dynamic contrast-enhanced imaging sequences (videlicet T1-weighted VIBE sequence obtained every 7 s during 5–10 min). PET emission data were iteratively reconstructed 3 iterations, 21 subsets, voxel size: 2.09x2.09x2.03 mm^3, Gauss filtering: 4 mm).

Whole-body planar bone scintigraphy imaging was carried out after 2.5 to 4 hours of the administration of the median dose of 628.5 MBq (range: 584-652 MBq) Tc-99 m 3,3-diphosphono-1,2-propanodicarboxylic acid (DPD) radiopharmaceutical in a continuous mode at a rate of 15 cm/min on a 256x1024 acquisition matrix of anterior and posterior planes with a dual-head gamma camera equipped with a low-energy, high-resolution collimator (Symbia T2 or Intevo, Siemens Healthineers). In all cases of uncertain radionuclide accumulations on bone scan, SPECT/CT images 15 sec/view step and shoot with 128x128 matrix were acquired.

Time interval between the PET image acquisitions was between 1 to 5 weeks. Image interpretation was performed using a dedicated workstation and software (SyngoVia; Siemens, Erlangen, Germany). All available imaging modalities were present for retrospective image reading. All PET and bone scintigraphy images were interpreted by two nuclear medicine physicians, while MRI images were interpreted by two radiologists. Two nuclear medicine physician performed semi-quantitative analyses of the PET data retrospectively in consensus. For example, a focal bone uptake of 18F-PSMA-1007 (Figure 1, A) showing

contrast enhancement (Figure 1, D), diffusion restriction (Figure 1, E) and radiotracer uptake in 68Ga-PSMA PET (Figure 1, B) and bone scintigraphy (Figure 1, C) was rated as bone metastasis. Conversely, a focal 18F-PSMA-1007 uptake of the bone without any suspicious finding on bone scan, 68Ga-PSMA-11 and MRI was rated as false positive (Figure 1, F-H).

Statistical Analysis

IBM SPSS Statistics Version 22 (IBM Inc., Armonk, NY, USA) was used for statistical analyses. The compliance of variables to normal distribution was determined by Kolmogorov-Smirnov test. Patient characteristics were presented as median (IQR or range) or mean ± SD in accordance to the data distribution. The Chi-Square or Pearson Goodness-of-fit tests were used to compare the differences of bone metastases and UBU in between two PSMA PET agents. A p value of <0.05 was considered statistically significant. A Sankey diagram was designed with the online Diagram Generator (Acquire Procurement Services, http://sankey-diagram-generator.acquireprocure.com).

RESULTS

Rate of Reported Bone Metastases and UBU in the Inter-Individual Group (Comparing the 68Ga-PSMA-11 and 18F-PSMA-1007 Cohorts, n=792)

A total number of 792 PSMA PETs of patients with BCR were included (n=409 for 18F-PSMA-1007 and n=383 for-68Ga-PSMA-11) to evaluate the frequency of UBU and bone metastases. Among the patients who were imaged with 18F-PSMA-1007, 332 (81.2%), 33 (8%), 13 (3.2%), 3 (0.1%) and 115 (28.1%) patients underwent radical prostatectomy, definitive radiotherapy, transurethral prostate resection, local ablative treatments, and adjuvant/salvage radiotherapy as previous local therapy, respectively. Among the patients who were imaged with 68Ga-PSMA-11, 324 (84.6%), 28 (7.3%), 7 (1.8%), 1 (0.2%) and 99 (25.8%) patients underwent radical prostatectomy, definitive radiotherapy, transurethral prostate resection, local ablative treatments, and adjuvant/salvage radiotherapy as previous local therapy, respectively. Overall, there was no statistically significant difference for the bone metastases rate comparing the final reports of 18F-PSMA-1007 and 68Ga-PSMA-11 (72 vs. 64; p = 0.7). Stratifying by PSA value, 229/397 (57.7%) of 18F-PSMA-1007 and 201/360 (55.8%) of 68Ga-PSMA-11 PET patients had PSA levels lower than 1 ng/ml. A fraction of 138/397 (34.8%) of 18F-PSMA-1007 and 147/360 (40.8%) of 68Ga-PSMA-11 PET patients had PSA levels between 1 and 5 ng/ml. 30/397 (7.6%) of-18F- PSMA-1007 and 12/360 (3.3%) of 68Ga-PSMA-11 PET patients had >5 ng/ml of PSA. There was no statistically significant difference of bone metastasis detection between 18F-PSMA-1007 and 68Ga-PSMA-11 among different PSA groups (p: 0.2, 0.2, and 0.6 for PSA levels groups <1 ng/ml, 1-5 ng/ml and >5 ng/ml, respectively) *(Figure 2~~A~~).*

UBU was reported at a significantly higher rate with–18F-PSMA-1007, in comparison to68Ga-PSMA-11 group (140 (34.2%) vs. 64 (16.7%); p < 0.001). Moreover, there was at least one identifiable benign bone lesion with focal PSMA uptake in 22 (5.4%) and 11 (2.9%) of the 18F-PSMA-1007 and 68Ga-PSMA-11 PET reports, respectively. There was no significant difference between the PSA level groups and UBU rate for both agents (p: 0.4 and 0.6 for 18F-PSMA-1007 and 68Ga-PSMA-11).

Patient Characteristics of the 18F-PSMA-1007 and 68Ga-PSMA-11 PET Intraindividual Comparison Cohort (n=17)

Seventeen prostate cancer patients with mean age of 70.9 years and a median duration of disease of 43.7 months (IQR: 18.6-122.9) underwent both 68Ga-PSMA-11 and 18F-PSMA-1007 PET due to clinical indication. The median time interval between PET scans was 22 days (IQR 8.0-2s9.5) days. Most patients were also evaluated with bone scan and SPECT/CT (n=14) and whole-body MRI (n=15), while 12 patients were evaluated with all four modalities. All the patients had PSA recurrence after radical prostatectomy and 8/17 of the patients also had undergone adjuvant or salvage radiation therapy. 12/17 of the patients had PSA level lower than 1 and 5/17 had PSA levels between 1 and 5 ng/ml. Further characteristics of the patients were outlined in the *Table 1*.

Local recurrence was detected on 18F-PSMA-1007 in 7 (41.1%) of the patients with a median SUV_{max} of 8.1 (range: 3.48-24.6); 41.1% (7/17) of the patients were rated as pelvic lymph node positive on [^{18}F]18F-PSMA-1007 PET. The median SUV_{max} and size of the most prominent pelvic lymph node was 10.9 (range: 3.2-37.6) and 0.5 cm (range: 0.4-1.2), respectively. Moreover, 4 patients staged as extra-pelvic lymph node positive (n=2 inguinal, n=2 retroperitoneal, median SUV_{max}= 5.1 (range: 3.4-10.2) by [^{18}F]18F-PSMA-1007 PET.

Intraindividual Analysis of 18F-PSMA-1007 Bone Uptake by Bone Scan and [^{68}Ga]PSMA-11 PET/MRI

In 18F-PSMA-1007 PET, a total number of 34 suspicious bone uptakes (in 17 patients) were seen (see supplemental Figure 1-17 for details on patients). Evaluation of the UBUs and final decisions are summarized in *Figure 3.* Eleven patients (64.7%) showed unifocal, four patients (23.5%) showed oligofocal, two patients (11.8%) multifocal [^{18}F]18F-PSMA-1007 bone uptake without any correlative lesion on CT (n=13 ribs, n=10 pelvis, n=4 vertebrae, n=3 scapula, n=2 sternum, n=1 clavicula, n=1 humerus head). Distribution of the false positive bone uptakes on 18F-PSMA-1007 is presented in *Figure 4.*

The per-patient true positive rate was 8.3%, the per lesion (n=28) true positive rate was 3.6%; PPV of bone uptake seen in 18F-PSMA-1007 PET was 8.3 % (95%CI -7-23.8%) per patient (n=12) and 3.6% (95%CI -3.3-10.5 %) per lesion (n=28) (only n=12 patients with all modalities, i.e. MRI, bone scan and 68Ga-PSMA-11 PET were included).

One lesion with PSMA expression (SUV_{max} 6.7 and 3 on 18F-PSMA-1007 and 68Ga- PSMA-11 PET, respectively) in the left ischiopubical junction without any correlative CT lesion was regarded as true positive, because it is also positive on bone scan and showed contrast enhancement in T1 weighted images with diffusion restriction on MRI (*Figure 1*). The patient with true positive pelvic bone metastasis had a PSA level of 0.91 ng/ml, PSA-DT of one month, 83 IU/l of ALP and 21.5 ug/l of bone specific ALP.

One lesion with PSMA expression (SUV_{max} 6.1 and 2.3 on 18F-PSMA-1007 and 68Ga-PSMA-11 PET, respectively) without any significant CT correlation was evaluated as enchondroma on MRI *(Supplementary Figure 17).* Follow up examinations of the bone findings were summarized in *Figure 3.*

All other sites of 18F-PSMA-1007 focal bone uptake were rated as false positive and likely UBU.

DISCUSSION

In this manuscript, we investigated 18F-PSMA-1007 PET unspecific bone uptake (UBU) in patients with BCR by 68Ga-PSMA-11 PET, MRI and bone scan correlation. In patients with correlative imaging, the positive predictive value of 18F-PSMA-1007 PET for bone metastases was very low. We present a systematic confirmation of 18F-PSMA-1007 PET UBU. However, the higher rate for 18F-PSMA-1007 vs. 68Ga-PSMA-11 PET did not translate into more frequent diagnosis of bone metastases if images are read by experienced readers.

PSMA PET has become the reference standard examination of the staging and restaging of patients with prostate cancer (*11*,*12*). It was shown previously that PSMA PET is superior to CT and bone scan in primary staging of patients with high-risk prostate cancer (*12*). PSMA-11 was assessed in most prospective trials on PSMA-directed imaging, which led to recent FDA approval. Several other PSMA ligands have been studied. For example, 18F-DCF-Pyl showed high diagnostic accuracy and was also approved by the FDA (*13*). Head-to-head comparison of 18F-DCF-Pyl and 18F- PSMA-1007 revealed near equal tumor detection in a small group of patients with newly-diagnosed prostate cancer (*14*). In France, the ligand 18F-PSMA-1007 is available through expanded access.

PSMA ligands show comparable tumor uptake and distribution, but also have distinctive biodistribution features (*5*). 18F-PSMA-1007 has a liver dominant excretion, which offers advantages for the assessment of local prostate cancer infiltration (*6*). Due to lesser ligand accumulation in the bladder, the differentiation between true tracer uptake and urinary background activity is often easier, which facilitates the detection of local recurrence.

The rise of 18F-PSMA-1007 is mainly caused by the ease of cyclotron-based [^{18}F]fluorine production, which enables the syntheses of larger quantities of PSMA ligands compared with 68Gallium generators (*4*). Additionally, 18F-fluorine offers a longer half-life compared with 68Gallium, which enables

an optimized patient management (*4*). Moreover, the lower positron energy of 18fluorine enables a higher spatial resolution and the higher signal-to-background ratio compared with 68Gallium (*4*) .

Despite the above mentioned benefits of–18F-PSMA-1007, it has been reported that the rate of unspecific bone uptake is notably higher compared with 68Ga-PSMA-11 (*8,15*). In our study, 33 UBUs have been reported for 18F-PSMA-1007 PET and 4 for 68Ga-PSMA-11 (triple validation was only available in a subcohort). This makes the clear delineation of bone metastases challenging in patient cohorts, in which bone metastases have a low prevalence, such as men with biochemically recurrent prostate cancer at low PSA level. Anticipating the same high specificity of other PSMA ligands, the false positive assessment of bone may potentially lead to inadequate treatment.

Unspecific bone uptake has also been reported in other PSMA targeting tracers. For example, preliminary reports indicate that rhPSMA-7 also shows unspecific bone uptake (*16*). The cause of unspecific bone uptake is not yet known. Unconjugated fluorine, activated bone marrow granulocytes (*15*) and PSMA expression in non-prostate cancer tissue have been discussed previously (*17,18*).

Interestingly, UBUs of 18F-PSMA-1007 show a distinct distribution pattern. Especially uptake in the ribs and pelvis can be observed, yet the explanation for this is unknown. Despite a higher UBU rate for 18F-PSMA-1007, the rate of bone metastases was not different in the cohorts of patients imaged with 18F-PSMA-1007 versus 68Ga-PSMA-11 in patients with BCR. For this, all patients scanned in the year before transition to 18F-PSMA-1007 were compared to all patients scanned in the year after the tracer switch. This observation indicates that experienced nuclear medicine physician can detect the UBU pattern and identify the lesions as unspecific. The distinctive pattern of UBU at the above-described locations may contribute to this observation. Current knowledge on UBU for 18F-PSMA-1007 and radioligands with similar bone pattern should be summarized in a comprehensive reader training before local implementation of these tracers.

This study comes with limitations. First, the comparison of patient cohorts prior to and after the change of PSMA tracers (from 68Ga-PSMA-11 to 18F-PSMA-1007) were analyzed retrospectively. Therefore, the analysis might be prone to selection bias and missing information. In the subgroup of patients receiving MRI, bone scan, and 68Ga-PSMA-11 as well as18F-PSMA-1007 PET, the additional PSMA PET and bone scintigraphy was performed only when clinically indicated and following patient approval and the data collection was done retrospectively. Therefore, our cohort with four imaging assessments was relatively small, and the results may not be transferable to larger cohorts. Finally, histopathological confirmation and follow-up imaging was not acquired for this study.

CONSLUSION

In patients with BCR of prostate cancer and PSA≤5 ng/mL, focal bone uptake on 18F- PSMA-1007 PET (SUV>4) was most often false positive/UBU when compared to 68Ga-PSMA-11 PET, MRI and bone scan. 18F-PSMA-1007 false positive/UBU findings were most commonly located in ribs and pelvis. Bone uptake in 18F-PSMA-1007 and 18F radioligands with similar bone pattern should therefore be evaluated carefully with regards to the location and clinical context. Most likely due to reader experience, the rate of bone metastases was not higher comparing clinical cohorts of patients with BCR imaged with 68Ga-PSMA-11 and 18F-PSMA-1007. To prevent false bone upstaging and consequently incorrect therapy management of the patients, 18F-PSMA-1007 PET should be performed by experienced physicians with knowledge of UBU distribution pattern and characteristics.

DISCLOSURES

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KEY POINTS

QUESTION: How clinically relevant is the previously reported occurrence of unspecific bone uptake on 18F-PSMA-1007 PET in prostate cancer?

PERTINENT FINDINGS: Bone uptake seen on 18F-PSMA-1007 PET in patients with biochemical recurrence, PSA≤5 ng/mL and SUV>4 is likely false positive. Common locations for false positive findings were ribs and pelvis. However, in the clinical routine, the rate of reported bone metastases of patients imaged with18F-PSMA-1007 or 68Ga-PSMA-11 is comparable, indicating that reporting physician adapt to the tracer characteristics.

IMPLICATIONS FOR PATIENT CARE: When metastatic disease is suspected in biochemical recurrent prostate cancer, osseous 18F-PSMA-1007 uptake without morphological correlate has to be carefully assessed.

REFERENCES

1. Mullins JK, Feng Z, Trock BJ, Epstein JI, Walsh PC, Loeb S. The impact of anatomical radical retropubic prostatectomy on cancer control: the 30-year anniversary. *J Urol*. 2012;188:2219-24.

2. Phillips R, Shi WY, Deek M, et al. Outcomes of Observation vs Stereotactic Ablative Radiation for Oligometastatic Prostate Cancer: The ORIOLE Phase 2 Randomized Clinical Trial. *JAMA Oncol*. 2020;6:650-659.

3. Cornford P, van den Bergh RCN, Briers E, et al. EAU-EANM-ESTRO-ESUR-SIOG Guidelines on Prostate Cancer. Part II-2020 Update: Treatment of Relapsing and Metastatic Prostate Cancer. *Eur Urol*. 2021;79:263-282.

4. Rauscher I, Krönke M, König M, et al. Matched-Pair Comparison of 68Ga-PSMA-11 PET/CT and 18F-PSMA-1007 PET/CT: Frequency of Pitfalls and Detection Efficacy in Biochemical Recurrence After Radical Prostatectomy. *J Nucl Med*. 2020;61:51-57.

5. Eiber M, Herrmann K, Calais J, et al. Prostate cancer molecular imaging standardized evaluation (PROMISE): Proposed miTNM classification for the interpretation of PSMA-ligand PET/CT. *J Nucl Med*. 2018;59:469-478.

6. Dietlein F, Kobe C, Hohberg M, et al. Intraindividual Comparison of 18F-PSMA-1007 with Renally Excreted PSMA Ligands for PSMA PET Imaging in Patients with Relapsed Prostate Cancer. *J Nucl Med*. 2020;61:729-734.

7. Seifert R, Schafigh D, Bogemann M, Weckesser M, Rahbar K. Detection of Local Relapse of Prostate Cancer With 18F-PSMA-1007. *Clin Nucl Med*. March 2019.

8. Arnfield EG, Thomas PA, Roberts MJ, et al. Clinical insignificance of [18F]PSMA-1007 avid non-specific bone lesions: a retrospective evaluation. *Eur J Nucl Med Mol Imaging*. 2021;48:4495-4507.

9. Pattison DA, Debowski M, Gulhane B, et al. Prospective intra-individual blinded comparison of

[18F]PSMA-1007 and [68 Ga]Ga-PSMA-11 PET/CT imaging in patients with confirmed prostate cancer. *Eur J Nucl Med Mol Imaging*. 2022;49:763-776.

10. Vollnberg B, Alberts I, Genitsch V, Rominger A, Afshar-Oromieh A. Assessment of malignancy and PSMA expression of uncertain bone foci in [18F]PSMA-1007 PET/CT for prostate cancer-a single-centre experience of PET-guided biopsies. *Eur J Nucl Med Mol Imaging*. 2022;49:3910-3916.

11. Fendler WP, Calais J, Eiber M, et al. Assessment of 68Ga-PSMA-11 PET Accuracy in Localizing Recurrent Prostate Cancer: A Prospective Single-Arm Clinical Trial. *JAMA Oncol*. 2019;5:856-863.

12. Hofman MS, Lawrentschuk N, Francis RJ, et al. Prostate-specific membrane antigen PET-CT in patients with high-risk prostate cancer before curative-intent surgery or radiotherapy (proPSMA): a prospective, randomised, multicentre study. *Lancet*. 2020;395:1208-1216.

13. Morris MJ, Rowe SP, Gorin MA, et al. Diagnostic Performance of 18F-DCFPyL-PET/CT in Men with Biochemically Recurrent Prostate Cancer: Results from the CONDOR Phase III, Multicenter Study. *Clin Cancer Res*. 2021;27:3674-3682.

14. Giesel FL, Will L, Lawal I, et al. Intraindividual Comparison of 18F-PSMA-1007 and 18F-DCFPyL PET/CT in the Prospective Evaluation of Patients with Newly Diagnosed Prostate Carcinoma: A Pilot Study. *J Nucl Med*. 2018;59:1076-1080.

15. Grünig H, Maurer A, Thali Y, et al. Focal unspecific bone uptake on [18F]-PSMA-1007 PET: a multicenter retrospective evaluation of the distribution, frequency, and quantitative parameters of a potential pitfall in prostate cancer imaging. *Eur J Nucl Med Mol Imaging*. June 2021.

16. Eiber M, Kroenke M, Wurzer A, et al. 18F-rhPSMA-7 PET for the Detection of Biochemical Recurrence of Prostate Cancer After Radical Prostatectomy. *J Nucl Med*. 2020;61:696-701.

17. Silver DA, Pellicer I, Fair WR, Heston WD, Cordon-Cardo C. Prostate-specific membrane antigen expression in normal and malignant human tissues. *Clin cancer Res*. 1997;3:81-85.

18. Backhaus P, Noto B, Avramovic N, et al. Targeting PSMA by radioligands in non-prostate disease—current status and future perspectives. *Eur J Nucl Med Mol Imaging*. 2018;45:860-877.

Tables

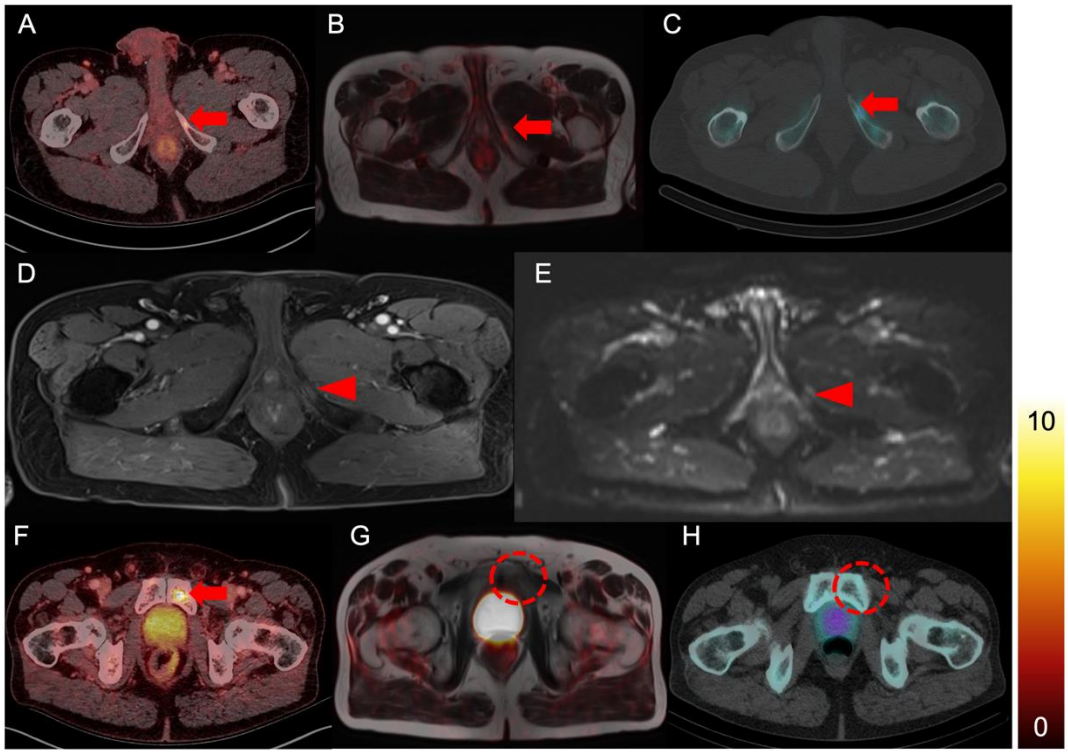
Table 1: Patient characteristics

Patient characteristics (n = 17)	
Age (years), median (IQR)	71 (69.5-74)
Initial T, n (%)	
T1	0
T2	5 (29.5%)
T3	8 (47%)
T4	0
Unknown	4 (23.5%)
Gleason Score, n (%)	
3+3	1 (5.9%)
3+4	2 (11.8%)
4+3	5 (29.4%)
4+4	2 (11.8%)
5+5	1 (5.9%)
Unknown	6 (35.3%)
Previous therapy to prostate, n (%)	
Radical Prostatectomy	17 (100%)
Additional adjuvant/salvage radiotherapy	8 (47.1%)
Blood levels	
PSA (ng/ml), median (IQR)	0.5 (0.2-1)
ALP (IU/l), median (IQR)	70 (55-83)
Bone-Specific ALP, median (IQR)	12.7 (11.5-17.8)

PSA= prostate-specific antigen, ALP = alkaline phosphatase.

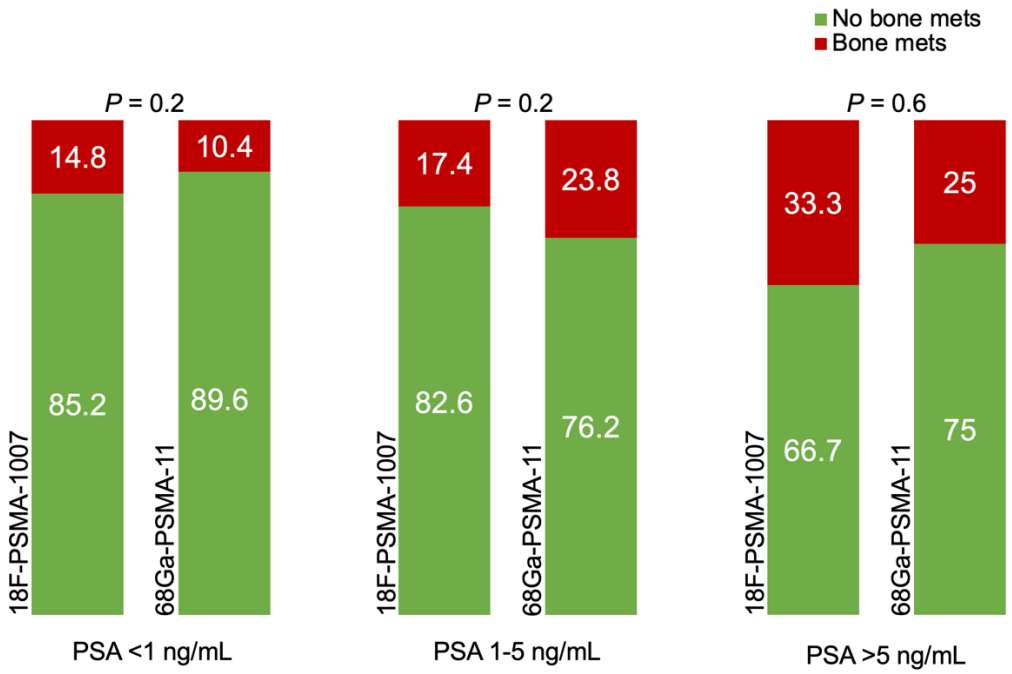
Figures

Figure 1: Exemplary cases of UBU regarded as true positive and false positive



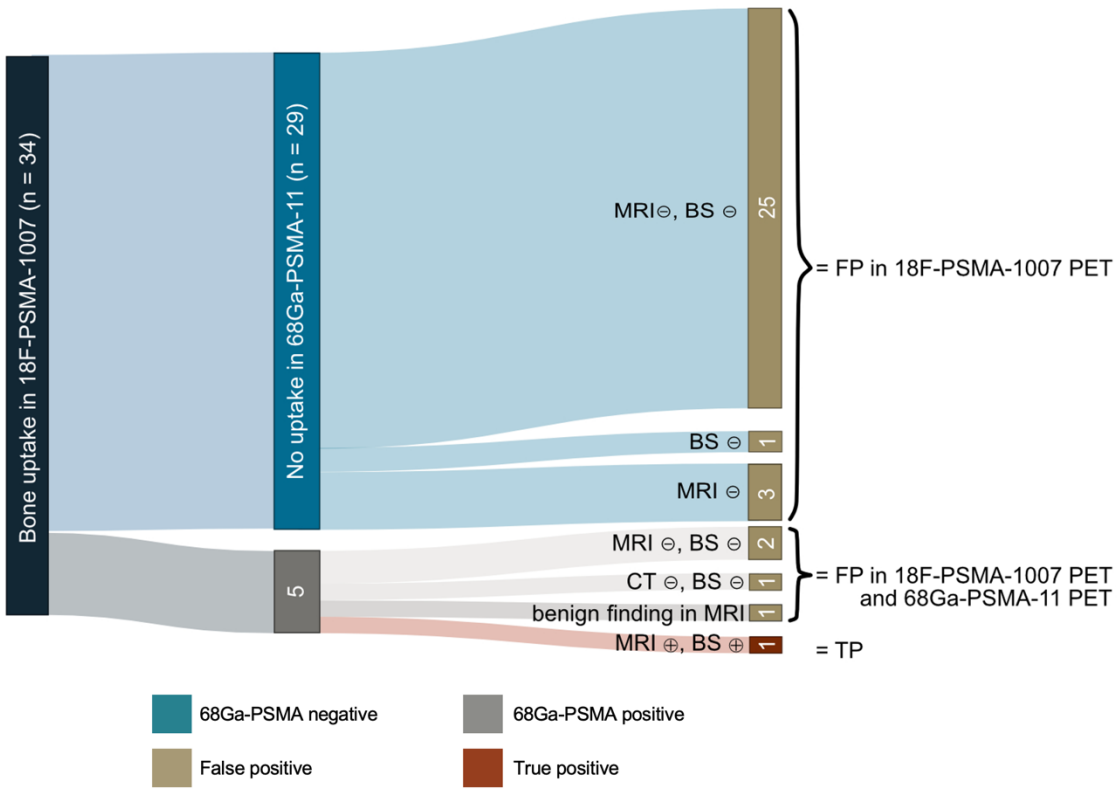
Axial slices of a patient with suspected unspecific bone uptake in 18F-PSMA-1007 PET (A, arrow). Suspicious uptake was seen on 68Ga-PSMA-11 PET/MRI (B, arrow) and on bone scan SPECT/CT (C, arrow). Corroborating these findings, the MRI showed contrast enhancement (D, arrowhead) and diffusion restriction (E, arrowhead). Therefore, the bone uptake was rated as true positive. A second patient is shown by panels F-H. Axial slices of a patient with unspecific 18F-PSMA-1007 uptake rated as false positive in the left inferior pubic ramus (SUVmax: 5.6) without any CT correlate (F, arrow) are shown. There was no suspicious finding either in 68Ga-PSMA-11 PET/MRI (G, dashed circle) or bone SPECT/CT (H, dashed circle). Therefore, this bone uptake was considered as false positive.

Figure 2: The frequency of bone metastases is presented separately for the PSA groups and the PET tracers (18F-PSMA-1007 or 68Ga-PSMA-11).



There was no statistically significant difference of bone metastasis detection between 18F-PSMA-1007 and 68Ga-PSMA-11 among three different PSA level groups.

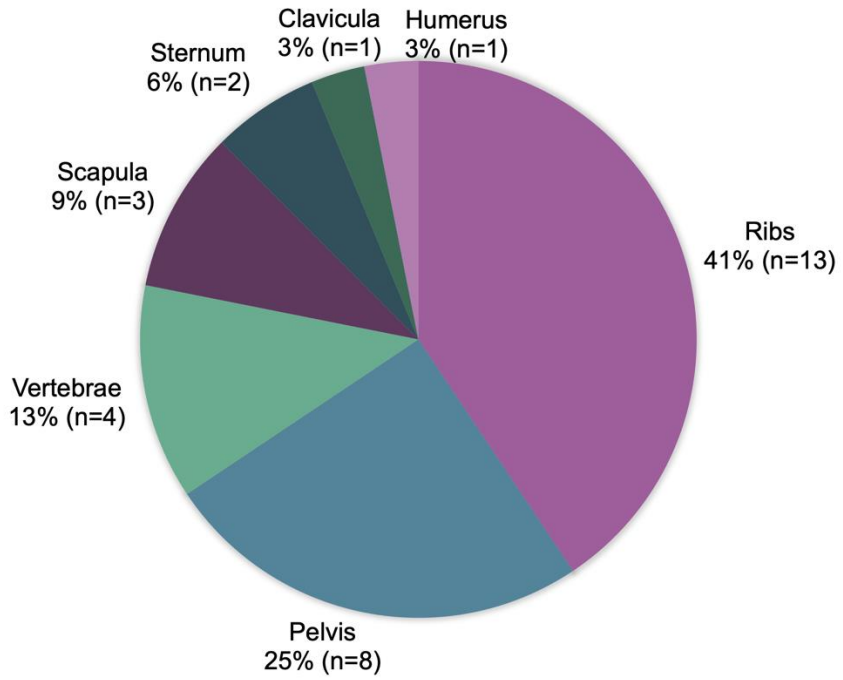
Figure 3: Sankey Diagram summarizing the evaluation of UBUs seen in 18F-PSMA-1007 PET



Abbreviations: BS = Bone scan, FP = False Positive, TP = True Positive, MRI = Magnetic resonance Imaging, PSMA = Prostate Specific Membrane Antigen, UBU = Unspecific bone uptake, ⊖ = no suspicious finding, ⊕ = suspicious finding.

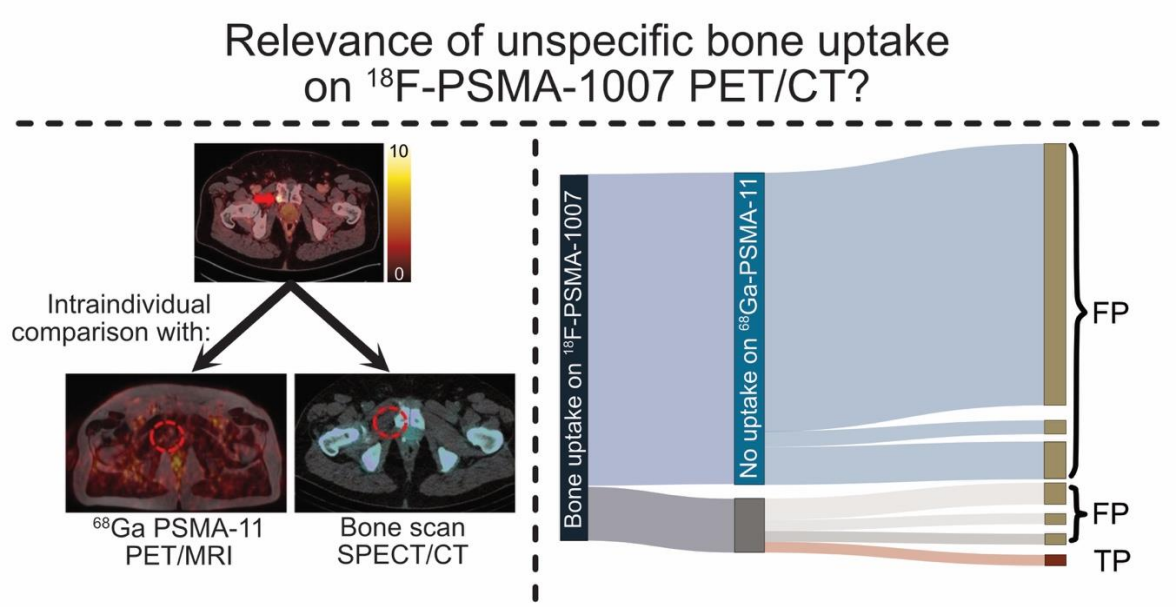
A total number of 34 UBUs were detected in 18F-PSMA-1007 PET. One lesion was regarded as true positive (bone metastasis) and one lesion was rated as benign because of characteristic MRI findings. 33 UBU were rated as false positive in 18F-PSMA-1007 PET and 4 false positive bone uptakes were seen in 68Ga-PSMA-11 PET (triple validation was only available in a subcohort).

Figure 4: Anatomic distribution of unspecific bone uptakes seen in 18F-PSMA-1007 PET



32 bone uptakes were seen on 18F-PSMA-1007 PET (in multiple regions) and 4 bone uptakes were seen on 68Ga-PSMA-11 (all located in ribs). Most common UBU localizations for 18F-PSMA-1007 were ribs and pelvis.

Graphical Abstract



Supplement

Supplementary Table: Summary of the patients

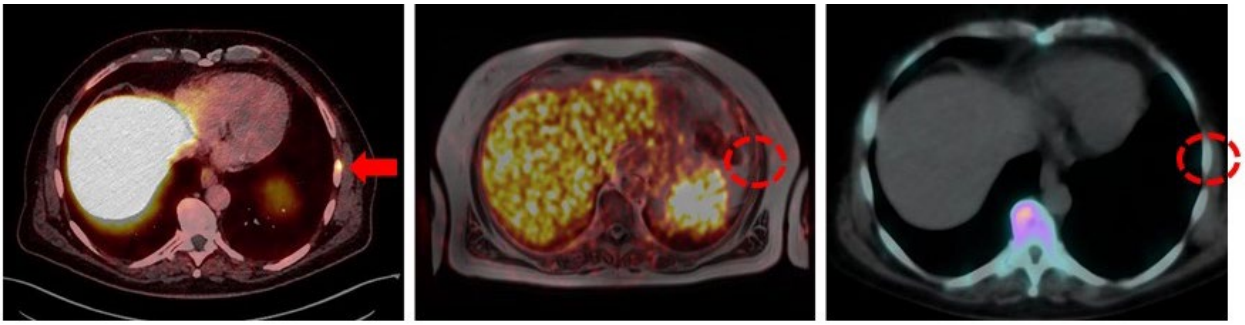
ID	GS	RT	PSA	AP	BAP	[18F]PSMA-1007 PET Scanner	[68Ga]PSMA-11 PET Scanner	MRI Scanner	T-N staging with [18F]PSMA-1007	UBU (n) on [18F]PSMA-1007	UBU Evaluation on [68Ga]PSMA-11	UBU Evaluation on Bone Scan and MRI	Final assessment of UBU	Follow-up
1	5+5=10	Yes	0,22	43	11	Biograph Vision	Biograph mMR	Biograph mMR	T0N1	1	+	-/-	False positive	N/A
2	4+4=8	No	0,58			Biograph mCT	Biograph mMR	Biograph mMR	TrN2	1	-	N/A/-	False positive	N/A
3	4+3=7b	Yes	1,3	61	13	Biograph mCT	Biograph Vision	Siemens Skyra	T0N2M1a	1	-	-/-	False positive	N/A
4	4+4=8	No	1,07	70	12	Biograph mCT	Biograph Vision	-	TrN0M1a	1	+	-/N/A	False positive	N/A
5		Yes	2,97	83	15	Biograph Vision	Biograph mMR	Biograph mMR	T0N1	1	-	-/-	False positive	*
6	3+3=6	Yes	2,53	48	12	Biograph mCT	Biograph mMR	Biograph mMR	TrN0	1	-	-/-	False positive	N/A
7		No	1,06	47		Biograph Vision	Biograph mMR	Biograph mMR	T0N0	2	-	-/-	False positive	*
8	3+4=7a	Yes	0,52	57	11	Biograph mCT	Biograph mMR	Biograph mMR	T0N0	1	-	-/-	False positive	N/A
9		No	0,21	119	25	Biograph Vision	Biograph mMR	Biograph mMR	T0N1M1a	4	-	-/-	False positive	N/A
10	4+3=7b	No	0,31	55	11	Biograph Vision	Biograph mMR	Biograph mMR	TrN1	1	-	N/A/-	False positive	N/A
11	4+3=7b	No	0,44	78	14	Biograph Vision	Biograph mMR	Biograph mMR	T0N0	2	-	-/-	False positive	N/A
12		No	0,25	63	12	Biograph Vision	Biograph mMR	Biograph mMR	TrN2	1	-	-/-	False positive	N/A
13	4+3=7b	Yes	0,91	83	22	Biograph Vision	Biograph mMR	Biograph mMR	T0N0	1	+	+/+	Metastasis	**
14		Yes	0,59	82	21	Biograph Vision	Biograph mMR	Biograph mMR	T0N0M1a	11	+ for only 1	-/-	False positive	***
15	3+4	No	0,5	71	13	Biograph Vision	Biograph mMR	Biograph mMR	TrN0	2	-	-/-	False positive	N/A
16	4+3=7b	Yes	0,24	106		Biograph Vision	Biograph Vision	-	TrN0	1	-	-/N/A	False positive	N/A
17		No	0,14			GE DiscoverySTE	Biograph mMR	Biograph mMR	T0N0	2	+ for only 1	N/A/Enchondroma	Benign	N/A

+: Positive finding for prostate cancer, -: no correlative finding. * Stable findings on PSMA PET/CT without any additional bone uptake or any correlative finding on the CT component of the PET/CT. ** Radiotherapy of the single bone metastasis. ***Stable PSA values during the follow up. Abbreviations: AP: alkaline phosphatase (IU/l), BAP: Bone specific alkaline phosphatase (ug/l), MRI. Magnetic resonance imaging, N/A: not available, PSA (ng/ml): Prostate Specific Antigen, PSMA: Prostate-Specific Membrane Antigen

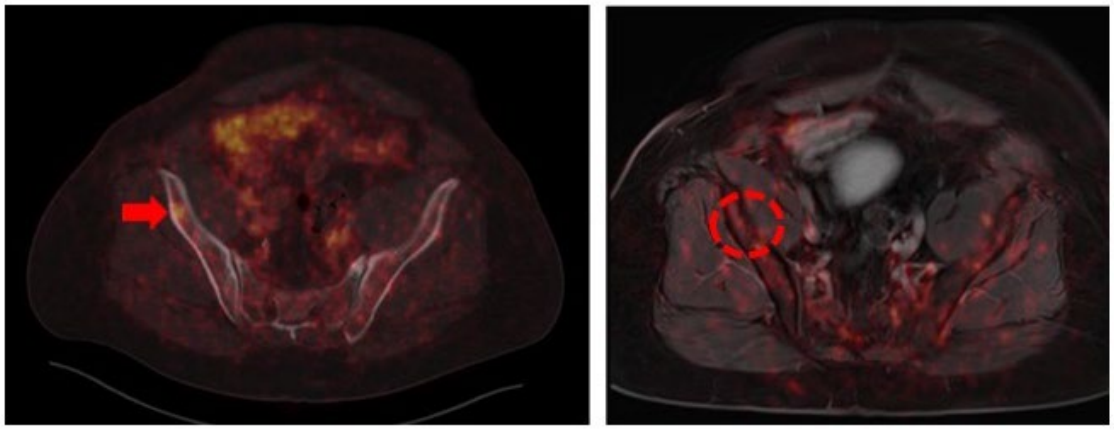
Supplementary Figures:

[18F]-F-PSMA-1007, [68Ga]PSMA-11 PET CT or MRI and bone SPECT/CT transaxial fusion images of the bone uptakes were demonstrated.

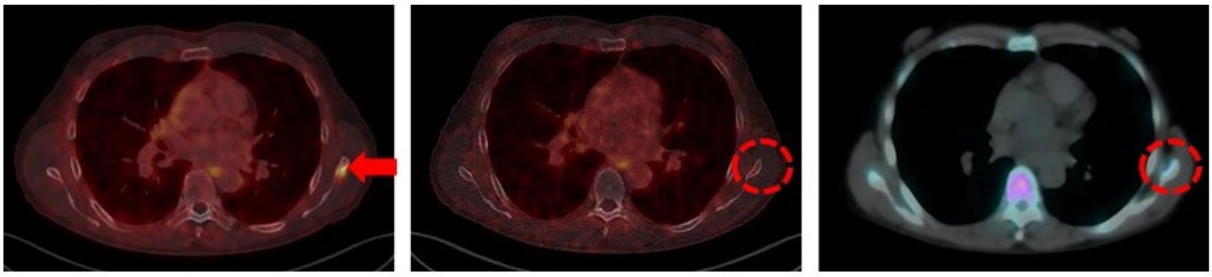
Supplementary Figure 1: Patient no: 1. Focal [18F]-F-PSMA-1007 uptake (SUVmax: 5.1) in lateral arcus of 7th left rib without any CT correlate (Arrows). There is no correspondent finding on either [68Ga]PSMA-11 PET/MRI or bone SPECT/CT (Dotted circles).



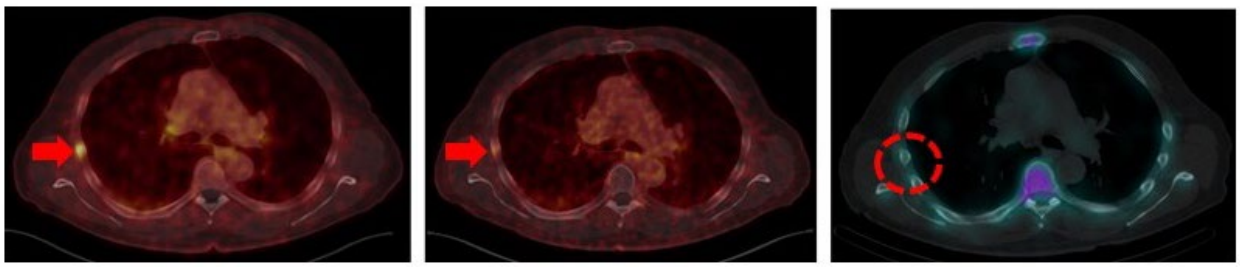
Supplementary Figure 2: Patient no: 2. Focal [18F]-F-PSMA-1007 uptake (SUVmax: 4.8) in the right iliac bone without any CT correlate (arrows). There is no corresponding finding on [68Ga]PSMA-11 PET/MRI (Dotted circles).



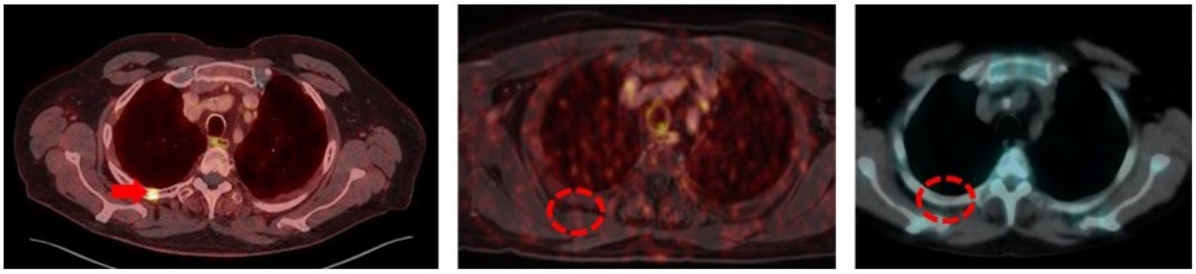
Supplementary Figure 3: Patient no: 3. Focal [18F]-F-PSMA-1007 uptake (SUVmax: 4.4) in lateral angle of left scapula without any CT correlate (arrows). There is mild uptake (SUVmax: 2) on the [68Ga]PSMA-11 PET/CT and no correspondent finding on bone SPECT/CT (Dotted circles).



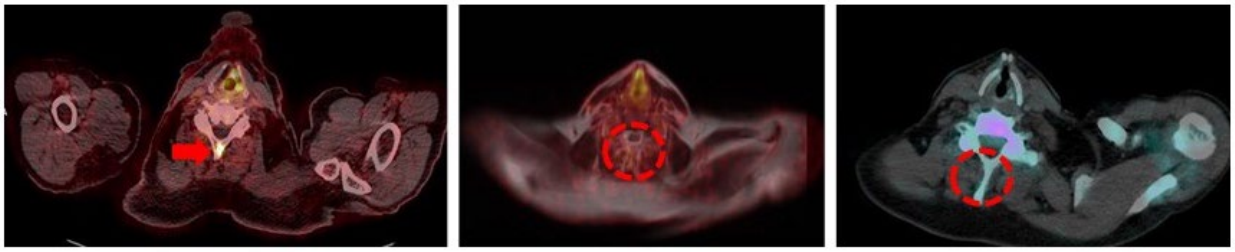
Supplementary Figure 4: Patient no: 4. Focal [18F]-F-PSMA-1007 (SUVmax: 4.5) and low grade [68Ga]PSMA-11 (SUVmax: 2.8) (Arrows) uptake in posterolateral arcus of the right 5th rib without any CT correlate. There is no equivalent uptake on bone SPECT/CT (Dotted circles).



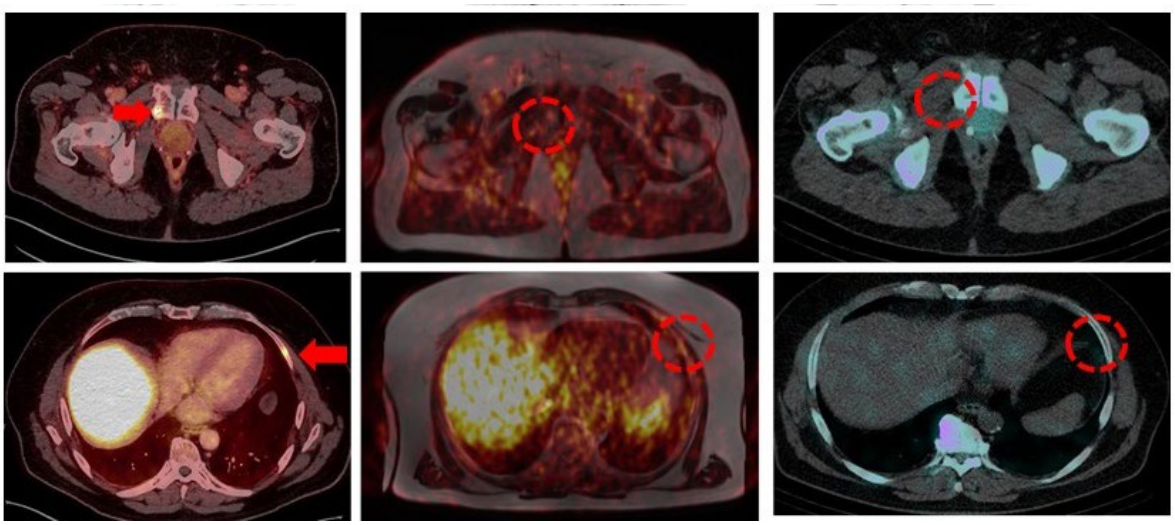
Supplementary Figure 5: Patient no: 5. Focal [18F]-F-PSMA-1007 uptake (SUVmax: 9.6) in posterior arcus of 4th right rib without any CT correlate (Arrows). There is no correspondent finding on either [68Ga]PSMA-11 PET/MRI or bone SPECT/CT (Dotted circles).



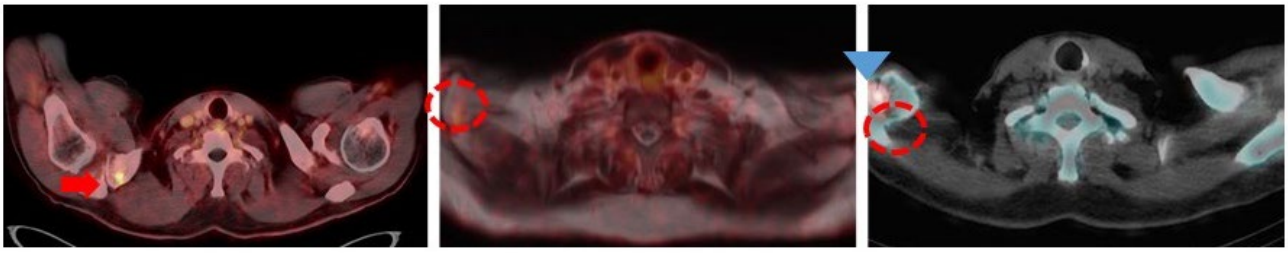
Supplementary Figure 6: Patient no: 6. Focal [18F]-F-PSMA-1007 uptake (SUVmax: 10.2) in the spinous process of the C7 vertebra without any CT correlate (Arrows). There is no correspondent finding on either [68Ga]PSMA-11 PET/MRI or bone SPECT/CT (Dotted circles).



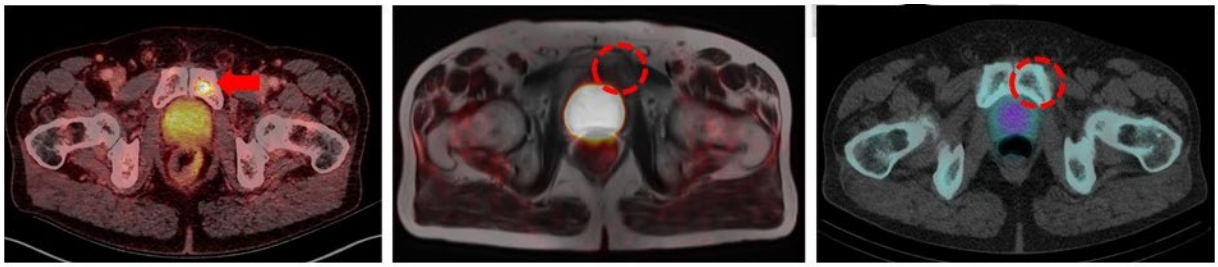
Supplementary Figure 7: Patient no: 7. Focal [18F]-F-PSMA-1007 uptake in right inferior pubic ramus (SUVmax: 9) and anterior arcus of 5th left rib (SUVmax: 4.5) without any CT correlate (Arrows). There is no correspondent finding on either [68Ga]PSMA-11 PET/MRI or bone SPECT/CT (Dotted circles).



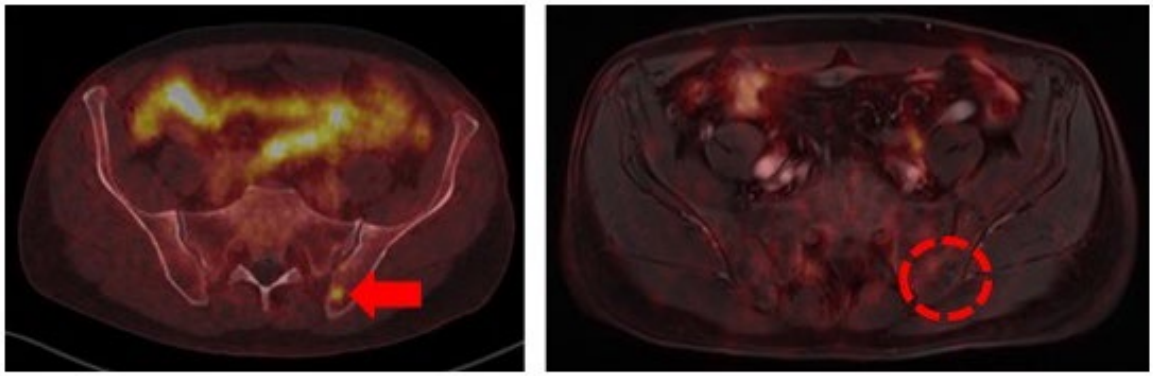
Supplementary Figure 8: Patient no: 8. Focal [18F]-F-PSMA-1007 uptake in the acromial end of right clavicle (SUVmax: 6.1) without any CT correlate (Arrows). There is no correspondent finding on either [68Ga]PSMA-11 PET/MRI or bone SPECT/CT (Dotted circles) except for degenerative changes in right acromioclavicular joint (arrowhead).



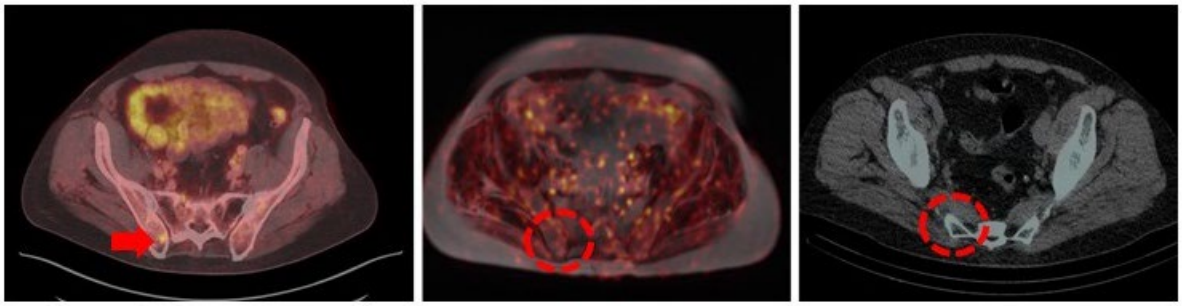
Supplementary Figure 9: Patient no: 9 had multifocal uptake on [18F]-F-PSMA-1007PET. Only focal [18F]-F-PSMA-1007 uptake (SUVmax: 8) in left inferior pubic ramus without any CT correlate was demonstrated in the images (Arrows). There is no correspondent finding on either [68Ga]PSMA-11 PET/MRI or bone SPECT/CT (Dotted circles).



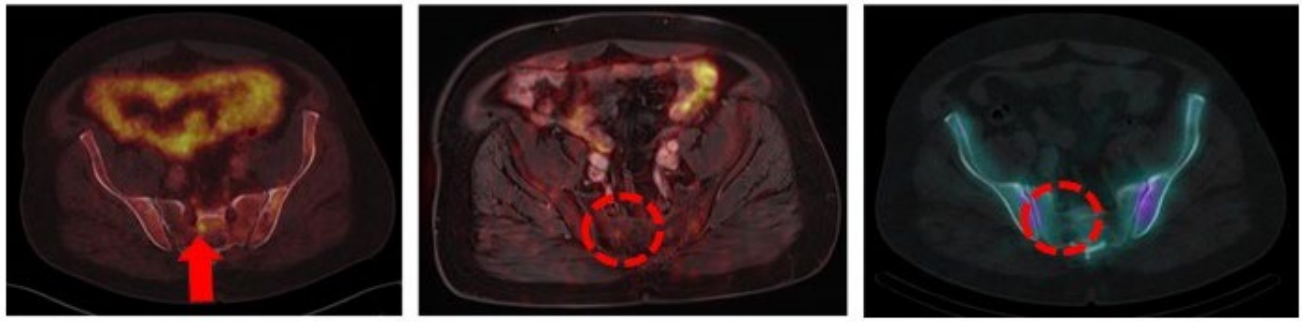
Supplementary Figure 10: Patient no: 10. Focal [18F]-F-PSMA-1007 uptake in the left iliac posterior crest (SUVmax: 5.6) without any CT correlate (Arrows). There is no corresponding finding on [68Ga]PSMA-11 PET/MRI (Dotted circles).



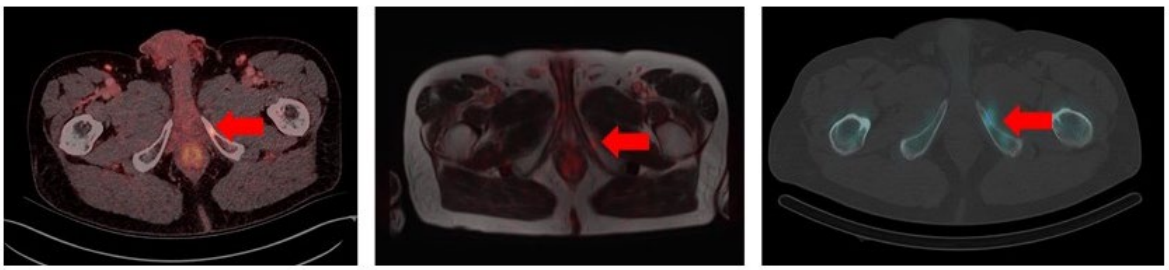
Supplementary Figure 11: Patient no: 11. Focal [18F]-F-PSMA-1007 uptake in right ilium (SUVmax: 4.1) without any CT correlate (Arrows). There is no correspondent finding on either [68Ga]PSMA-11 PET/MRI or bone SPECT/CT (Dotted circles).



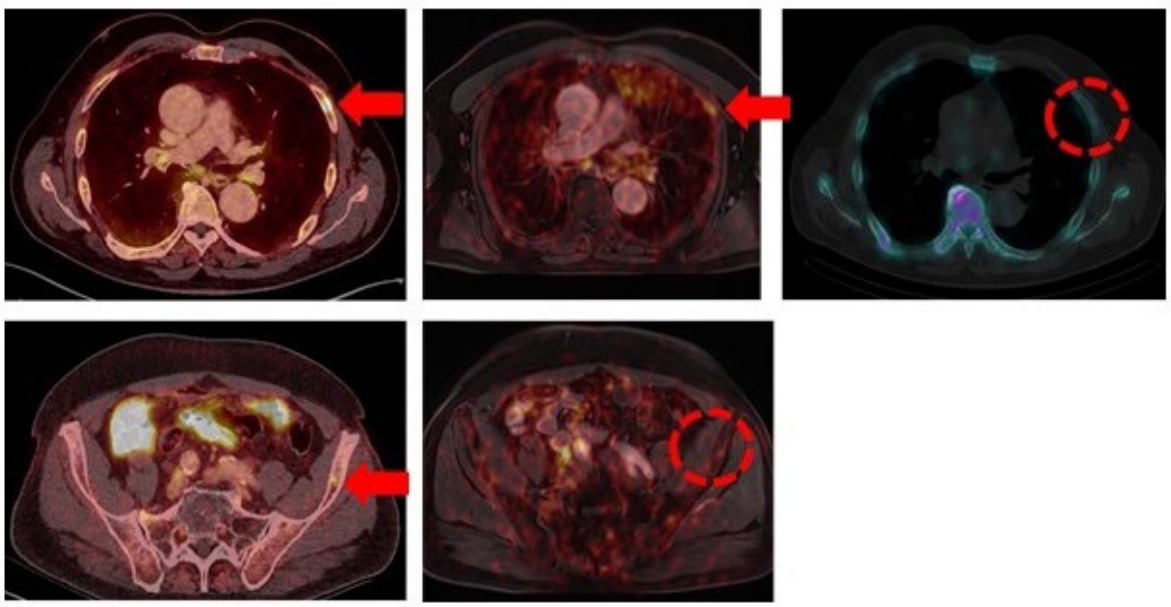
Supplementary Figure 12: Patient no: 12. Focal [18F]-F-PSMA-1007 uptake in S2 vertebra, close to the right sacral foramina (SUVmax: 5.2) without any CT correlate (Arrows). There is no corresponding finding on either [68Ga]PSMA-11 PET/MRI or bone SPECT/CT (Dotted circles).



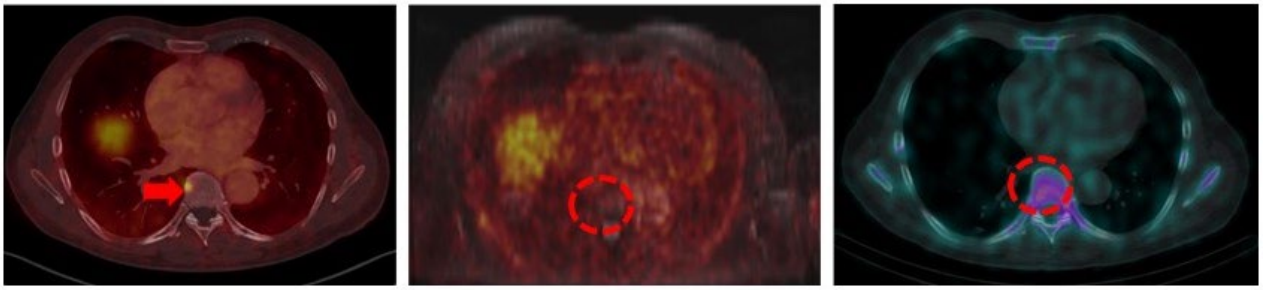
Supplementary Figure 13: Patient no: 13. Focal [18F]-F-PSMA-1007 uptake in the left ischiopubic junction (SUVmax: 6.7) was confirmed and regarded as metastasis (true positive) by [68Ga]PSMA-11 PET/MRI (SUVmax: 2.9) and bone SPECT/CT (Arrows).



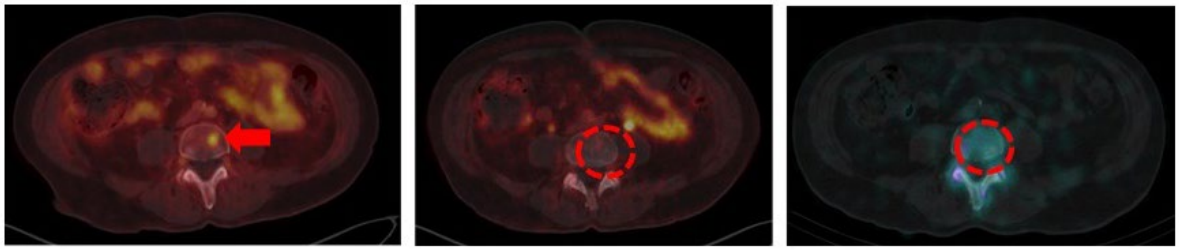
Supplementary Figure 14: Patient no: 14. Multifocal [18F]-F-PSMA-1007 uptake in the right spina scapula, ribs (e.g. anterior arcus of left 4th rib), and left iliac wing (Arrows), without any CT correlate. Low uptake in the left 4th rib was also detected on [68Ga]PSMA-11 PET (SUVmax: 3.3) without any lesion on the correlative MRI. There are no matching findings on either [68Ga]PSMA-11 PET/MRI or bone scintigraphy/SPECT/CT (Dotted circles).



Supplementary Figure 15: Patient no: 15. Focal [18F]-F-PSMA-1007 uptake in anterior of T8 vertebral body (SUVmax: 4.5) without any CT correlate (Arrows). There is no correspondent finding on either [68Ga]PSMA-11 PET/MRI or bone SPECT/CT (Dotted circles).



Supplementary Figure 16: Patient no: 16. Focal [18F]-F-PSMA-1007 uptake in the left of the L4 vertebral body (SUVmax: 4.5) without any CT correlate (Arrows). There is no equivalent finding on either [68Ga]PSMA-11 PET/MRI or bone SPECT/CT (Dotted circles).



Supplementary Figure 17: Patient no: 17. Focal [18F]-F-PSMA-1007 uptake in left of manubrium sterni without any CT correlate (Arrows) evaluated as enchondroma by [68Ga]PSMA-11 PET/MRI with mild uptake (SUVmax: 1.1) (arrowheads).