

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

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Abstract

Purpose

Improved logistics and availability led to a rapid increase in the use of [^{18}F]-PSMA-1007 for prostate cancer PET imaging. Initial data suggests increased uptake in benign lesions compared to [^{68}Ga]-PSMA-11, and clinical observations found increased unspecific bone uptake (UBU). We therefore investigate the frequency and characteristics of UBU in [^{18}F]-PSMA-1007 PET.

Methods

We retrospectively analyzed [^{18}F]-PSMA-1007 PET scans from four centers for the presence of UBU, defined as a focal mild-to-moderate uptake ($\text{SUV}_{\text{max}} < 10.0$) not obviously related to a benign or malignant cause. If present, up to three leading UBUs were quantified (SUV_{max}), localized, and correlated to clinical parameters, such as age, PSA, injected dose, Gleason-score, tumor size (T1–T4), and type of PET scanner (analog vs. digital). Additionally, clinical and imaging follow-up results and therapeutic impact were evaluated.

Results

UBUs were identified in 179 out of 348 patients (65.2%). The most frequent localizations were ribs (57.5%) and pelvis (24.8%). The frequency of UBUs was not associated with PSA, Gleason-score, tumor size, age, or the injected [^{18}F]-PSMA-1007 dose. UBUs were significantly more frequent in images obtained with digital scanners (70.1%) than analog scanners ($p=.0001$). In 80 out of 179 patients (44.7%), the interpretation of UBUs was critical for therapeutic management and therefore considered clinically relevant. For 65 UBUs, follow-ups were available: three biopsies, three radiotherapies with PSA follow-up, and 59 cases with imaging. After follow-up UBUs were still considered unclear in 28 of 65 patients (43.1%), benign in 28 (43.1%), and malignant in nine (13.8%) patients.

Conclusion

UBUs occur in two-thirds of patients imaged with [^{18}F]-PSMA-1007 PET/CT and are significantly more frequent on digital PET scanners than analog scanners. UBUs should be interpreted carefully to avoid over-staging.

Introduction

Positron emission tomography (PET), combined with either computer tomography (CT) or magnetic resonance imaging (MRI), utilizing radiotracers that bind to prostate-specific membrane antigen (PSMA) is an excellent diagnostic tool for prostate cancer imaging. In the past few years, PSMA-PET has evolved to become the leading advanced imaging modality in the Western world, especially for patients with early biochemical recurrence (EBR) [1,2]. In various studies, PSMA-PET/CT has shown better detection efficacy

in EBR than MRI, CT, conventional imaging [3–6], or choline-labeled PET ligands [7]. Moreover, the examination is gaining increasing importance for the initial staging of intermediate and high-risk prostate cancer [8–13].

Several PSMA ligands are available, radiolabeled with different positron-emitting isotopes, such as gallium-68 [^{68}Ga], fluorine-18 [^{18}F], and copper-64 [^{64}Cu], although the most commonly used PSMA agent in Europe was initially [^{68}Ga]-PSMA-11, with well-established application for cancer localization in EBR, with high detection rates, and an impact on management following 60% of scans [14]. More recently, [^{18}F]-PSMA ligands have become commercially available, replacing [^{68}Ga]-PSMA ligands. The major advantages of [^{18}F]-PSMA ligands over [^{68}Ga]-PSMA ligands are the longer half-life (110min vs. 68min) and higher production capacity, as it is produced in cyclotrons rather than generators, resulting in greater availability and fewer logistical challenges. The lower positron emission energy of [^{18}F]-PSMA ligands than [^{68}Ga]-PSMA ligands (0.6 MeV vs. 2.3 MeV) also leads to a higher image resolution. One of the candidate ligands already implemented in clinical routines in several hospitals in Switzerland is [^{18}F]-PSMA-1007, which benefits from low background activity in the urinary tract [15], which is an important advantage in suspected local recurrence [5,16,17].

However, with the greater use of [^{18}F]-PSMA-1007, initial studies have reported a higher frequency of unclear focal uptakes than for [^{68}Ga]-PSMA ligands, especially in the lymph nodes, ganglia, and bones [18]. In contrast to the nonspecific uptake in the axillary or mediastinal lymph nodes and the physiologic uptake in the ganglia, unspecific bone uptake (UBU) without morphological correlates might be interpreted as metastasis, with the potential for over-staging the patient, leading to inadequate therapy. The aim of this retrospective multicenter study was to analyze the frequency, anatomical distribution, characteristics, and influencing parameters for UBUs in [^{18}F]-PSMA-1007 PET and to evaluate their therapeutic impact.

Methods

Study design and population

In this study, we analyzed all [^{18}F]-PSMA-1007 scans from four centers (Centers A, B, C, and D) taken between October 2019 and July 2020. General consent was present from all patients at three centers and was waived by the local ethics committee for the fourth (EKNZ ID: 2020-01775). The study was conducted in compliance with ICH-GCP rules and the Declaration of Helsinki.

Patients with histology-proven prostate cancer of any tumor stage underwent [^{18}F]-PSMA-1007-PET due to EBR, for staging, or for general tumor evaluation (TE). Patient characteristics were collected, including age, initial tumor stage (TNM classification) if available, ISUP score for histological grading [19], bone metastasis, and PSA value less than four weeks before the scan.

A hybrid PET/CT scanner or a hybrid PET/MR scanner incorporating MR and PET scanners with time of flight was used for the acquisition of the datasets. Imaging was performed using five analog PET/CT scanners (GE PET-CT Discovery 600 and 690, GE Healthcare, Waukesha, WI; Siemens PET/CT Biograph mCT Flow, Siemens Healthineers, Munich, Germany), two digital PET/CT scanners (GE Discovery Molecular Insights – DMI PET/CT, GE Healthcare, Waukesha, WI), and one digital PET/MR with silicon photomultiplier technology (Signa PET/MR, GE Healthcare, Waukesha, WI, USA). At Center A, only digital PET scanners were available (two PET/CT and one PET/MR). The injected dose of [^{18}F]-PSMA was 3–4 MBq/kg at all the centers, and the uptake time was 60 to 90 min. The maximal injected dose was not more than 350 MBq.

UBU-based assessment

All scans were analyzed for the presence of UBU, defined as lesions with SUV_{max} below 10 and with neither morphological correlates that suggest metastatic disease nor clear benign findings, such as inflammatory joint diseases or fractures. If present, the three most active UBUs in each patient were quantified (SUV_{max}) and localized (*Fig. 1*). UBUs were localized in the skull, spine, ribs, sternum, pelvis, and extremities. The datasets were read by physicians who were double board-certified in radiology and nuclear medicine.

Patient-based assessment

The relationships between the frequency of UBUs and clinical parameters such as age (y), PSA (ng/ml), Gleason score categorized according to the International Society of Urological Pathology (ISUP), with prognostic grade groups 1 to 5, and tumor size (T1 to T4) were analyzed. For patients with UBUs, the therapeutic impact was evaluated: a clinical problem (CP) was considered to be present if the UBUs would alter management when judged as probably benign or malignant—for example, in patients with EBR with a solitary UBU in the skeleton or in patients referred for staging with UBUs that would prevent local radical therapy if interpreted as malignant. No CP due to UBUs was considered present with either multiple bone metastasis or several clear lesions that had already been excluded from targeted therapy. Furthermore, we retrospectively analyzed whether further clinical investigations were performed, such as additional imaging, biopsy, or PSA value, after radiotherapy. For those patients, the UBUs were classified as malignant, benign, or still unclear based on the follow-up investigation.

Differences between institutions and scanners

The numbers of patients, numbers of analog and digital PET scanners, frequency of UBUs, and mean SUV_{max} of the UBUs for each center were collected. The relationships between the frequency of UBUs and both the injected dose of [^{18}F]-PSMA-1007 and scanner type (analog vs. digital) were analyzed.

Statistical analysis

Continuous variables were summarized as medians and IQR, and categorical variables were summarized as numbers and percentages. All continuous variables were tested for normal distribution with the D'Agostino–Pearson test, and normality was rejected if $p < .05$. Continuous data were compared with the Mann–Whitney test, and the U, Z, p values and 95% CI were calculated and presented in box–whisker plots. Categorical data were compared using chi-squared tests; if significant, Pearson's contingency coefficient (C) was calculated. Sankey diagrams were used to visualize the clinical impact of UBUs and the outcomes of different follow-up methods. A p -value $< .05$ was considered statistically significant in all cases. Statistical analysis was performed using MedCalc Statistical Software version 19.1 (MedCalc Software bv, Ostend, Belgium). Sankey diagrams were designed with eSankey 5.2.1 (ifu Institut für Umweltinformatik Hamburg GmbH, Hamburg, Germany).

Results

Patient characteristics and demographic data

Patient characteristics and demographic data are shown in *Table 1*.

UBU-based assessment

A total of 348 scans were evaluated, and 351 UBUs were identified in 227 (65.2%) of the patients. The most frequent localization was the ribs (57.5%), with a mean SUV_{max} of 3.8, followed by the pelvis (24.8%, SUV_{max} 5.0), spine (9.7%, SUV_{max} 4.7), extremities (5.4%, SUV_{max} 4.6), sternum (2.0%, SUV_{max} 4.3), and skull (0.6%, SUV_{max} 5.9). The mean SUV_{max} of all UBUs was 4.2 ± 2.0 (*Fig. 2*).

Patient-based assessment

Age was not associated with frequency of UBUs (U = 13014.00, Z = 2.25, $p = .02$), although the p -value was $< .05$, the 95% CI of median difference was not significant (median difference -2.0, 95% CI -3.0 to 0.0) (*Fig. 3a*). The frequency of UBUs was not associated with PSA value (U = 11090.00, Z = 0.68, $p = .50$) (*Fig. 3b*). Chi-squared tests showed no relationship between the frequency of UBUs and either tumor size ($\chi^2(3) = 5.61$, $p = .0573$) or ISUP score ($\chi^2(4) = 4.78$, $p = .3108$) (*Fig. 2c-d*).

Overall, in 80 out of 179 patients (44.7%) with UBUs, the lesions were considered a CP that could alter management. Regarding the indication for the PET scan, CPs were present in 55 of 227 patients with EBR (24.2%), in 15 of 49 for tumor staging (30.6%), and in 10 of 72 for TE (13.9%). UBUs with no CPs were present in 60 of 227 (26.4%) patients with EBR, 16 of 49 for tumor staging (32.7%), and 23 of 72 for TE (31.9%). Overall, 39 out of 348 patients (13.8%) were followed up by imaging, biopsy, or radiotherapy with PSA follow-up. Only 25 out of 80 patients (31.3%) with a CP were followed up (*Fig. 4*).

Follow-up was available for 65 UBUs: three (4.6%) biopsies (all benign), three (4.6%) radiotherapies with PSA follow-up (two malignant and one benign), and 59 (90.8%) imaging follow-ups (seven malignant, 24 benign, 28 unknown). Overall, 59 UBUs were followed up by imaging: 23 (39.0%) by PET, 17 (28.8%) by

CT, 14 (23.7%) by MRI, and five (8.5%) by SPECT. However, after follow-up, 28 (43.1%) UBUs were still considered unknown, with 28 (43.1%) benign and nine (13.8%) malignant (*Fig. 5*).

Differences between institutions and scanners

Of the 348 PET scans, 132 (37.9%) were performed in Center A, 126 (36.2%) in Center B, 72 (20.7%) in C, and 18 (5.2%) in D; 221 (63.5%) patients were scanned on an analog PET/CT scanner, 74 (21.3%) on a digital PET/CT scanner, and 53 (15.2%) on a digital PET/MRI scanner. Only in Center A were digital PET/CT scanners or PET/MRI scanners available; in Center A, only six PET/CT scans were performed on an analog scanner. There were also significantly more UBUs present on digital PET scanners (70.1%) than analog scanners (40.7%) ($\chi^2(1) = 27.74, p = .0001, C = 0.27$) (*Fig. 6a*).

The number of patients with UBUs at Center A was 92 (69.7%), at Center B was 50 (39.7%), at Center C was 26 (36.1%), and at Center D was 11 (61.1%) (*Supp. 1*). The mean SUV_{max} and number of UBUs at Center A were 4.6 and 193 (55.0%), respectively; at Center B, they were 3.9 and 98 (27.9%), respectively; at Center C, they were 3.0 and 42 (12.0%), respectively; and at Center D, they were 5.8 and 18 (5.1%), respectively (*Fig. 6b*). At none of the centers was an association between the occurrence of UBUs and injected activity found (Center A: $U = 1649.00, Z = 0.95, p = .34$; Center B: $U = 1806.50, Z = -0.47, p = .64$; Center C: $U = 446.50, Z = 1.78, p = .08$; Center D: $U = 17.00, Z = -1.95, p = .05$) (*Supp. 2*). The mean and SD for injected activity at Center A was 233 MBq \pm 40.4, for Center B was 299.4 MBq \pm 35.2, for Center C was 282 MBq \pm 34.9, and for Center D was 258.8 MBq \pm 50.0.

Discussion

Our study showed a high frequency (60%) of UBUs in patients undergoing [^{18}F]-PSMA-1007 PET. The first publication that reported an increased number of benign and unspecific lesions using [^{18}F]-PSMA-1007, compared to [^{68}Ga]-PSMA-11, also found a substantially higher number of unclear or likely benign findings in the bones (48% vs. 14.7%), lymph nodes (39.2% vs. 13.7%), and ganglia (66.7% vs. 11.8%) [18]. The lower positron energy with higher spatial resolution and the higher signal-to-background ratio due to the longer half-life of [^{18}F] compared to [^{68}Ga] were suggested as possible explanations for this higher incidence [18]. Another potential reason for the increased bone uptake might be free [^{18}F] accumulating in the bones when the [^{18}F]-PSMA-1007 is unstable. However, it is unclear why the accumulation would be so focal without evidence of increased sclerosis on CT. In addition, immunohistochemistry studies have shown that PSMA is not only expressed in prostate tissue, but is also present in inflammatory and neovascular tissue [20,21]. Activated granulocytes in the bone marrow might therefore also lead to focal bone marrow uptake. Ultimately, the exact mechanism remains unclear; given that UBUs usually persist in follow-up scans, a morphological correlate seems likely. In our cohort, only three UBUs were biopsied, all of them localized in the pelvis and all diagnosed as benign (two hyperplastic bone marrow and one Paget's disease).

In our cohort, there was no association between UBU and age, ISUP score, tumor size (T classification), or PSA level, further underlining the difficulty of interpreting the lesions. The most common site of UBU was in the ribs, followed by the pelvis and spine. Wang et al. analyzed the distribution of prostate cancer bone metastases based on bone scans [22] and found that patients with a low number of lesions were most likely to have metastases in the spine, followed by the pelvic bones. They also found that only 1% of patients had bone metastasis outside the spine and pelvis without also having metastasis in those regions. This reinforces the theory that singular or multiple UBUs in the ribs without coexisting suspicious lesions in the spine or pelvis are most likely benign. However, although unlikely, there are cases with solitary bone metastasis in the sternum or ribs, as shown in *Fig. 1a-c*. More sensitive imaging tools than bone scans might also detect more uncommon locations of bone lesions.

Bone metastasis occurs in approximately 10% of patients with newly diagnosed prostate cancer, rising to 80–90% of patients in the advanced stage [23–25]. Gandaglia et al. found a 1.5-fold higher risk of dying with metastasis than with only nodal involvement [25]; this non-negligible increase in the mortality rate strengthens the need for accurate determination of the site of metastases in staging newly diagnosed prostate cancer.

There was a wide variation of frequencies between the different centers, ranging from 36.1% to 69.7%. This difference might be attributed to the higher scanner sensitivity, given that Center A, at 69.7%, was the only institution with digital PET technology. Several studies have shown improvements in lesion detection with digital scanners compared to analog systems for ^{18}F -FDG PET, possibly also leading to higher detectability of UBUs using [^{18}F]-PSMA-1007 [26,27]. This was suggested by Alberts et al., who reported a higher detection rate of both prostate cancer lesions and benign PSMA-avid lesions with digital than with analog systems [28]. It can therefore be assumed that, with more installations of high-end digital PET systems, the frequency of UBU in ^{18}F -PSMA-1007 imaging will become even more challenging.

The increase in UBU in [^{18}F]-PSMA-1007 imaging might impair clinical decisions and could lead to an increase in follow-ups with imaging in cases of ambiguity. Due to the significantly higher number of UBUs with [^{18}F]-PSMA-1007, the previously suggested standardized image interpretation for [^{68}Ga]-PSMA-PET/CT published by Fanti et al. should not be adopted for [^{18}F]-PSMA-1007 [29], else the frequency of findings defined as pathological could be significantly higher, leading directly to an overdiagnosis of bone metastasis. *Fig. 7* shows an example of PSMA-avid bone lesions over-diagnosed as bone metastasis in [^{18}F]-PSMA-1007 PET/MRI, with a potential impact on the patient's primary treatment protocol.

The clinical significance of lesions is very subjective and can only be evaluated by incorporating clinical information, as well as the patient's decision, which was beyond the scope of this retrospective study. We therefore evaluated the hypothetical impact of UBUs on patient management in the different imaging settings and tried to reflect how often UBUs actually resulted in a CP. Based on this assessment, 80 out of 179 patients with UBUs were considered to have CPs (44.7%), but despite this relatively high number, only 39 of the 179 (21.8%) had a follow-up examination. This might be partly due the high number of still-unclear results after follow-up imaging (*Fig. 5*).

This is a retrospective analysis with associated limitations, most important being the lack of histopathological findings for the bone lesions. Histopathological analysis of UBUs was performed in only three out of 179 patients, showing the difficulty of biopsies for lesions without morphological correlates. Furthermore, while the differences in scanners and protocols at the different centers offer some insights into, for example, the impact of scanner technology on the incidence of UBUs, the asymmetric contributions of the different institutions may have led to a certain bias (e.g., Center D having a relatively high number of UBUs [63.5%] despite analog detectors, but an overall low number of scans). In addition, unspecific bone lesions were selected and clinical implications interpreted subjectively, without a second reading or consensus.

Conclusion

Despite the above-mentioned advantages of [¹⁸F]-PSMA-1007 over [⁶⁸Ga]-PSMA-11, we found a high incidence of UBUs—which are clinically challenging—in a significant number of patients. If examinations are performed using digital PET scanners, UBUs are detected more frequently than using analog PET scanners. UBUs should be interpreted carefully to avoid over-staging.

Declarations

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Conflicts of interest/Competing interests

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Availability of data and material

The analyzed data may be available from the corresponding author upon reasonable request and with the permission of University Hospital Zurich, University of Zurich, Switzerland.

Code availability

Not applicable

Authors' contributions

Joachim Müller, Klaus Strobel, and Irene. A. Burger contributed to the study conception and design. All authors contributed to the data collection. Alexander Maurer performed the data processing and analysis. The first draft of the manuscript was written by Hannes Grünig and Alexander Maurer. All authors read and approved the final manuscript.

Ethics approval

General consent was present or was waived by the local ethics committee.

Consent to participate

Not applicable

Consent for publication

Not applicable

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Tables

Table 1: Patient characteristics and demographic data	
	348
Number of patients	
Age (y) (median, IQR)	71.0 (IQR 66–76)
Indication for [¹⁸ F]-PSMA-1007-PET, n = 348	
<i>EBR</i>	227 (65.2%)
<i>Tumor evaluation</i>	71 (20.7%)
<i>Staging</i>	49 (14.1%)
Initial T classification, n = 281	
<i>T1</i>	30 (10.7%)
<i>T2</i>	88 (31.3%)
<i>T3</i>	151 (53.7%)
<i>T4</i>	12 (4.3%)
Initial N classification, n = 267	
<i>N0</i>	163 (61.0%)
<i>N1</i>	97 (36.3%)
<i>Nx</i>	7 (2.6%)
Initial M classification, n = 267	
<i>M0</i>	215 (83.7%)
<i>M1</i>	23 (8.9%)
<i>Mx</i>	19 (7.4%)
Resection boundaries (R), n = 142	
<i>R0</i>	62 (43.7%)
<i>R1</i>	80 (56.3%)
Patients with bone metastasis	79 (22.7%) of 348
Median of PSA values [ng/ml]; n = 306	
<i>overall</i>	2.5
<i>EBR</i>	1.2
<i>Tumor evaluation</i>	10.7

<i>Staging</i>	11.7
ISUP grade groups, n = 291	
<i>ISUP 1</i>	23 (7.9%)
<i>ISUP 2</i>	48 (16.5%)
<i>ISUP 3</i>	83 (28.5%)
<i>ISUP 4</i>	74 (25.4%)
<i>ISUP 5</i>	63 (21.6%)
Values are given as absolute numbers and percentages in parentheses or median. EBR: early biochemical recurrence. IQR: interquartile range.	

Figures

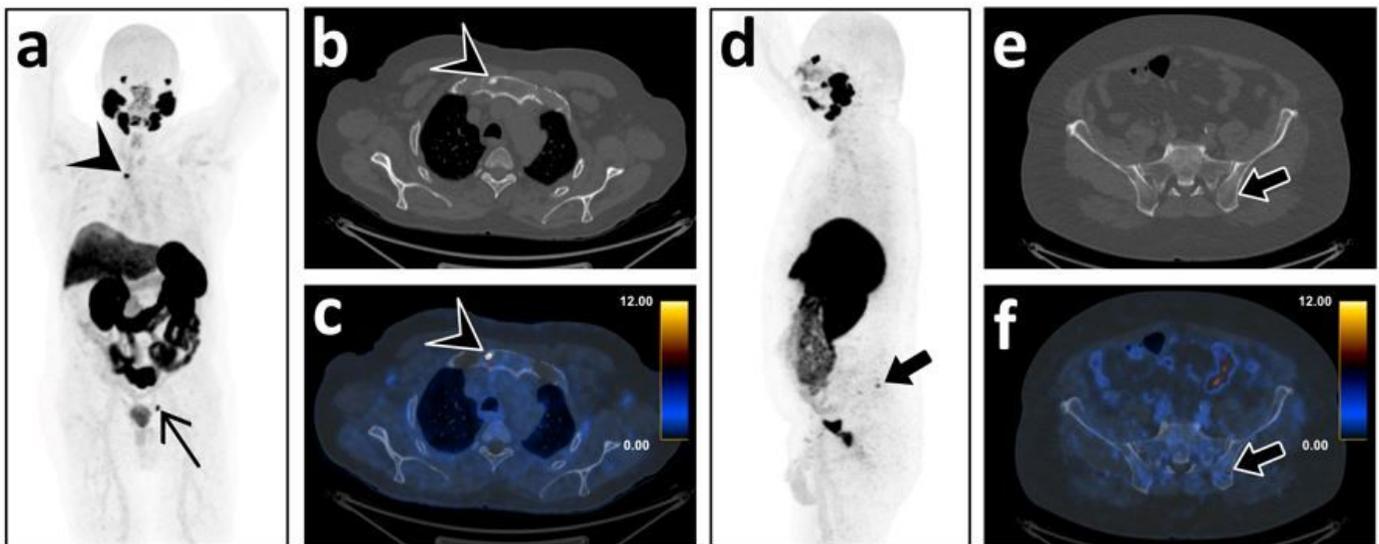


Figure 1

[¹⁸F]-PSMA-1007-PET/CT on a digital scanner illustrates bone metastasis and UBU in two different patients with prostate cancer: (a) a whole-body maximum intensity projection of PET shows a high PSMA-positive bone lesion (SUV_{max} 23.8) in the manubrium sterni (arrowhead) and a lymph node metastasis in the left pelvis (thin black arrow). (b) Focal sclerosis in the manubrium sterni (arrowhead) on axial CT, (c) corresponding to the high PSMA uptake on the fused images, suggests bone metastasis. (d)

A whole-body maximum intensity projection of PET with a moderate PSMA-positive lesion (SUVmax 9.5) in the left ischium (bold arrow), (e) without morphological correlation on axial CT, was rated as an unspecific finding on PET/CT imaging (f).

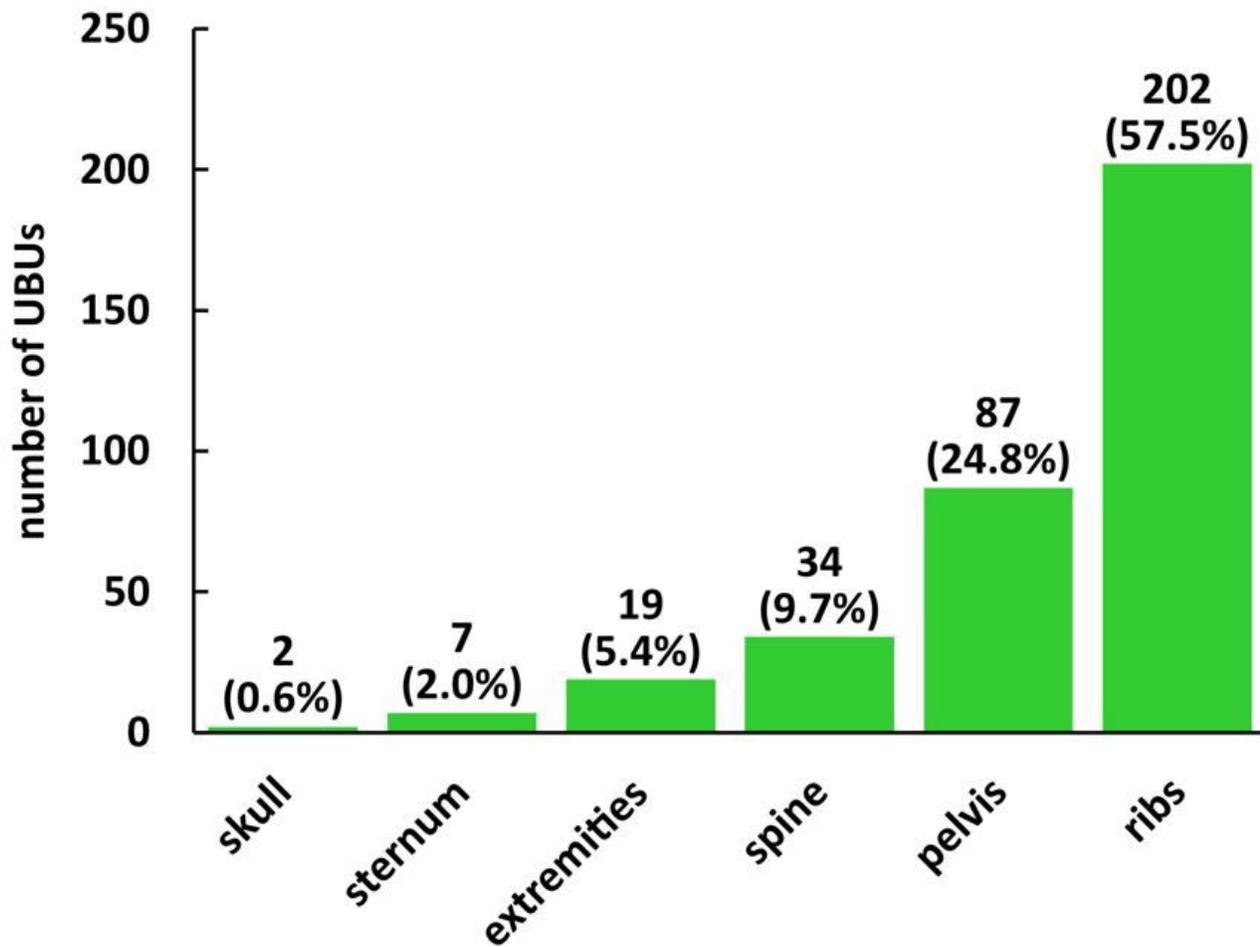


Figure 2

Number of the three most active UBUs by anatomic region in [18F]-PSMA-1007-PET.

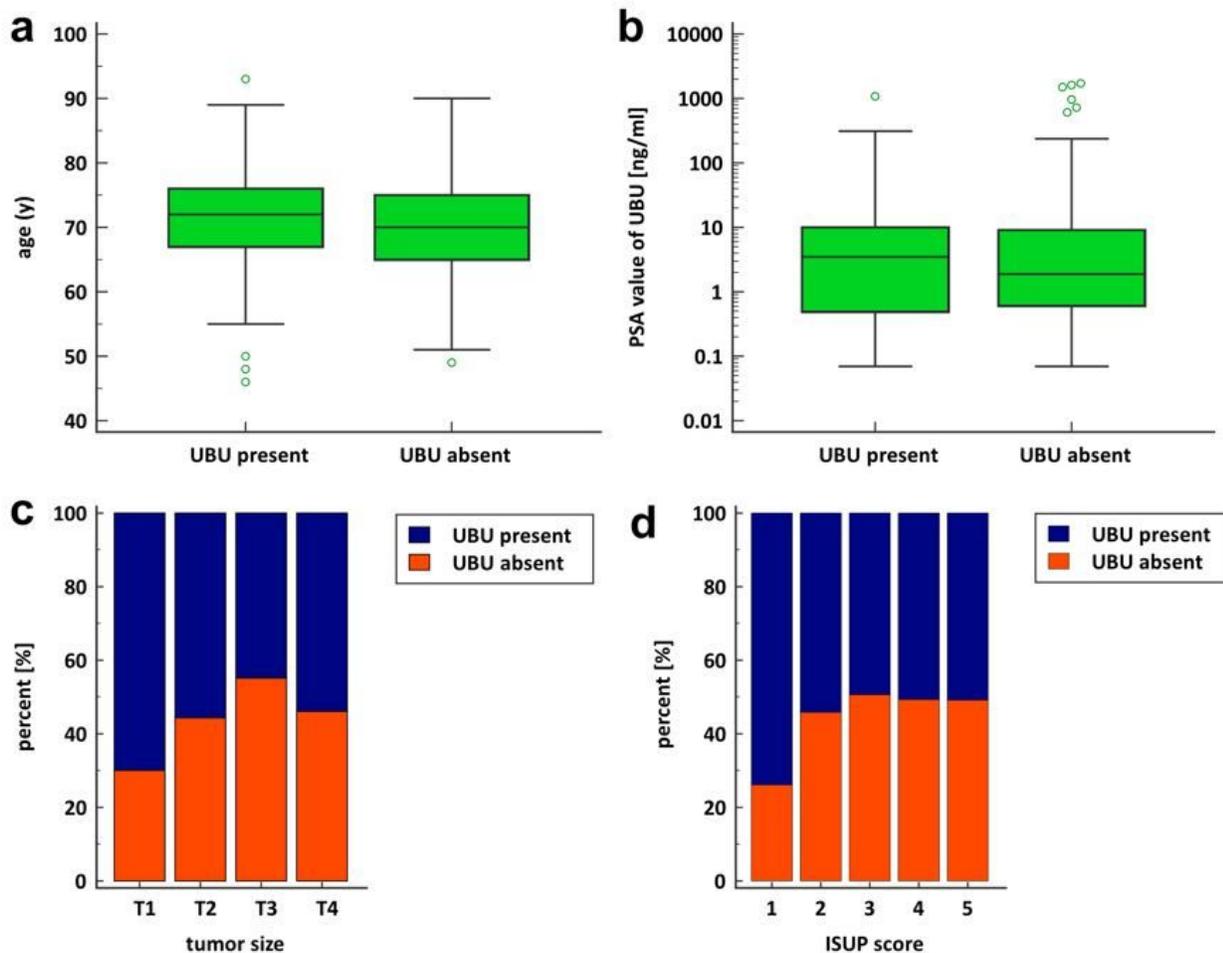


Figure 3

(a) Box-whisker plots show no significant association between age and frequency of UBUs ($p = .02$, but the 95% CI of median difference was not significant) (b) Box-whisker plots show no significant association between PSMA value and the frequency of UBUs ($p = .05$). (c) Bar charts with the percentage distribution of the frequency of UBUs for each tumor size. (d) Bar charts with the percentage distribution of the frequency of UBUs for each ISUP score.

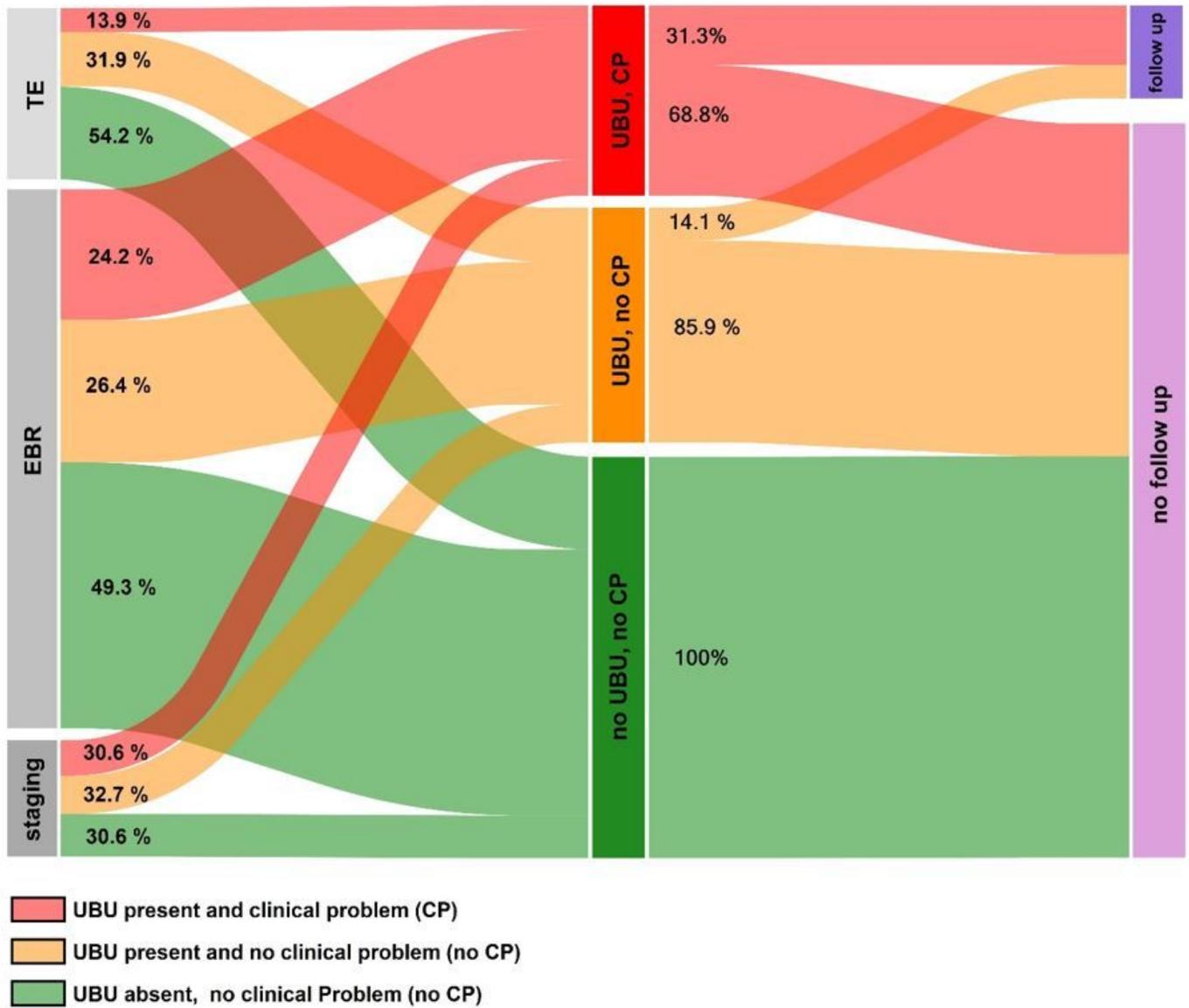


Figure 4

The left part of the Sankey diagram shows the frequencies of patients with UBU-related clinical problems (CP) or without UBU-related CPs for early biochemical recurrence (EBR), tumor evaluation (TE), and tumor staging. The right part of the Sankey diagram shows the percentages of patients with and without follow-up examinations.

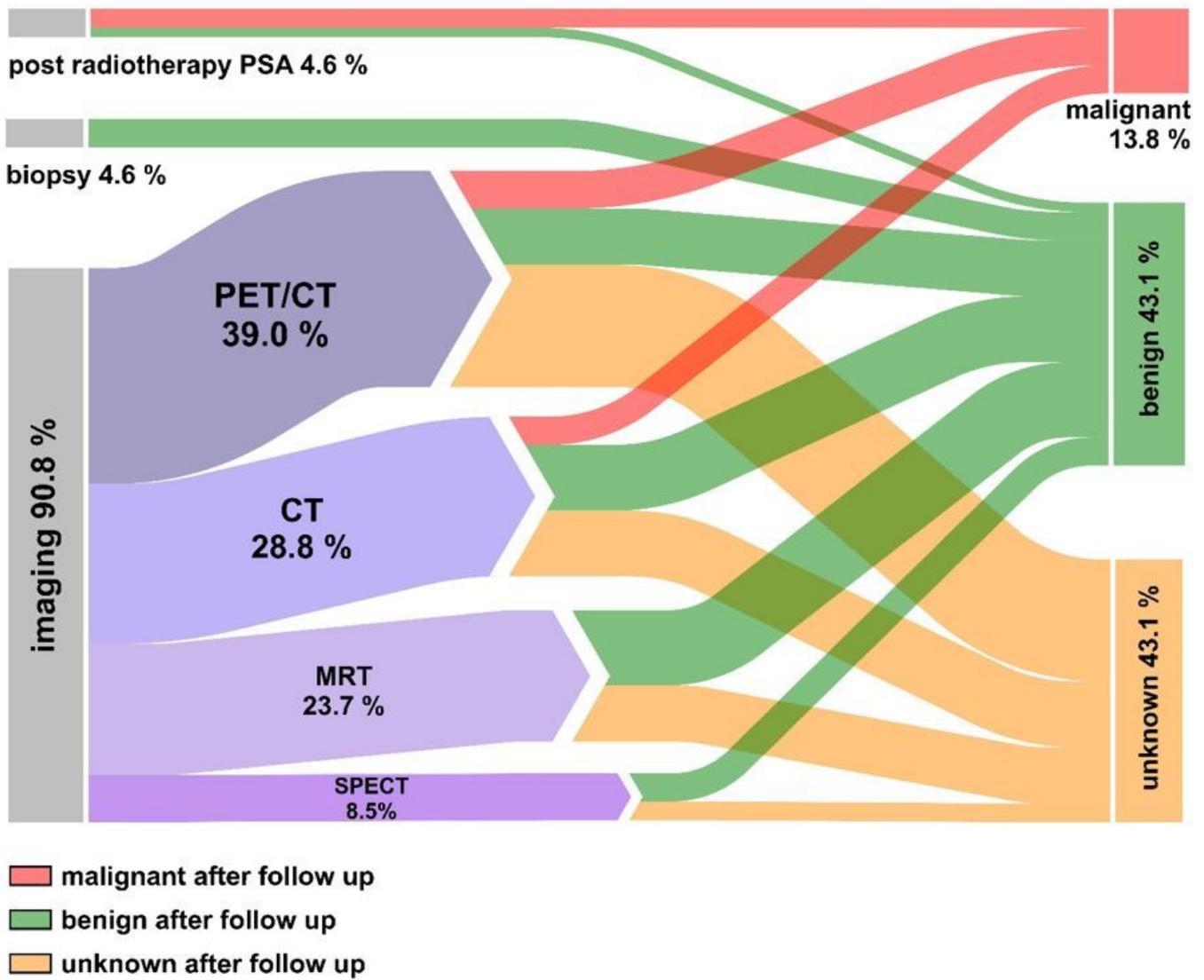


Figure 5

The Sankey diagram shows the percentages of UBUs that were followed up by imaging, biopsy, and post-radiotherapy PSA, as well as the final assessment of the lesions after follow-up (malignant, benign, and unknown).

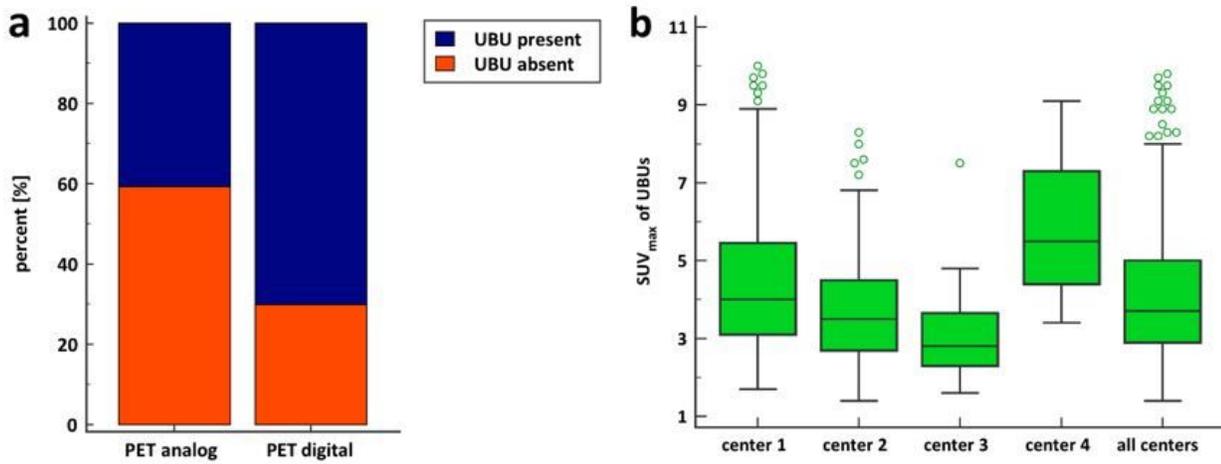


Figure 6

(a) Bar charts with the percentage distribution of the frequency of UBUs for analog and digital PET scanners. (b) Box-whisker plots showing the SUV_{max} for UBUs at each center separately and for all centers combined.

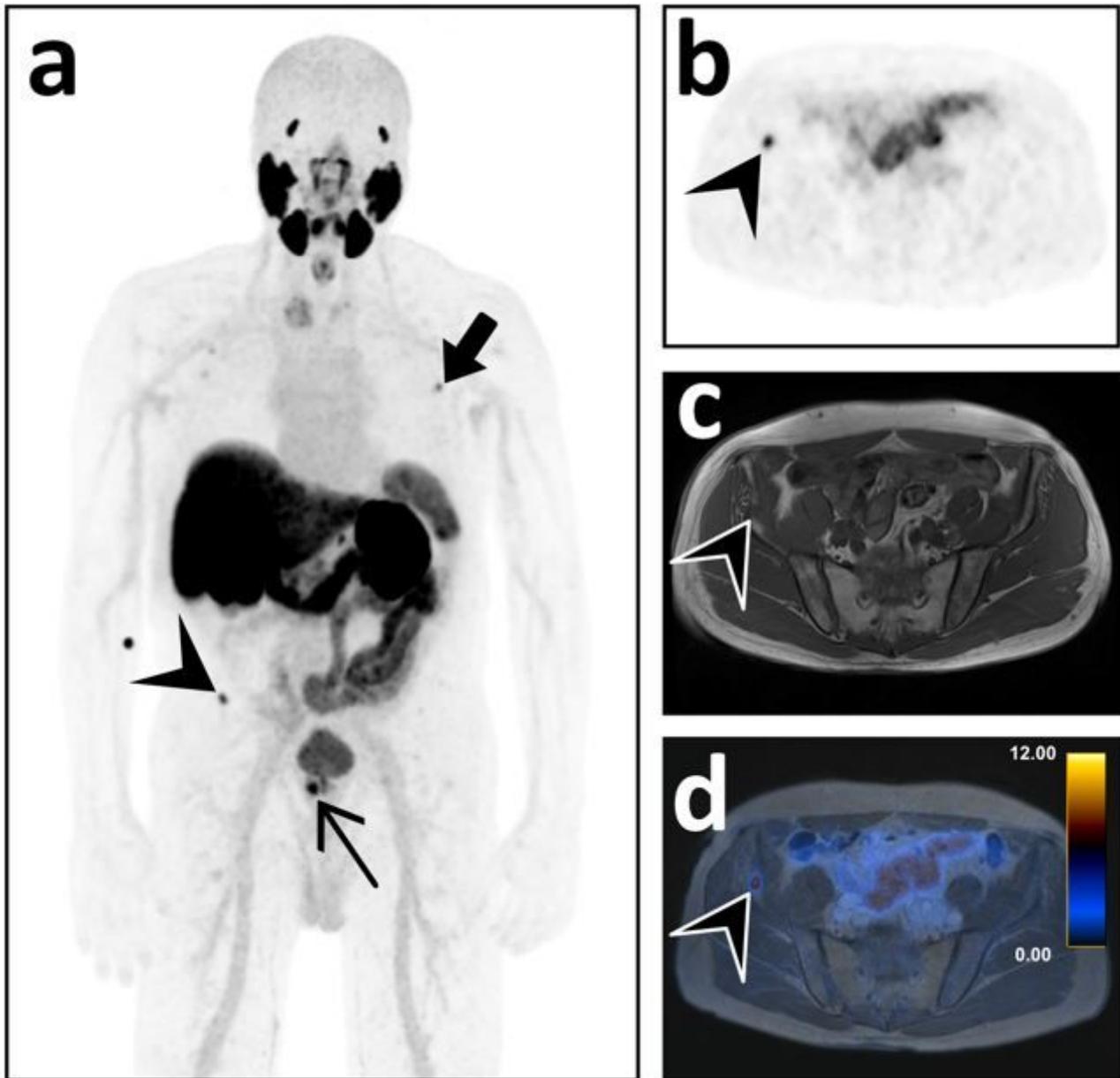


Figure 7

Pretherapeutic [18F]-PSMA-1007-PET/MRI staging examination of a 71-year-old patient with prostate cancer, tumor stage pT3b pN0, ISUP 4, and initial PSA of 24.4 $\mu\text{g/l}$: (a) A whole-body maximum intensity projection showing the PSMA-positive prostate cancer (thin arrow), no lymph node metastasis, an unspecific bone uptake (SUVmax 7.0) in one left rib (bold arrow), and a stronger PSMA-positive bone lesion in the right pelvis (SUVmax 8.7). (b) The pelvic bone lesion in PET (arrow head). (c) A hypointense morphological correlate on T1-weighted imaging. (d) The lesion on fused PET/MRT (arrow head). After radical prostatectomy, the PSA normalized (several follow-ups with a PSA of $< 0.05 \mu\text{g/l}$) without further therapy, suggesting that both bone lesions were most likely benign.

Supplementary Files

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- [SupplementalFigures.docx](#)