# Clinical Insignificance of [$^{18}$F]PSMA-1007 Avid Non-specific Bone Lesions: A Retrospective Evaluation

**Evyn G. Arnfield** ( evyn.arnfield@uqconnect.edu.au )
Royal Brisbane and Women's Hospital https://orcid.org/0000-0003-2462-6318
**Paul A. Thomas**
Royal Brisbane and Women's Hospital
**Matthew J. Roberts**
Royal Brisbane and Women's Hospital
**Anita M. Pelecanos**
QIMR: QIMR Berghofer Medical Research Institute
**Stuart C. Ramsay**
Royal Brisbane and Women's Hospital
**Charles Y. Lin**
Royal Brisbane and Women's Hospital
**Melissa J Latter**
Royal Brisbane and Women's Hospital
**Peter L. Garcia**
Royal Brisbane and Women's Hospital
**David A. Pattison**
Royal Brisbane and Women's Hospital

**Research Article**

**Keywords:** prostate cancer, [18F]PSMA-1007 PET, bone metastases

**Posted Date:** March 22nd, 2021

**DOI:** https://doi.org/10.21203/rs.3.rs-326201/v1



**Version of Record:** A version of this preprint was published at European Journal of Nuclear Medicine and Molecular Imaging on June 16th, 2021. See the published version at https://doi.org/10.1007/s00259-021-05456-3.

# Abstract

**Purpose**: [$^{18}$F]PSMA-1007 offers advantages of low urinary tracer excretion and improved resolution for imaging prostate cancer. However, non-specific bone lesions (NSBLs), defined as mild to moderate focal bone uptake without a typical morphological correlate on CT, are a common finding on [$^{18}$F]PSMA-1007 PET/CT. The purpose of this study was to investigate the clinical outcomes of patients with [$^{18}$F]PSMA-1007 avid NSBLs, to determine whether patients with NSBLs represent a higher risk clinical cohort, and to determine whether SUVmax can be used as a classifier of bone metastasis.

**Methods**: A retrospective audit of 214 men with prostate cancer was performed to investigate the clinical outcomes of [$^{18}$F]PSMA-1007 avid NSBLs according to defined criteria. We also compared the serum PSA, Gleason score and uptake time of patients with [$^{18}$F]PSMA-1007 avid NSBLs to patients without [$^{18}$F]PSMA-1007 avid bone lesions. Finally, we assessed whether SUVmax is a good classifier of bone metastases using ROC curve analysis.

**Results**: No [$^{18}$F]PSMA-1007 avid NSBLs met criteria for a likely malignant or definitely malignant lesion after a median 15.8-month follow-up interval (11.9% definitely benign, 50.3% likely benign, and 37.7% equivocal). There were no statistically significant differences in serum PSA, Gleason score and uptake time between patients with [$^{18}$F]PSMA-1007 avid NSBLs and those without [$^{18}$F]PSMA-1007 avid bone lesions. All NSBLs with adequate follow-up had SUVmax $\leq$11.1. When comparing NSBLs to definite prostate cancer bone metastases, the highest SUVmax value recorded was a good classifier of bone metastasis, and an SUVmax cut-point of $\geq$7.2 maximised the Youden's index.

**Conclusion**: [$^{18}$F]PSMA-1007 avid NSBLs rarely represent prostate cancer bone metastases. When identified in the absence of definite metastatic disease elsewhere, it is appropriate to classify those with SUVmax <7.2 as likely benign. NSBLs with SUVmax 7.2-11.1 may be classified as equivocal or metastatic, with patient clinical risk factors, scan appearance, and potential management implications used to guide interpretation.


# Introduction

Prostate-specific membrane antigen (PSMA) is a transmembrane cell surface protein which is overexpressed on prostate cancer cells. [$^{68}$Ga]Ga-PSMA-11 PET/CT imaging has greater diagnostic accuracy, management impact and fewer equivocal findings than conventional imaging with CT and bone scan in staging men with high risk prostate cancer[1]. [$^{18}$F]PSMA-1007 offers multiple potential advantages over [$^{68}$Ga]Ga-PSMA-11[2]. [$^{18}$F]PSMA-1007 is excreted primarily in bile rather than urine, and may increase reporter confidence in interpreting small locoregional lesions adjacent to the urinary tract in the absence of intensely avid radiourine present with [$^{68}$Ga]Ga-PSMA-11[3]. Furthermore, the [$^{18}$F] radionuclide is derived from a cyclotron rather than generator produced and has a longer half-life (110 minutes versus 68 minutes for [$^{68}$Ga]Ga-PSMA-11), therefore allowing a centralised and scalable

manufacturing process. $^{18}$F also has a lower positron energy than $^{68}$Ga, theoretically improving spatial resolution and target to background ratio. [$^{18}$F]PSMA-1007 has been reported to be non-inferior to [$^{68}$Ga]Ga-PSMA-11 for lesion detection sensitivity in patients with prostate cancer[4, 5]. One potential disadvantage is the reported increased incidence of [$^{18}$F]PSMA-1007 avid non-specific bone lesions (NSBLs), which do not meet criteria for definite prostate cancer bone metastases. A comparative study reported that 48% of 102 patients matched by clinical variables who underwent [$^{18}$F]PSMA-1007 PET/CT displayed NSBLs, compared to 15% of 102 patients who underwent [$^{68}$Ga]Ga-PSMA-11 PET/CT[6]. Similarly, a recent intraindividual comparison of [$^{18}$F]PSMA-1007 PET to one of three other prostate cancer PET tracers ([$^{68}$Ga]Ga-PSMA-11, [$^{18}$F]DCFPyL, and [$^{18}$F]JK-PSMA-7) identified 15 non-specific avid bone marrow foci on [$^{18}$F]PSMA-1007 PET that were not evident with other tracers, with none demonstrating a morphological correlate on CT and post-contrast MRI[3]. The natural history, likelihood of true prostate cancer metastases and optimal management of [$^{18}$F]PSMA-1007 avid NSBLs is unclear. The primary aim of this study was to perform a retrospective audit to investigate the clinical outcomes of patients with [$^{18}$F]PSMA-1007 avid NSBLs. A secondary aim was to compare the serum prostate specific antigen (PSA), Gleason score and uptake time of patients with [$^{18}$F]PSMA-1007 avid NSBLs to patients without [$^{18}$F]PSMA-1007 avid bone lesions to assess if patients with NSBLs represent a higher clinical risk cohort. A final aim was to determine whether maximum standardised uptake value (SUVmax) is a good classifier of bone metastases, by comparing [$^{18}$F]PSMA-1007 avid NSBLs in the retrospective cohort and definite prostate cancer bone metastases from a prospective research trial (defined by concordant typical avidity independently identified on both [$^{18}$F]PSMA-1007 and [$^{68}$Ga]Ga-PSMA-11 PET/CT).

# Materials And Methods

### Retrospective Patient Population:

Patients who underwent [$^{18}$F]PSMA-1007 PET/CT at the Royal Brisbane and Women's Hospital, a large tertiary referral hospital, between May 2018 to November 2019 were retrospectively considered (Figure 1). Inclusion criteria were men with histologically proven prostate cancer. Exclusion criteria were patients with [$^{18}$F]PSMA-1007 avid bone metastases, defined as PSMA-RADS 4 or 5 bone lesions[7] which were unequivocally reported as bone metastases by two experienced specialists. Indications for [$^{18}$F]PSMA-1007 PET-CT were (i) histologically proven prostate carcinoma staging prior to radiation therapy or surgery in intermediate or high-risk disease (i.e. PSA >20, or Gleason score ≥4+3=7, or clinically ≥T3), or (ii) restaging in the context of biochemical recurrence (PSA ≥0.2ng/ml post prostatectomy or ≥2.0ng/ml above the nadir post radiotherapy). The Gleason score at diagnosis, previous and / or current treatment, and most recent PSA value were also recorded. This audit was approved by the institutional review board of the Royal Brisbane and Women's Hospital, and the need for written informed consent was waived.

### [$^{18}$F]PSMA-1007 Manufacture and Quality Control:

[$^{18}$F]PSMA-1007 was manufactured on site using a kit-based approach on GE FASTlab or MX Tracerlab platforms, with comprehensive quality control testing of each batch to monograph standards for other F-18 radiopharmaceuticals (pH, chemical and radiochemical purity, radionuclide identity and purity, residual solvents, sterilising filter integrity, endotoxin and sterility). Product radiochemical purity was measured by high performance liquid chromatography (HPLC) with a pre-defined acceptance criterion of >95% [$^{18}$F]PSMA-1007. In separate experiments, free fluoride was also injected in our HPLC system to determine retention time and limit of detection for our instrument. While small radiopeaks (cumulatively less 5%) were observed close to the retention time of the product, no radiopeaks were observed corresponding to the retention time of free fluoride, excluding the presence of this impurity. In site validation processes, TLC tests were undertaken in parallel and no free fluoride was detected, further supporting the quantitative results of the HPLC testing. A product expiry of seven hours was assigned based on testing from end of synthesis.

### [$^{18}$F]PSMA-1007 PET/CT:

[$^{18}$F]PSMA-1007 was administered as an IV bolus (mean 250 MBq, range 218-272MBq, based upon Giesel et al. [4]), and all patients were scanned (median uptake time 126 minutes, range 119-137 minutes) on a Biograph mCT scanner (Siemens Medical Solutions) from vertex to thighs. A low-dose non-diagnostic CT was also performed for the purpose of anatomical localisation and attenuation correction. PET scans were acquired in three-dimensional mode with an acquisition time of 2.5 minutes per bed position, and a 4-minute bed position over the pelvis. Emission data were corrected for randoms, dead time, scatter, and attenuation, and were reconstructed iteratively using ordered-subsets expectation maximization (3 iterations, 21 subsets) with time of flight and point-spread function resolution recovery, followed by a post-reconstruction smoothing gaussian filter (5mm in full width at half maximum).

### Image Analysis:

All images were dual-reported by two experienced nuclear medicine specialists using Syngo Via software (Siemens Medical Solutions). The presence or absence of [$^{18}$F]PSMA-1007 avid NSBLs, defined as PSMA-RADS 3B lesions (i.e. equivocal uptake in a bone lesion not definitive but also not atypical of prostate cancer on anatomical imaging, including uptake without an anatomical correlate on CT)[7], were identified on reports and the scans were retrospectively reviewed. If present, the number (1,2,3,4,5,>5), regional site(s) (skull, cervico-thoraco-lumbar spine, pelvis including sacrum, ribs, sternum, pectoral girdle, upper limbs, lower limbs), and SUVmax of these lesions were recorded. The SUVmax was determined by placing a volume of interest encompassing the target lesion.

### Retrospective Outcome Measures:

Follow-up information was obtained from the electronic medical records of patients with NSBLs at a minimum of 12 months post [$^{18}$F]PSMA-1007 PET-CT scan. Follow-up measures sought were clinical notes, biochemistry (PSA, ALP), imaging (PET, bone scan, MRI, CT), and histopathology. Of patients with

follow-up available, clinical outcomes of NSBLs were assessed using the following criteria, adapted from Hofman et al.[1]:

1. Malignant hard criteria:
    a. Histopathology demonstrating prostate carcinoma metastasis
    b. Change to sclerotic / blastic on any follow-up imaging assessment
2. Malignant soft criteria:
    a. Showing increased avidity (SUVmax increase of ≥30%, analogous to PERCIST[8]) on follow-up [$^{18}$F]PSMA-1007 PET/CT, with or without treatment
    b. Showing reduced avidity (SUVmax reduction of ≥30%) or treatment induced changes (reduced size, increased sclerosis) on follow-up [$^{18}$F]PSMA-1007 PET/CT after therapy
    c. Typical appearance of a metastatic lesion on a different imaging modality (e.g. [$^{68}$Ga]Ga-PSMA-11 PET/CT, [$^{18}$F]DCFPyL PET/CT, bone scan, MRI, CT)
    d. Decreasing size following disease-appropriate treatment from one imaging exam to the next
    e. Lesion associated with clinical symptoms suggesting malignancy
    f. Increasing PSA or ALP in keeping with clinical scenario of disease progression, or decreasing levels as expected in response to treatment
    g. Localised treatment administered for metastasis (e.g. radiotherapy)
3. Benign hard criteria:
    a. Histopathology demonstrating no prostate carcinoma metastasis
    b. PSA <0.1ng/ml post local curative surgical treatment
    c. No longer present on follow-up [$^{18}$F]PSMA-1007 PET/CT without any interval treatment
4. Benign soft criteria:
    a. Showing unchanged avidity (SUVmax +/- 30%) on follow-up [$^{18}$F]PSMA-1007 PET/CT with or without treatment after ≥6 months
    b. Considered benign on other imaging modalities (e.g. [$^{68}$Ga]Ga-PSMA-11 PET/CT, [$^{18}$F]DCFPyL PET/CT, bone scan, MRI, CT)
    c. PSA consistent with non-malignant aetiology (e.g. stable PSA, or undetectable PSA nadir following definitive local therapy)
    d. Managed as likely benign after clinical consideration

NSBLs were then classified as one of:

1. Definitely malignant (meeting ≥1 malignant hard criteria)
2. Likely malignant (meeting ≥2 malignant soft criteria)

3. Definitely benign (meeting ≥1 benign hard criteria)
4. Likely benign (meeting ≥2 benign soft criteria)
5. Equivocal (not meeting criteria for any other classification)

**Retrospective Subgroups:**

Three subgroups were identified from the retrospective cohort for further analysis (Figure 1):

Group A - consecutive patients with at least one NSBL

Group B - consecutive patients with at least one NSBL and adequate follow-up

Group C - consecutive patients without [$^{18}$F]PSMA-1007 avid bone lesions

**Prospective definite bone metastases group (Group D):**

To avoid confounding by reporting bias (i.e. an arbitrary SUVmax threshold for reported NSBL versus bone metastasis in the retrospective cohort), a consecutive group of 13 patients with definite [$^{18}$F]PSMA-1007 avid bone metastases (all PSMA-RADS 4 or 5 bone lesions, and all concordantly avid and independently identified on both [$^{18}$F]PSMA-1007 and [$^{68}$Ga]Ga-PSMA-11 PET/CT performed within 6 weeks) was identified from a separate research trial at our institution (ACTRN12618000665235) for the purpose of comparison with NSBLs in our retrospective cohort (Table 1). This was a prospective intraindividual comparative study, and imaging was performed according to the same protocol on the same PET camera as described above for the retrospective cohort. Apart from age ≥60 years in the prospective cohort, inclusion criteria were the same as the retrospective cohort for primary staging and biochemical recurrence indications, with an additional group imaged for restaging of metastatic disease. There were no overlapping patients between retrospective and prospective cohorts. The SUVmax of the most avid concordant bone metastasis on [$^{18}$F]PSMA-1007 PET/CT in each patient was evaluated and recorded by an experienced nuclear medicine specialist, for the purpose of comparison to the most avid NSBL in the retrospective group (highest SUVmax measurement per patient) and for classification of bone metastasis.

**Statistical Methods:**

STATA 15[9] was used for all analyses. Data were described as mean and standard deviation (SD) for continuous normally distributed variables, median and interquartile range (IQR) for continuous non-normally distributed variables, and frequency and percent for categorical variables. Associations between categorical variables were assessed with either chi-square tests, or Fisher's exact tests when the percentage of cells with expected counts <5 was >20%. Continuous normally distributed variables were compared between groups with t-tests and continuous non-normally distributed variables were compared between groups with Mann-Whitney U tests. Statistical significance was indicated where a p-value was <0.05. An ROC curve analysis was performed to assess the classification performance of SUVmax in

distinguishing NSBLs in Group B from bone metastases in the Group D. A cut-point maximising the sensitivity and specificity was derived using Youden's Index (sensitivity + specificity – 1). This ROC curve analysis excluded patients from the retrospective group aged <60 years (n=6) to align with the inclusion criteria of the prospective trial cohort.

# Results

*Demographics*

Of the considered 289 patients who had [$^{18}$F]PSMA-1007 PET/CT, 17 patients were excluded because they did not have a histological diagnosis of prostate cancer (8 with clear cell renal cell carcinoma, 2 with prostatic intra-epithelial neoplasia, and 7 with a clinical diagnosis of prostate carcinoma only), and 58 were excluded because they had reported [$^{18}$F]PSMA-1007 avid bone metastases (44 patients with PSMA-RADS 5 bone lesions and 14 patients PSMA-RADS 4 bone lesions), leaving a total of 214 men for analysis. Ninety-four of 214 (43.9%) patients demonstrated at least one NSBL (Group A), resulting in a total of 199 [$^{18}$F]PSMA-1007 avid NSBLs, from which the number of NSBLs per patient were: 1 (37/94, 39.4%), 2 (27/94, 28.7%), 3 (16/94, 17%), 4 (10/94, 10.6%), and 5 NSBLs (4/94, 4.3%). No patients had more than five NSBLs reported. NSBLs were most commonly distributed in the ribs (122/199, 61.3%), followed by the pelvis (40/199, 20.1%), spine (23/199, 11.6%), pectoral girdle (5/199, 2.5%), sternum (4/199, 2%), lower limb (3/199, 1.5%), upper limb (1/199, 0.5%) and skull (1/199, 0.5%). The median SUVmax of NSBLs was 3.5 (IQR, 2.8-4.4, range 1.8-13.5). 120 men did not have NSBLs (Group C).

*NSBL characterisation and clinical outcomes*

Seventy-seven of 94 (81.9%) patients with NSBLs had adequate follow-up (Group B; median 15.8 months, range 12.4–19.0 months, see Figure 1). There were no statistically significant differences in baseline characteristics between those patients with and without follow-up (Table 2).

These 77 patients had a total of 159 NSBLs (median SUVmax 3.4, IQR 2.7-4.4, range 1.8-11.1), and according to a per lesion analysis, no NSBLs met the defined endpoint criteria for a likely or definitely malignant lesion during follow-up. Most lesions were likely benign (80/159, 50.3%) or definitely benign (19/159, 11.9%), while 60/159 remained equivocal (37.7%). Subsequent per patient analysis (based on the most investigated NSBL) was similar to the per lesion analysis (likely benign 41/77, 53.2%; definitely benign 10/77, 13%; equivocal 26/77, 33.8%).

The clinical implications of NSBLs on management (per patient) included: no change (ignored or assumed benign without any further investigation, n=46/77, 59.7%), evaluated with further imaging (n=23/77, 29.9%), considered irrelevant to management e.g. due to the presence of other definite metastases (usually nodal, n=3/77, 3.9%), presumed due to rib fracture (n=3/77, 3.9%), or percutaneously biopsied (n=2/77, 2.6%; a right iliac lesion showing "bland fibroblastic reaction", and a right sacral ala lesion showing "woven bone, as can be seen in fibrous dysplasia"). Of the 23 patients evaluated with further imaging (noting that some patients were evaluated with more than one imaging modality), the

modalities were: $^{99m}$Tc bone scan (n=11), computed tomography (CT; n=7), magnetic resonance imaging (MRI; n=6), [68Ga]Ga-PSMA-11 PET/CT (n=4), and repeat [18F]PSMA-1007 PET/CT (n=2). Interestingly, the NSBLs were not identifiable in the four patients who had subsequent [$^{68}$Ga]Ga-PSMA-11 PET, and were unchanged in the two patients who had repeat [$^{18}$F]PSMA-1007 PET.

*Clinical factors according to NSBL status*

The median serum PSA and total Gleason scores of patients with NSBLs (Group A, n=94) were similar to patients without NSBLs (Group C, n=120) (p=0.91, p=0.23 respectively; Table 3). The median uptake time of patients with and without NSBLs were also similar (p=0.77; Table 3).

*Comparison with definite bone metastases (Group D)*

Patients from the retrospective cohort with at least one NSBL and adequate follow-up (Group B, excluding 6 patients aged ≥60 years, n=71) were used as a comparator group to a cohort of patients with definite bone metastases (concordantly avid and independently identified on [$^{18}$F]PSMA-1007 and [$^{68}$Ga]Ga-PSMA-11) from a prospective intraindividual comparative study imaged according to the same protocol (Group D, n=13). The SUVmax of the most avid concordant bone metastasis per patient on [$^{18}$F]PSMA-1007 PET in Group D ranged from 7.2-70.4 (with most of these metastases demonstrating typical sclerotic / blastic change), while the SUVmax of the most avid NSBLs in Group B ranged from 1.9-11.1. The SUVmax of the most avid lesion (i.e. one SUVmax measurement per patient) was generally higher with more variability for patients with concordant avid bone metastases in Group D than NSBLs in Group B (Figure 2). ROC curve analysis showed that the highest SUVmax recorded was a good classifier of bone metastasis, with an area under the curve of 99.5% (95% confidence interval 98.3–100%, Figure 2). An SUVmax cut-point of ≥7.2 maximised the Youden's index (sensitivity 100% and specificity 98.6%). Only 5/159 NSBLs with follow-up (Group B) (3.1%) had an SUVmax ≥7.2, and of these 1/5 was definitely benign, 3/5 were likely benign, and 1/5 was equivocal.

# Discussion

[$^{18}$F]PSMA-1007 avid NSBLs were a frequent finding (43.9%). Our findings suggest that [$^{18}$F]PSMA-1007 avid NSBLs are not prostate cancer bone metastases, with no NSBLs meeting endpoint criteria for a likely or definitely malignant lesion within the median 15.8-month follow-up interval. The serum PSA levels and Gleason scores were also similar in consecutive patients with NSBLs and patients without NSBLs, suggesting that patients with NSBLs do not represent a higher risk cohort. In our series, ribs were by far the most common NSBL location, representing 60.4% of all NSBLs, consistent with previous reports[6]. Rib metastases are known to occur in prostate cancer, but they only account for 12-20% of bone metastases in autopsy studies, with most metastases occurring in the spine[10, 11]. Only around 10% of prostate cancer bone metastases are solitary[12], and rib metastases are thought to be extremely rare in the absence of vertebral metastases[13]. A recent retrospective cohort study of 62 men with a solitary avid rib lesion on staging [$^{68}$Ga]Ga-PSMA-11 PET found that the vast majority of these lesions (61/62,

98.4%) met criteria for a benign lesion, and the authors recommended against percutaneous rib biopsy in this scenario unless there are high risk clinical features[14].

The aetiology of [$^{18}$F]PSMA-1007 avid NSBLs remains uncertain. The possibility of free $^{18}$F accounting for NSBLs in this study is highly unlikely due to stringent quality control measures (described in methods), similar uptake times between patients with NSBLs and those without any avid bone lesions, and the lack of diffuse skeletal uptake. Alternative malignant marrow pathologies are also unlikely because the ribs have minimal marrow production compared to other skeletal sites but showed a disproportionately high proportion of NSBLs. Marrow-based pathologies like myeloma, myelodysplasic syndrome and other myeloproliferative neoplasms would also often result in diffuse rather than focal marrow involvement, and would not be expected in over 40% of men. A benign cause of NSBLs seems more likely, and benign avid bone lesions are well described, with PSMA uptake having been demonstrated in healing fractures, osteoblastic activity, Paget's disease, haemangiomas, and fibrous dysplasia using [$^{68}$Ga]Ga-PSMA-11 or [$^{18}$F]DCFPyL[15-18]. These lesions are usually distinguished from typical sclerotic prostate cancer bone metastases on anatomical imaging and pose few problems for experienced readers. However, the presence of mild to moderate focal bone avidity without a typical morphological correlate on anatomical imaging is challenging because it is difficult to exclude atypical or low-volume bone metastases.

We identified multiple cases in which [$^{18}$F]PSMA-1007 avid NSBLs were not identifiable on subsequent [$^{68}$Ga]Ga-PSMA-11 PET in the absence of treatment change. This is consistent with findings from a recent intraindividual comparison of [$^{18}$F]PSMA-1007 PET to one of three other prostate cancer PET tracers ([$^{68}$Ga]Ga-PSMA-11, [$^{18}$F]DCFPyL, and [$^{18}$F]JK-PSMA-7), which identified 15 non-specific bone marrow foci on [$^{18}$F]PSMA-1007 PET only, that were not evident when using the other tracers[3]. Small molecule PSMA inhibitors such as [$^{68}$Ga]Ga-PSMA-11 and [$^{18}$F]PSMA-1007 share the glutamate-urea-lysine pharmacophore, which targets the catalytic domain of PSMA. Structurally, they differ in how they are conjugated to linking groups and radiometal chelators (e.g. HBED-CC) or prosthetic groups. The much higher incidence of NSBLs on [$^{18}$F]PSMA-1007 PET/CT with comparison to the other PSMA tracers in routine clinical use suggests an issue that is inherent to the molecule itself.

The highest SUVmax of a skeletal lesion recorded within a patient was a good classifier of bone metastasis when compared to a group of definite [$^{18}$F]PSMA-1007 avid bone metastases (Group D, defined by concordant focal uptake independently identified on [$^{68}$Ga]Ga-PSMA-11 PET). If formulating a clinical report for an [$^{18}$F]PSMA-1007 PET/CT study, we therefore suggest that the SUVmax of the 'hottest' [$^{18}$F]PSMA-1007 avid NSBL (i.e. lesion without characteristic sclerotic / blastic changes) can measured to determine the likelihood of bone metastasis in patients who otherwise have no distant metastatic disease. Based on our findings we suggest classifying NSBLs with SUVmax <7.2 as likely benign. The 5 NSBLs in our cohort with follow-up and SUVmax 7.2-11.1 are also most likely benign according to our findings, however there are insufficient numbers to provide greater certainty within this SUVmax range, and given that metastatic lesions may have a similar SUVmax, we recommend

classifying these as either equivocal or metastatic, depending upon the context of scan appearance (noting that NSBLs are frequently found in the ribs and isolated rib prostate cancer metastases are rare), clinical risk factors (including PSA level, ISUP grade, known extra-prostatic disease), and potential management implications to guide interpretation. For example, an equivocal lesion on an initial staging scan may not preclude an attempt at curative therapy, however  a lower threshold for intervention may apply when restaging for biochemical recurrence.

Clinical context is important to the interpretation of NSBLs, and all NSBLs in our study were clinically managed as benign. Clearly the presence of a NSBL is irrelevant to patient management in the context of widespread metastatic disease, and no further investigation is warranted. However, the interpretation of a NSBL as a metastatic site in a patient with otherwise only locoregional disease would reclassify the patient as having oligometastatic disease, and potentially preclude curative intent treatment. It has recently been shown that local prostate radiotherapy with planned systemic therapy in patients with prostate cancer oligometastases (≤3 sites) improves overall survival[19], and notably >85% of patients in our study had ≤3 NSBLs. Therefore, clinicians may consider proceeding with planned prostate radiotherapy in conjunction with androgen deprivation therapy in the context of equivocal [$^{18}$F]PSMA-1007 avid skeletal findings and repeat the PET in 3-6 months to assess the progress of the baseline NSBL. For high-risk patients in the biochemical recurrence setting, re-evaluation with PSMA PET/CT in six months may be appropriate. True metastatic disease is likely to have either responded or progressed in response to therapy[1].

The most significant limitations of our study were its retrospective nature and the small number of NSBLs with a histopathological gold standard. Furthermore, it is possible that a longer follow-up period could see some NSBLs re-classified as likely or definitely malignant. The statistical cut-point analysis was also limited by the small sample size of the prospective comparison group of definite bone metastases (n=13). Finally, applicability of our SUVmax thresholds at other centres is dependent upon like comparison to our imaging protocol, including PET/CT scanner resolution, reconstruction parameters, and uptake time.

# Conclusion

Non-specific mild to moderate focal [$^{18}$F]PSMA-1007 bone uptake without a typical morphological correlate on CT is common, and our findings suggest that these foci rarely represent prostate cancer metastases. When identified in the absence of definite metastatic disease elsewhere, our results indicate that it is appropriate to classify those with SUVmax <7.2 as likely benign. NSBL with SUVmax 7.2-11.1 may be classified as equivocal or metastatic, with patient clinical risk factors, scan appearance and potential management implications used to guide interpretation in this situation.

# Declarations

**Funding**: No funding was received for conducting this study. Matthew J Roberts is supported by a Clinician Research Fellowship from the Metro North Office of Research, Queensland Health, and a Doctor in Training Research Scholarship from Avant Mutual Group Pty Ltd.

**Conflicts of interest / Competing interests**: The authors have no conflicts of interest to declare that are relevant to the content of this article.

**Availability of data and material:** not applicable.

**Code availability:** not applicable.

**Ethics approval and consent to participate** This retrospective audit was approved by the institutional review board of the Royal Brisbane and Women's Hospital the need for written informed consent was waived.

**Consent for publication:** not applicable.

# References

1. Hofman MS, Lawrentschuk N, Francis RJ, Tang C, Vela I, Thomas P, 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. The Lancet. 2020;395:1208-16. doi:10.1016/S0140-6736(20)30314-7.
2. C. Kesch CK, W. Mier, K. Kopa and F. Giesel. Gallium-68 or Fluorine-18 for prostate cancer imaging? The Journal of Nuclear Medicine. 2017:687-8.
3. Dietlein F, Kobe C, Hohberg M, Zlatopolskiy BD, Krapf P, Endepols H, et al. Intraindividual Comparison of 18 F-PSMA-1007 with Renally Excreted PSMA Ligands for PSMA PET Imaging in Patients with Relapsed Prostate Cancer. J Nucl Med. 2020;61:729.
4. Giesel FL, Hadaschik B, Cardinale J, Radtke J, Vinsensia M, Lehnert W, et al. F-18 labelled PSMA-1007: biodistribution, radiation dosimetry and histopathological validation of tumor lesions in prostate cancer patients. Eur J Nucl Med Mol Imaging. 2017;44:678-88. doi:10.1007/s00259-016-3573-4.
5. M. Debowski BH, S. Ramsay, P. Thomas, P. Garcia, M. Latter, S. Tapper, D. Pattison. A prospective intra-individual blinded comparison of 18F-PSAM-1007 and 68GA-PSMA-11 PET/CT imaging in patients with confirmed prostate cancer. Internal Medicine Journal. 2019;49:27.
6. Rauscher I, Kronke M, Konig M, Gafita A, Maurer T, Horn T, et al. Matched-Pair Comparison of (68)Ga-PSMA-11 PET/CT and (18)F-PSMA-1007 PET/CT: Frequency of Pitfalls and Detection Efficacy in Biochemical Recurrence After Radical Prostatectomy. J Nucl Med. 2020;61:51-7. doi:10.2967/jnumed.119.229187.
7. Rowe SP, Pienta KJ, Pomper MG, Gorin MA. Proposal for a Structured Reporting System for Prostate-Specific Membrane Antigen-Targeted PET Imaging: PSMA-RADS Version 1.0. Journal of nuclear

medicine : official publication, Society of Nuclear Medicine. 2018;59:479. doi:10.2967/jnumed.117.195255.

8. Wahl RL, Jacene H, Kasamon Y, Lodge MA. From RECIST to PERCIST: Evolving Considerations for PET response criteria in solid tumors. Journal of nuclear medicine : official publication, Society of Nuclear Medicine. 2009;50 Suppl 1:122S. doi:10.2967/jnumed.108.057307.
9. StataCorp. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC; 2017.
10. Bubendorf L, Schöpfer A, Wagner U, Sauter G, Moch H, Willi N, et al. Metastatic patterns of prostate cancer: An autopsy study of 1,589 patients. Human Pathology. 2000;31:578-83. doi:10.1053/hp.2000.6698.
11. Lamothe F, Kovi J, Heshmat MY, Green EJ. Dissemination of prostatic carcinoma: an autopsy study. Journal of the National Medical Association. 1986;78:1083-6.
12. Agheli A, Patsiornik Y, Chen Y, Chaudhry MR, Gerber H, Wang JC. Prostate carcinoma, presenting with a solitary osteolytic bone lesion to the right hip. Radiology Case Reports. 2009;4. doi:10.2484/rcr.v4i4.288.
13. Wang C, Shen Y. Study on the distribution features of bone metastases in prostate cancer. Nuclear Medicine Communications. 2012;33:379-83. doi:10.1097/MNM.0b013e3283504528.
14. Chen MY, Franklin A, Yaxley J, Gianduzzo T, McBean R, Wong D, et al. Solitary rib lesions showing prostate-specific membrane antigen (PSMA) uptake in pre-treatment staging 68Ga-PSMA-11 positron emission tomography scans for men with prostate cancer: benign or malignant? BJU international. 2020;126:396-401. doi:10.1111/bju.15152.
15. Hofman MS, Hicks RJ, Maurer T, Eiber M. Prostate-specific Membrane Antigen PET: Clinical Utility in Prostate Cancer, Normal Patterns, Pearls, and Pitfalls. Radiographics : a review publication of the Radiological Society of North America, Inc. 2018;38:200. doi:10.1148/rg.2018170108.
16. Keidar Z, Gill R, Goshen E, Israel O, Davidson T, Morgulis M, et al. 68Ga-PSMA PET/CT in prostate cancer patients - patterns of disease, benign findings and pitfalls.(Report). Cancer Imaging (BioMed). 2018;18. doi:10.1186/s40644-018-0175-3.
17. Sheikhbahaei S, Afshar-Oromieh A, Eiber M, Solnes L, Javadi M, Ross A, et al. Pearls and pitfalls in clinical interpretation of prostate-specific membrane antigen (PSMA)-targeted PET imaging. European Journal of Nuclear Medicine and Molecular Imaging. 2017;44:2117-36. doi:10.1007/s00259-017-3780-7.
18. Shetty D, Patel D, Le K, Bui C, Mansberg R. Pitfalls in Gallium-68 PSMA PET/CT Interpretation-A Pictorial Review. Tomography. 2018;4:182-93. doi:10.18383/j.tom.2018.00021.
19. Parker CC, James ND, Brawley CD, Clarke NW, Hoyle AP, Ali A, et al. Radiotherapy to the primary tumour for newly diagnosed, metastatic prostate cancer (STAMPEDE): a randomised controlled phase 3 trial. The Lancet. 2018;392:2353-66. doi:https://doi.org/10.1016/S0140-6736(18)32486-3.

# Tables

TABLE 1: Patient characteristics

| Characteristic | Group A*: Total (n=94) | Group B†: Total (n=77) | Group C‡: Total (n=120) | Group D§: Total (n=13) |
|---|---|---|---|---|
| Age (years) | (n=94) | (n=77) | (n=120) | (n=13) |
| Mean (SD) | 69.8 (6.7) | 69.7 (7) | 69.4 (7.9) | 74.3 (7.7) |
| Total Gleason score, n (%) | (n=84) | (n=69) | (n=103) | (n=9) |
| <8 | 44 (52.4) | 37 (53.6) | 63 (61.2) | 2 (22.2) |
| ≥8 | 40 (47.6) | 32 (46.4) | 40 (38.8) | 7 (77.8) |
| Indication for scan, n (%) | (n=94) | (n=77) | (n=120) | (n=13) |
| Staging | 46 (48.9) | 39 (50.6) | 54 (45) | 2 (15.4) |
| Biochemical recurrence | 48 (51.1) | 38 (49.4) | 66 (55) | 3 (23.1) |
| Metastatic Disease restaging | 0 (0) | 0 (0) | 0 (0) | 8 (61.5) |
| PSA (ng/ml) | (n=94) | (n=77) | (n=120) | (n=13) |
| Median (IQR) | 5.2 (0.95-10) | 6.1 (0.97-10) | 4.85 (1.2-10) | 9.7 (2.6-21) |
| [$^{18}$F]PSMA-1007 activity (MBq) | (n=94) | (n=77) | (n=120) | (n=13) |
| Mean (SD) | 249.7 (12.6) | 249.3 (13) | 253.1 (11.1) | 251.2 (7.6) |
| Uptake time (minutes) | (n=94) | (n=77) | (n=120) | (n=13) |
| Median (IQR) | 126 (120-137) | 126 (120-137) | 126 (119-137.5) | 122 (120-127) |

*Retrospective patients with NSBLs.

†Retrospective patients with NSBLs and follow-up.

‡Retrospective patients without NSBLs (no avid bone lesions).

§ Prospective trial group with concordant bone metastases avid on both [18F]PSMA 1007 PET/CT and [68Ga]Ga-PSMA-11 PET/CT).

TABLE 2: Characteristics of patients with at least one non-specific [$^{18}$F]PSMA-1007 avid bone lesion (NSBL), comparing follow-up status

| Characteristic | Total (n=94) | No-follow up (n=17) | Followed-up (n=77) | p |
|---|---|---|---|---|
| Age in years, mean (SD) | 69.8 (6.7) | 70.5 (5.6) | 69.7 (7.0) | 0.64 |
| Total Gleason score, n (%)* | | | | |
| 6 – 7 | 44 (52) | 7 (47) | 37 (54) | 0.62 |
| 8 – 10 | 40 (48) | 8 (53) | 32 (46) | |
| Indication for scan, n (%) | | | | |
| Staging | 46 (49) | 7 (41) | 39 (51) | 0.48 |
| Biochemical recurrence | 48 (51) | 10 (59) | 38 (49) | |
| PSA (ng/ml), median (IQR) | 5.2 (0.9 – 10.0) | 4.3 (0.9 – 7.4) | 6.1 (1.0 – 10.0) | 0.57 |
| Dose of [$^{18}$F]PSMA-1007, mean MBq (SD) | 249.7 (12.6) | 251.6 (11.1) | 249.3 (13.0) | 0.50 |
| Uptake time in min, median (IQR) | 126 (120 – 137) | 124 (120 – 128) | 126 (120 – 137) | 0.58 |
| Number of NSBL†, n (%) | | | | |
| 1 | 36 (38) | 5 (29) | 31 (40) | 0.58 |
| ≥2 | 58 (62) | 12 (71) | 46 (60) | |

*Gleason score was not available for all patients

† [18F]PSMA-1007 non-specific bone lesion

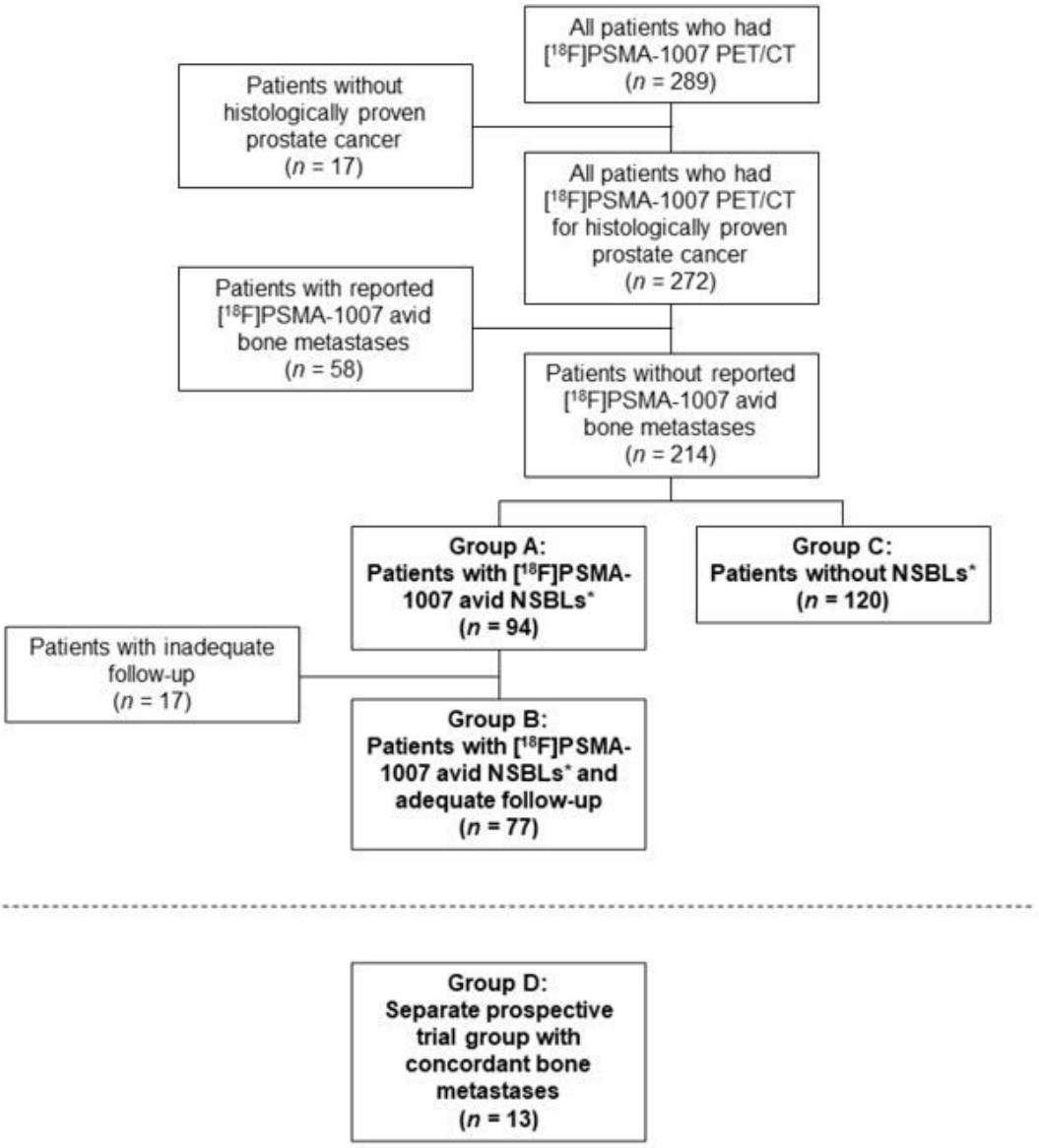
TABLE 3: Comparison of patients with NSBLs versus patients with no [$^{18}$F]PSMA-1007 avid bone lesions

| Characteristic | NSBL* (Group A: n=94) | No avid bone lesions (Group C: n=120) | p |
|---|---|---|---|
| PSA, median (IQR) | 5.2 (0.9 – 10.0) | 4.8 (1.2 – 10.0) | 0.91 |
| Gleason score, n (%)† | | | |
| <8 | 44 (52.4) | 63 (61.1) | 0.23 |
| ≥8 | 40 (47.6) | 40 (38.8) | |
| Uptake time, median (IQR) | 126.0 (120.0 – 137.0) | 126.0 (119.0 – 137.5) | 0.77 |

*[18F]PSMA-1007 non-specific bone lesion

†n=84 in Group A, and n=103 in Group C (Gleason score was not available in some patients)

# Figures

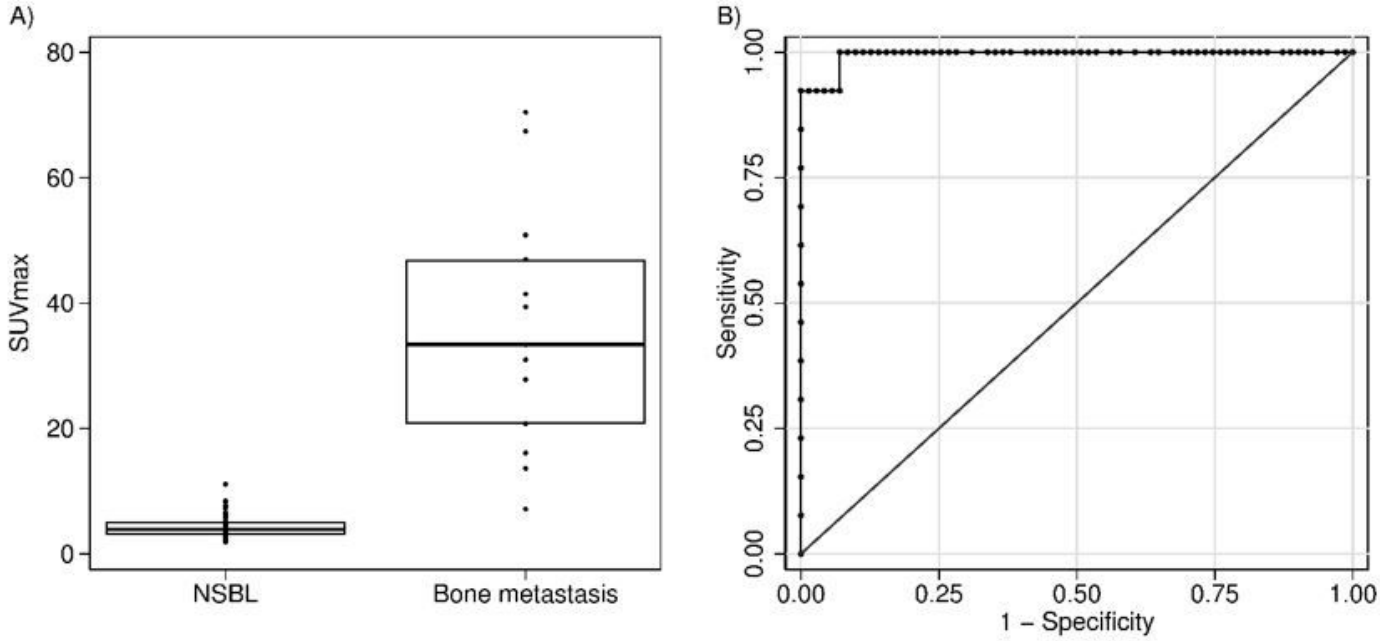



Participant flow diagram demonstrating identification and selection of study population and subgroups.

*Non-specific bone lesions

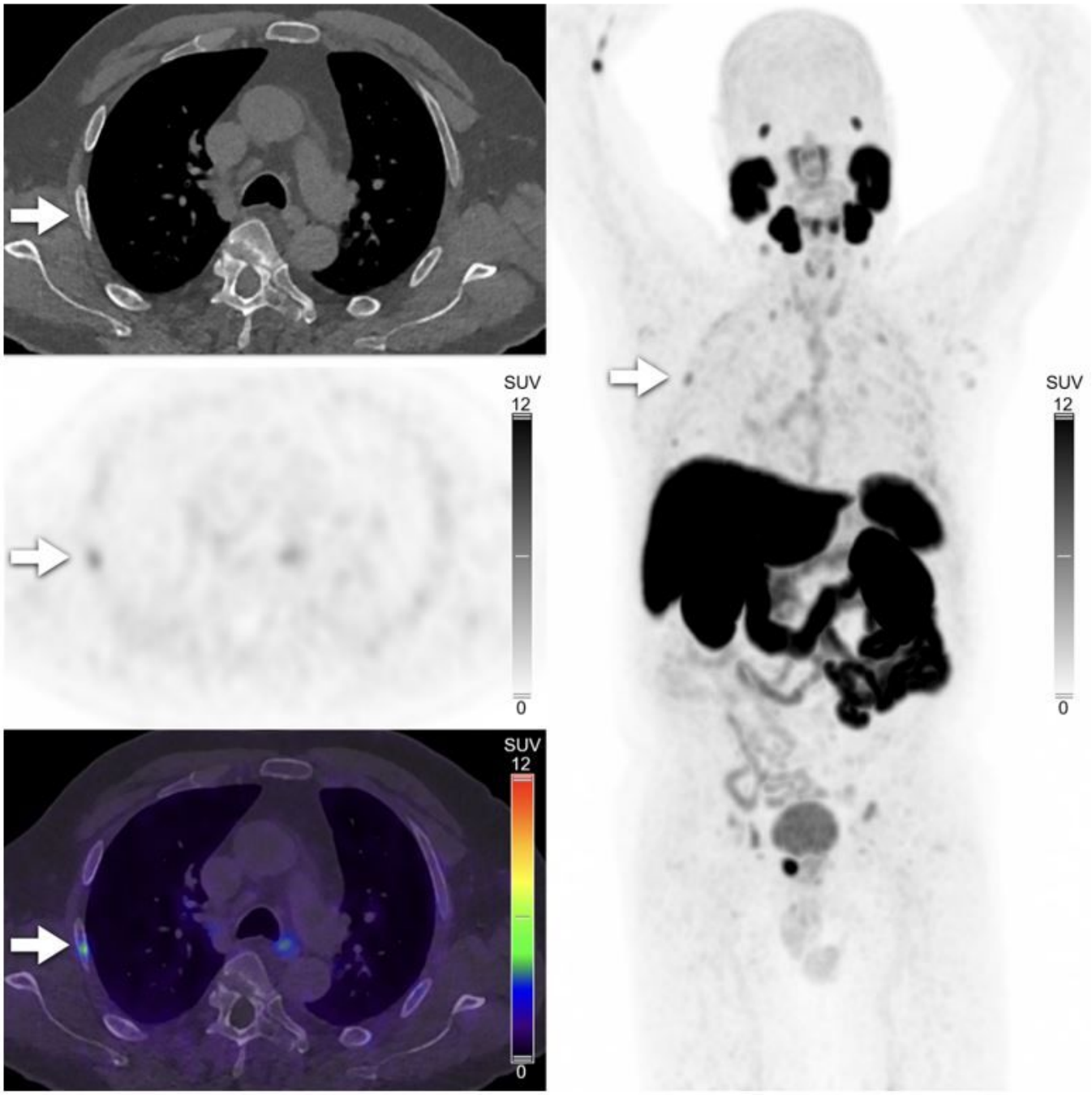
## Figure 1

Participant flow diagram demonstrating identification and selection of study population and subgroups. *Non-specific bone lesions




## Figure 2

A) SUVmax of most avid NSBL from Group B compared to definite bone metastases from Group D (each point represents a measurement for the highest bone lesion SUVmax within a single patient). B): ROC curve of highest SUVmax within a patient as a classifier of NSBL from Group B compared to definite bone metastases from Group D.




## Figure 3

Example of an [18F]PSMA-1007 avid non-specific bone lesion (NSBL) in the right 4th rib (SUVmax 4.6) in a 75-year-old male undergoing staging PET/CT for prostate carcinoma, Gleason 4 + 4 = 8, PSA 6.1 ng/ml. The patient proceeded to have local curative surgical treatment only, and post-operative PSA was undetectable. This NSBL was therefore classified as definitely benign on endpoint analysis.