Staging ^{68}Ga-PSMA PET/CT in 963 Consecutive Patients with Newly Diagnosed Prostate Cancer: Incidence and Characterization of Skeletal Involvement

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Research Article

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Abstract

Purpose: The aim of the study was to elaborate the incidence and type of skeletal involvement in a large cohort of patients with newly diagnosed prostate cancer (PCa) referred for Ga-68 PSMA-11 PET/CT staging in a single center.

Methods: Study cohort included 963 consecutive patients with newly diagnosed PCa referred Ga-68 PSMA-11 PET/CT study for staging. The incidence of bone involvement, type of bone metastases, extent of disease were determined and correlated with the ISUP Grade Group (GG) criteria, and PSA levels.

Results: Bone metastases were found in 188 (19.5%) of 963 patients. Osteoblastic type metastases were the most common type of bone metastases presented in 133 of the patients with malignant bone involvement (70.7%). Slightly more than half of them (54.1%) had "pure" osteoblastic lesions, while the other 45.9% had also intramedullary and/or osteolytic type lesions. Intramedullary metastases were found in 97 patients (51.6%), while 41 (21.8%) of them were "pure" intramedullary lesions. Osteolytic metastases were detected in 36 patients (19.2%), of which 8 were "pure" osteolytic lesions. Bone metastases were found in 10.7% of patients with PSA<10 ng/dL and in 27.4% of patients with PSA>10 ng/dL; in 6.1% of patients with GG≤2/3 and in 8.9% of patients with GG 4/5. In 7.6% of the patients, skeletal involvement was extensive, while 11.9% of patients had oligometastatic disease.

Conclusion: Although traditionally bone metastases of PCa are considered osteoblastic; osteolytic and intramedullary metastases are common, as identified on PET with labeled-PSMA.

Introduction

Advanced prostate cancer (PCa) metastasizes primarily to bone [1]. Autopsy series revealed that more than 90% of patients diagnosed with metastatic PCa show evidence of bone metastases [2]. Treatment algorithms for patients with newly diagnosed PCa reflect the need to identify metastatic involvement of the skeleton prior to definitive therapy, particularly in patients at high-risk for advanced disease. Identification of early skeletal spread and accurate determination of disease extent has been an ongoing challenge of imaging modalities [1, 3, 4].

For decades, bone scintigraphy (BS) with Tc-99m methylene diphosphonate (Tc-99m MDP) has been the most commonly used modality for detection of bone metastases [5]. Bone metastases of PCa are considered traditionally as “osteoblastic” (OB) by conventional radiographs and CT. Uptake of Tc-99m MDP is closely associated with osteoblastic activity and increased blood flow and therefore is highly sensitive for detection of OB type cortical metastases. Clinical and imaging guidelines recommend BS for initial staging of patients with intermediate-risk and high-risk disease [6–9]. However, data accumulated over the years explored the limitations of BS in detecting intramedullary (IM) and osteolytic (OL) type metastases that also present in PCa patients. The incidence of the latter types of metastases remains elusive [1, 5].

The use of positron emitting radiotracers accumulating directly in tumor tissue gave rise to a completely new concept of assessment of malignant skeletal involvement. F-18 Fluorodeoxyglucose (F-18 FDG), the most commonly used tracer in oncologic PET/CT, is unfortunately not always suitable for imaging of PCa [1]. The role of C-11 and F-18 choline PET/CT for lymph nodes or bone involvement in PCa was investigated. Labeled choline was found highly specific as well as allowing for early identification of IM and OL type metastases [10, 11].

Labeled prostate-specific membrane antigen (PSMA) is a relatively novel PET recently introduced in routine staging of prostate cancer patients with unequivocal superiority over routine BS in detecting bone metastases [12–18]. In the meta-analysis of 24 articles by Zhou J, et al on the role PSMA PET/CT, choline PET/CT, F-18 fluoride PET/CT, MRI, and BS in the diagnosis of bone metastasis, PSMA PET/CT was found with highest per-patient sensitivity and specificity [17).

The purpose of the current study was to elaborate the incidence and type of skeletal metastases in a large cohort of patients with newly diagnosed prostate cancer referred for PSMA PET/CT for staging prior to definitive therapy. Labeled PSMA PET/CT is nationally-reimbursed for staging of patients with newly diagnosed prostate cancer, which allowed us to perform the study on consecutive patients.

Materials And Methods

Patients

Having the institutional review board approval, we queried our database to retrieve 963 consecutive patients with newly diagnosed PCa, who had a staging Ga-68 PSMA-11 at our department between November 2015 and September 2020. Characteristics of the patients are summarized in Table 1. Gleason score was available in 839 of 963 patients. Patients were categorized based on the International Society of Urological Pathology (ISUP) Grade Group (GG) criteria [19].

Table 1
Characteristics of patients.

Number of pts	**963**
Mean age (y)	70.86 ± 7.796
ISUP	Pts, n (%)
1	126 (13.1%)
2/3	418 (43.4%)
4	167 (17.3%)
5	128 (13.3%)
Not available	124 (12.9%)
PSA (ng/dl)	Pts, n (%)
<5	149 (15.5%)
5-10	281 (29.2%)
10-20	217 (22.5%)
>20	250 (26.0%)
Not available	66 (6.8%)
Pts - patients; PSA - Prostate-specific antigen;	

PET/CT imaging

A dose of 148–166.5 MBq Ga-68 PSMA-11 was injected intravenously 50–100 min before acquisition. The patients were instructed to void immediately prior to acquisition. PET/CT studies were performed from the tip of the skull to mid-thigh using Discovery 690 or MI PET/CT systems (GE Healthcare).

CT acquisition of the PET/CT was performed using automatic mA-modulation and 120 kV. CT scans were reconstructed to a slice thickness of 2.5 mm. PET acquisition was performed with acquisition time of 3 min per bed position in 3D mode. PET images were reconstructed in a matrix size of 128 × 128 with a pixel size of 5.5 mm and slice thickness of 3.3 mm for the 690 system and a matrix size of 256 × 256 with a pixel size of 2.7 mm and slice thickness of 2.8 mm for the Discovery MI system. Reconstruction method was VUE Point FX by GE Healthcare that uses time of flight information and includes a fully 3D OSEM algorithm with 3 iterations. For the 690 systems reconstruction method used 24 subsets, and filter cutoff of 8 mm and for the Discovery MI we used 8 subsets, and filter cutoff of 6.0 mm. VUE Point FX algorithm also includes normalization and image corrections for attenuation, scatter, randoms, and dead time. A heavy Z-filter was applied to smooth between transaxial slices.

Image analysis

All scans were reviewed by nuclear medicine physicians (MK, JK, EES), body radiologist (CL) and musculoskeletal radiologist (ID).

Any skeletal lesion showing above normal uptake not associated with physiological uptake was recorded [20]. The nature of each bone lesion was based on its location within the bone (marrow-based or cortical), its morphologic appearance on CT or MRI data and the changes seen on follow up PET/CT scans after treatment. Equivocal bone lesions were evaluated according to the PSMA-RADS, version 1.0 system [21], which has been previously validated [22]. Lesions diagnosed as metastasis were classified as: 1. OB – focal increased uptake corresponding to a cortical lesion showing higher HU compared to surrounding bone tissue (Fig. 1). 2. OL – focal increased uptake corresponding to a cortical lesion showing bone destruction (Fig. 2). 3. IM – focal increased uptake located in the bone marrow with intact cortical bone on CT (Fig. 3).

Patients with bone lesions were further categorized based on the type of lesions identified: IM metastasis, cortical metastasis (OB, OL or mixed) and combined IM and cortical metastasis [1, 18]. Based on the number of metastatic lesions patients were categorized as having a single metastasis, oligometastatic disease (2-5 metastatic skeletal lesions) and patients with extensive metastatic spread (> 5 metastases) [23]. The incidence of bone metastasis and the extent of disease were correlated with clinical characteristics.

Statistical analysis

Categorical variables were described as frequency and percentage. Continuous variables were evaluated for normal distribution using histogram. Normally distributed variables were reported as mean and standard deviation (SD) and skewed variables as median and interquartile range (IQR). Independent sample T-test and Mann-Whitney test were applied to compare continuous variables between metastatic categories. The area under the receiver operating characteristic (ROC) curve was used to evaluate the discrimination ability of Gleason score, ISUP Grade Group and PSA. All statistical tests were two sided and $p<0.05$ was considered as statistically significant. Statistical analysis was performed using SPSS statistical software (IBM SPSS Statistics for Windows, version 27, IBM Corp., Armonk, NY, USA, 2020).

Results

Bone metastases were detected in 186 patients. In 45 additional patients, bone lesions detected on PET were interpreted as benign or equivocal: 16 were single sites of tracer accumulation in the ribs with no corresponding morphological changes on CT with no evidence of metastatic skeletal spread on follow up [24]. Twenty-seven scintigraphic lesions corresponded to benign findings on CT including fibrous dysplasia (n=16), hemangioma (n=5), fracture (n=3), enchondroma (n=2) and Paget's disease (n=1). Two equivocal lesions found in two patients were metastases based on the findings on follow-up PET. The latter patients were included in the results analysis to the group of patients with metastatic skeletal spread.

One hundred eighty eight of consecutive 963 patients with newly diagnosed PCa (19.5%), were diagnosed with metastatic skeletal involvement on staging Ga-68 PSMA-11 PET/CT. In 57 of the study patients (5.9%), a single metastasis was identified, 58 patients (6%) had oligometastatic disease and 73 (7.6%) had extensive skeletal involvement.

In 839 of the study cohort, the ISUP data was available. Bone metastases were found in 11.1% (14/126) patients with GG 1 representing 1.5% of the patients with low-risk disease; in 10.5% (44/418) patients with GG 2/3 representing 4.6% of the patients with intermediate risk disease and, in 21.6% (36/167) patients with GG 4 and 39.1% (50/128) patients with GG 5 representing 8.9% of the patients with high-risk disease. A total of 10.7% (58/544) of patients with Gleason Score $\leq$7 were found to have metastatic skeletal spread based on PET/CT findings.

Mean PSA±SD in patients with no evidence of metastatic skeletal involvement was significantly lower than in patients with bone metastases: 16.71±31.97 vs 138.27±401.82 ng/dL ($p<0.05$). Bone metastases were found in 10.7% (46/430) of patients with PSA<10 ng/dL and in 27.4% (128/467) of patients with PSA>10 ng/dL (14.1% (21/149) of patients with PSA<5 ng/dL, 8.9% (25/281) of patients with PSA 5-10 ng/dL, 13.8% (30/217) of patients with PSA 10-20 ng/dL and 39.2% (98/250) of patients with PSA >20 ng/dL).

Data on type of metastases, combination of metastases types and the extent of disease are summarized in Table 2. OB type metastases were the most common type of bone metastases presented in 133 of the patients with malignant bone involvement (70.7%). In 72 of the latter (54.1% of patients with OB bone metastases), "pure" OB lesions were identified while the other 61 patients had also IM and/or OL type lesions. IM metastases were found in 97 patients (51.6% of patients with bone metastases). In 41 patients (21.8%), IM metastases was the only type of lesion detected. OL metastases were detected in 36 patients (19.2% of patients with bone metastases). In 8 (4.3%) patients, OL lesions were the only type of bone metastasis identified.

Table 2
Characteristics of bone metastases.

Patients	**pts (%)**
All pts	963
Pts without bone mts	775 (80.5%)
Pts with bone mts	188 (19.5%)
Number of mts	
Single (1)	57 (5.6%*)
Oligo (2-5)	58 (6%)
Extensive (>5)	73 (7.9%)
Types of mts	
1. IM mts	41 (21.8%**)
2. Cortical mts	91 (48.4%)
- OB mts	72 (38.3%)
- OL mts	8 (4.3%)
- Mixed mts***	11 (5.8%)
3. IM + Cortical mts	56 (29.8%)
- IM + OB	39 (20.7%)
- IM + OL	6 (3.3%)
- IM + mixed	11 (5.8%)
Pts - patients; mts - metastases; IM - intramedullary; OB - osteoblastic; OL - osteolytic; SD - Standard deviation:	
** - The percentage is calculated from the sum of all patients with prostate cancer (963 patients).*	
*** - The percentage is calculated from the sum of all patients with bone metastases (188 patients).*	
**** - Mixed metastases - both OB and OL.*	

The percentage distribution of different types of metastases in histograms 1-3, shows that “pure” OB metastases dominate in patients with oligometastases, in patients with low- and intermediate risk disease (GG ≤ 2/3), and in patients with PSA <20 ng/dL. Patients with extensive disease, high-risk disease (GG 4/5) and high PSA levels (≥20 ng/dL), had more often combined IM+cortical metastases.

Discussion

Malignant skeletal involvement of PCa develops as a multistep process initiating as intramedullary lesions in the distribution of the red active marrow [25]. In the marrow, tumor cells follow a lag phase of undetermined duration comprising a dormant phase followed by a more aggressive active phase with tumor-associated osteolysis and tumor-induced bone formation that dictates the final appearance of the lesion as OB or OL. Thus, metastatic processes are present in the bone marrow long before they give rise to derangement of the normal bone tissue architecture [26].

The incidence of bone metastases at staging of patients with newly diagnosed high risk PCa varies between 6.6–36.1% in different publications depending on the size of cohort and either SPECT or PET technology was used [4, 27–32]. Clinical guidelines [6–9], recommend performance of BS at staging when PSA is ≥20, clinical stage is T2 and PSA is ≥10 ng/dL, clinical stage is T3 or T4, Gleason score is ≥8, or any symptoms are suggestive of bone metastases. In the current study, we found metastatic involvement in 19.5% of patients with newly-diagnosed prostate cancer. As expected, patients with skeletal metastatic involvement were those with higher risk based on ISUP score and PSA levels. It should be noted however that metastatic skeletal spread was found also in 1.5% of patients with low risk (GG 1) and 4.6% of patients with intermediate risk (GG 2/3) (a total of 10.7% of patients with Gleason Score ≤7) and in 10.7% of patients with PSA ≤10 ng/dL.

Metastatic skeletal spread was found in almost 9% of high-risk patients with GG 4 or 5, in 27% of patients with PSA >10 ng/dL (include as high as 39% of patients with PSA level of 20 ng/dL and higher).

In the clinical setting, the extent of skeletal involvement influences the choice of the treatment. Patients with 5 or fewer metastatic bone lesions were reported to have a longer overall survival than patients with more than 5 metastases (73% vs 45% at 5 years and 36% vs 18% at 10 years), as well as longer disease-free survival. A specific cohort of patients with "oligometastases" is now recognized at staging evaluation [22, 33]. Treatment options for oligometastatic and extensive disease vary greatly [34]. In the current study, while a total of 19.5% of the study cohort were found to have malignant skeletal involvement, only 7.6% had extensive disease and the others had a single lesion or oligometastatic disease.

Bone metastases of PCa are considered OB based on their appearance on conventional radiographs. However, studies have shown a high heterogeneity of lesions, with synchronous osteolysis, even when the blastic appearance predominates. Histomorphometric studies have shown that OB lesions are mixed in nature with increased activity of both osteoblasts and osteoclasts contributing to the histological frailty observed in the skeleton in PCa patients, even in the presence of dense metastatic lesions [1].

Among patients with bone metastases we found OB type metastases in 70.7%. In only slightly more than half of them (54.1%) OB type spread was "pure" while in other 45.9% OL and/or IM metastases were also present. Patients with extensive disease, with GG 4/5 and with high PSA levels, had more often combined IM+cortical metastases, probably reflecting the aggressiveness of the disease, when mature metastases cortical ones and new marrow deposits co-exist.

In almost one third of patients with bone metastases, only OL type and/or IM metastases were present. We did not perform a head-to head comparison between the PET findings and bone scintigraphy, but these results raise a question regarding the ability to relay on BS for staging of newly diagnosed prostate cancer and for assessment of disease extent in view of the limited sensitivity of BS in detection of lytic type and marrow-based metastases.

Two recent manuscripts, one evaluating 30 patients and the other evaluating 35 PCa patients, reported a high sensitivity of PSMA PET/CT in detection of the various types of bone metastases [18, 29]. In 2015, Ceci, et al [33] published a study on the incidence of various metastases type in 140 newly diagnosed prostate cancer patients with bone involvement as identified on C-11 Choline PET/CT. There are some differences in the findings presented by the above publication and ours probably. We found a higher incidence of IM metastases (21.8% of the patients with metastatic spread), compared to 6.5% in the C-11 Choline PET/CT report. We found "pure" OB type metastases in 38.3% of the patients and "pure" OL type metastases in 4.3% compared to 62.3% and 26.1% respectively, on the C-11 Choline PET/CT study. Possible causes for the differences may be the different performance of labeled choline and labeled PSMA, difference in cohort size, and the fact that our cohort is composed of consecutive patients. The national-reimbursement of PSMA PET/CT in newly diagnosed patients with intermediate and high risk prostate cancer, decreases the potential bias in referral of patients for PET/CT staging.

As previously described by others, increased uptake of labeled PSMA in the skeleton may be seen also in non-malignant lesions [21, 23, 35]. A list of benign bone lesions were reported to be associated with labeled PSMA accumulation including fibrous dysplasia, Paget’s disease, enchondroma, fracture. These lesions can be accurately diagnosed on the data of contemporaneous CT and should not be reported as metastases. Increased uptake in the rib with no morphological abnormality or other skeletal lesions is a common finding that is likely to be a false positive site of uptake and should be mentioned with caution. Only two lesions reported as equivocal were found in the current study to be metastases.

In summary:

PSMA PET/CT staging of 963 consecutive patients with newly diagnosed intermediate and high-risk PCa revealed malignant skeletal involvement in 19.5% of the patients but only 7.6% had extensive disease while the others had a solitary lesion or oligometastatic disease. Extensive disease was closely related with high ISUP Grade and high PSA level but was found also in patients with lower ISUP Grade and/or PSA level. Although bone metastases of PCa are considered OB, OL type and IM metastases are commonly identified on PET/CT.

Declarations

Author contribution: MK, OY, EES contributed to the conception of the study, data-collection, study design, writing, and revising the manuscript, KK, ID, JK, CL, DS, DK contributed to the data-collection, writing, and revising the manuscript, all authors read and approved the final manuscript.

Data availability: The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Ethics approval and consent to participate: All procedures performedin studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with human participants or animals performed by any of the authors. The study protocol was approved by the local institutional ethics committee (reference ID TLV-0327–20). All patients gave written informed consent.

Consent for publication: Not applicable.

Competing interests: The authors declare no competing interests.

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Figures

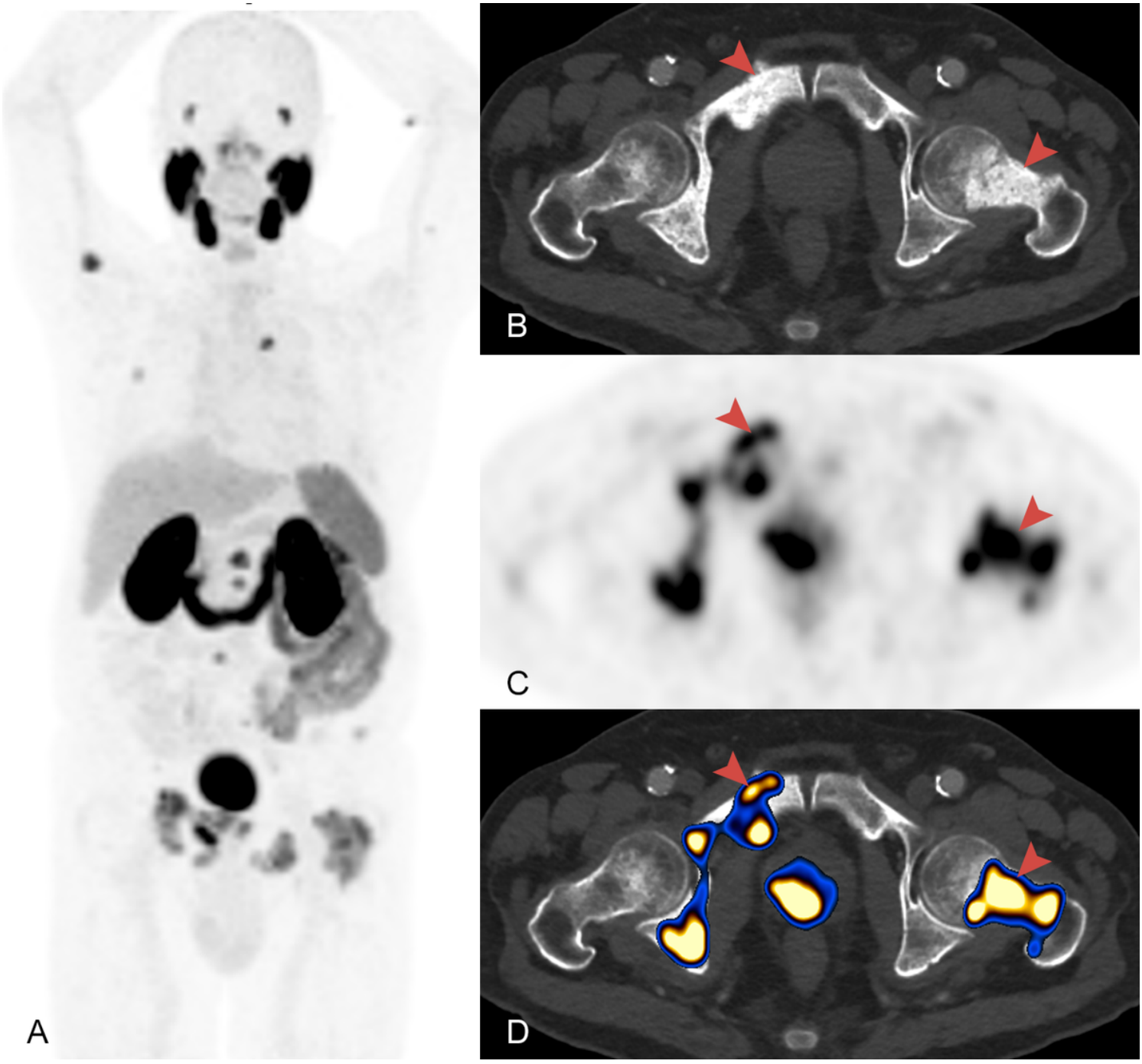

Figure 1

83-year old patient with a newly diagnosed prostate cancer, Grade Group 4, PSA 17.4 ng/dL. Extensive osteoblastic metastases (red arrowhead). A - maximum intensity projection, B - CT, C - PET, D - fusion

image.

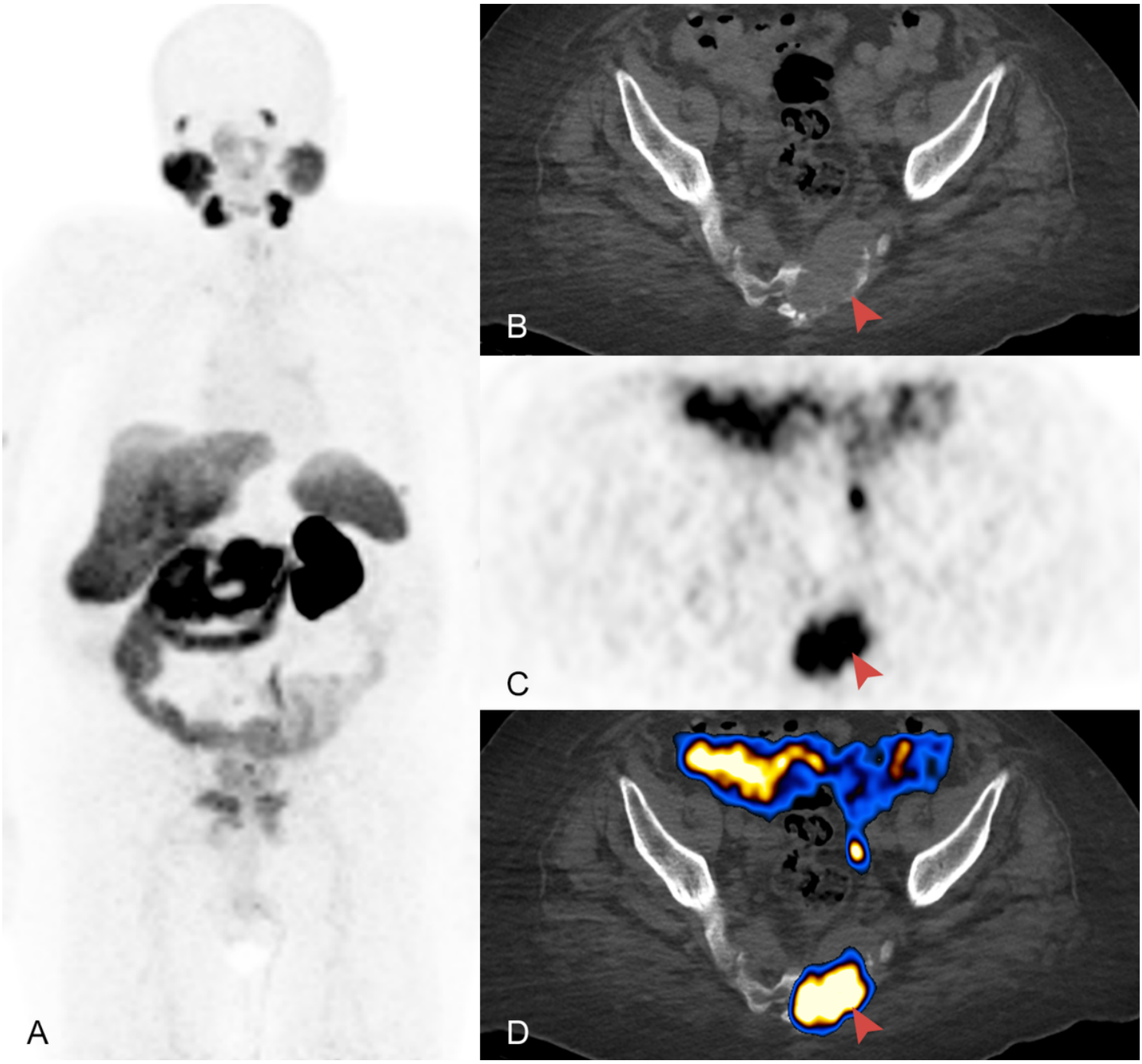

Figure 2

79-year old patient with a newly diagnosed prostate cancer, Grade Group 5, PSA 39.7 ng/dL. Osteolytic metastases with bone destruction and soft-tissue mass of the left sacrum (red arrowhead). A - maximum intensity projection, B - CT, C - PET, D - fusion image.

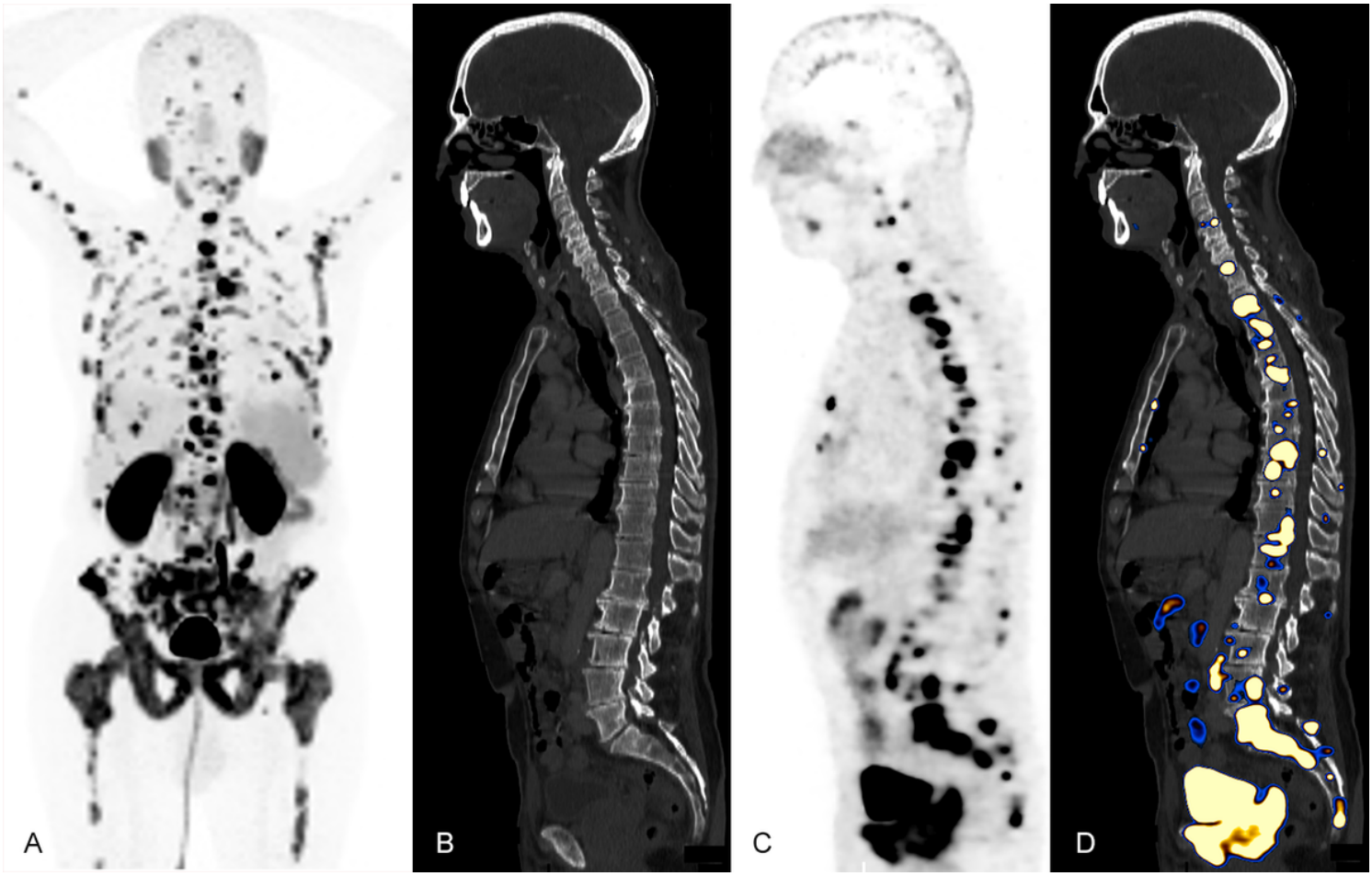

Figure 3

76-year old patient with a newly diagnosed prostate cancer, Grade Group 5, PSA 180 ng/dL. Extensive intramedullary metastases of the axial and appendicular skeleton with intact cortex. A - maximum intensity projection, B - CT, C - PET, D - fusion image.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- HistogramNo1.pdf
- HistogramNo2.pdf
- HistogramNo3.pdf