

Original Article

Imaging features of Paget's disease on ^{11}C choline PET/CT

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Abstract: The purpose of this study was to investigate the appearance of Paget's disease (PD) on ^{11}C choline PET/CT and correlate these findings to serum alkaline phosphatase (ALP) level and skeletal scintigraphy. With IRB approval, our institutional ^{11}C choline PET/CT database (9/2005-6/2015) was searched for patients with PD. Site of osseous involvement, CT appearance, and multiple semi-quantitative measures were measured and correlated with ALP and degree of uptake on bone scan. Our search identified 10 males (mean age 79.6 ± 7.8 years). Four had polyostotic disease and seven had more than one ^{11}C choline PET/CT. In total, 58 affected bones were evaluated on 25 PET/CTs. Mean lesion SUV_{max} was 2.6 ± 0.89 (range 1.0-4.4), $\text{SUV}_{\text{max}}/\text{Liver SUV}_{\text{mean}}$ 0.33 ± 0.13 (0.12-0.61), $\text{SUV}_{\text{max}}/\text{Liver SUV}_{\text{max}}$ 0.29 ± 0.11 (0.10-0.52), $\text{SUV}_{\text{max}}/\text{BP SUV}_{\text{mean}}$ 2.47 ± 0.86 (0.91-4.22), and $\text{SUV}_{\text{max}}/\text{BP SUV}_{\text{max}}$ 1.92 ± 0.71 (0.68-3.45). There was no correlation between ALP and any semiquantitative measure. Bone scan uptake was marked in 41 bones, moderate in nine, and mild in six. There was no correlation between lesion SUV_{max} and bone scan uptake ($P = 0.26$). Paget's disease on ^{11}C choline PET/CT demonstrates mild to moderate activity, which does not correlate with bone scan uptake or ALP level. It is important to recognize Paget's disease as a potential pitfall on ^{11}C choline PET/CT. However, the characteristic appearance on the CT portion of PET/CT examinations should allow confident diagnosis and differentiation from prostate cancer osseous metastases.

Keywords: Paget's disease, ^{11}C choline, PET, bone scintigraphy, PET/CT

Introduction

Paget's disease (PD) of the bone is characterized by increased osseous turnover and disorganized remodeling resulting in osseous enlargement, trabecular coarsening, and osseous deformity. It is a common disorder, affecting up to 3-4% of the population. Approximately 90% of patients with PD are older than 40 years, and most are of European descent [1]. It has no confirmed etiology, although viral infection and possibly genetic factors have been implicated [2].

The most common complication of PD is fracture due to weakened bones. Osseous enlargement of the calvarium and vertebrae can result in neural impingement, leading to deafness and radiculopathy. High-output heart failure and sarcomatous degeneration have also been described, but are increasingly rare. While most patients with PD are asymptomatic, those who do develop symptoms most frequently complain of bone pain. In asymptomatic patients,

alkaline phosphatase (ALP) elevation in the presence of normal liver tests may indicate the diagnosis, and ALP levels can be used to monitor disease activity [1-6].

Conventional radiographs and CT remain the best imaging tools to diagnose PD, and the appearance is dependent on the disease phase (lytic, mixed lytic/sclerotic, or sclerotic). The mixed phase exhibits the most characteristic findings, manifesting as whole bone involvement or extension to the end of long bones, trabecular coarsening, cortical thickening, and osseous enlargement on both CT and radiographs [1, 3-6]. Maintenance of intramedullary fat attenuation or signal intensity on CT or MRI, respectively, is also characteristic and allows delineation from other differential diagnoses.

PD typically demonstrates moderately intense uptake on bone scintigraphy when lesions are active and this modality can be useful to assess the distribution and extent of disease [6-8]. The increased metabolic activity of PD on ^{18}F FDG

PET/CT is well-documented and PD has been known to simulate prostate cancer skeletal metastases on staging or follow-up [7, 9-15]. More recently, PD has been shown to have increased uptake of ^{68}Ga PSMA in patients undergoing PSMA PET for prostate cancer evaluation, simulating skeletal metastases [16-18]. Increased uptake of ^{18}F fluorocholine in PD has also been reported [19].

Like ^{18}F fluorocholine PET/CT, ^{11}C choline PET/CT has proven utility in biochemically recurrent prostate cancer for identifying areas of locally recurrent and metastatic disease, and is especially useful in patients status-post systemic chemohormonal therapy and/or radiation therapy [20-22]. However, it is not 100% specific for prostate cancer. There has been only a single prior report detailing increased activity in pagetic bone on ^{11}C choline PET/CT [23], but otherwise little else regarding this potential interpretative pitfall. Therefore, the aim of this study was to investigate the appearance of PD on ^{11}C choline PET/CT and to correlate these findings with serum ALP level and degree of uptake on bone scan.

Materials and methods

With IRB approval, our institutional ^{11}C choline PET/CT database between 9/2005 and 6/2015 was cross-referenced to the electronic medical record for patients with a diagnosis of PD. The diagnosis of PD had been established by characteristic morphologic imaging features and/or stability over time. ^{11}C choline PET/CT studies (Discovery LS, RX, 690, or 710; GE Healthcare) were performed according to the standard institutional protocol. Administered ^{11}C choline dose was between 370-555 MBq, and imaging began 5 minutes after injection. Patients were imaged from orbits to midhighs with arms up when possible using a 128×128 matrix and a rate of 3 min per bed position. PET images were reconstructed with a 3-dimensional ordered-subsets expectation maximization algorithm (28 subsets, 2 iterations). Low-dose helical CT images were obtained for attenuation correction and anatomic localization.

All PET/CT and bone scintigraphy images were analyzed utilizing Osirix 3.3.2 DICOM viewer for Mac OS X by a board-certified radiologist with 5 years' experience in both musculoskeletal radiology and choline PET/CT. Site of osseous involvement, appearance on CT images used

for attenuation correction and localization, and semi-quantitative measures such as lesion maximum standardized uptake value (SUV_{max}), lesion $\text{SUV}_{\text{max}}/\text{Liver SUV}_{\text{mean}}$, lesion $\text{SUV}_{\text{max}}/\text{Liver SUV}_{\text{max}}$, lesion $\text{SUV}_{\text{max}}/\text{blood pool (BP) SUV}_{\text{mean}}$, and $\text{SUV}_{\text{max}}/\text{BP SUV}_{\text{max}}$ were measured. Lesion SUV_{max} was measured by visually identifying the region on PET images with the most intense choline uptake and then creating a 3-dimensional volume of interest (VOI) incorporating the total lesion volume for SUV_{max} determination. A 3-cm diameter spherical ROI placed in the right lobe of the liver was used for determination of liver SUV, and a 1-cm spherical ROI placed in the right atrium was used to determine blood pool SUV.

Electronic medical records were reviewed for any comparison imaging such as radiographs, CT, MRI, and bone scans. Bone scans obtained within three months of ^{11}C choline PET/CT were included for analysis. Anterior and posterior whole body planar images obtained at three hours following the administration of 740 MBq $^{99\text{m}}\text{Tc}$ -MDP, per institutional protocol, were reviewed. Osseous site of involvement and degree of radiotracer uptake relative to normal iliac crest uptake (mild, moderate, marked) was recorded for each patient with available bone scintigraphy. If the iliac bones were involved by PD, the inferior scapula was used as the reference standard. Serum ALP levels obtained within three months of ^{11}C choline PET/CT were included for analysis.

Statistical analysis was performed using JMP software on a Mac (JMP Pro, version 11.2.1, SAS Institute Inc.) Continuous variables are expressed as mean \pm SD. Categorical variables are presented with absolute and relative frequencies. *P* values for between-group comparisons of continuous data were calculated from Kruskal-Wallis one-way analysis of variance (ANOVA). Multivariate analysis was performed and correlation expressed by Pearson correlation coefficient. Statistical significance was established for *P* values of less than 0.05.

Results

Our search identified 10 patients (all male, mean age 79.6-years \pm 7.8 years). Four patients had polyostotic disease, including one patient with six sites of involvement, one with four sites, and two patients with two sites. There were a total of 20 bones involved by PD includ-

Paget's disease on ^{11}C choline PET/CT

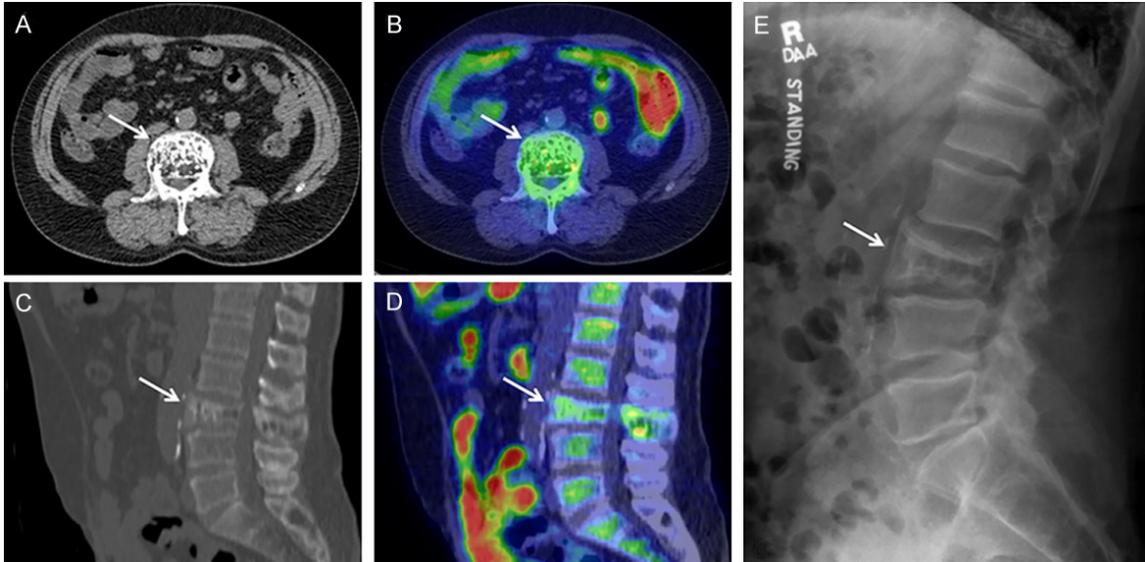


Figure 1. 73-year-old man with biochemically recurrent prostate cancer. Axial and sagittal CT (A, C) and fused ^{11}C choline PET/CT (B, D) images demonstrate Paget's disease of the L3 vertebral body with moderate choline activity (SUV_{max} 3.4). Note typical morphologic features including maintenance of internal fat attenuation, trabecular coarsening, cortical thickening, and whole bone involvement on CT (A, C) and radiograph (E). His ALP level was 60 IU/L.

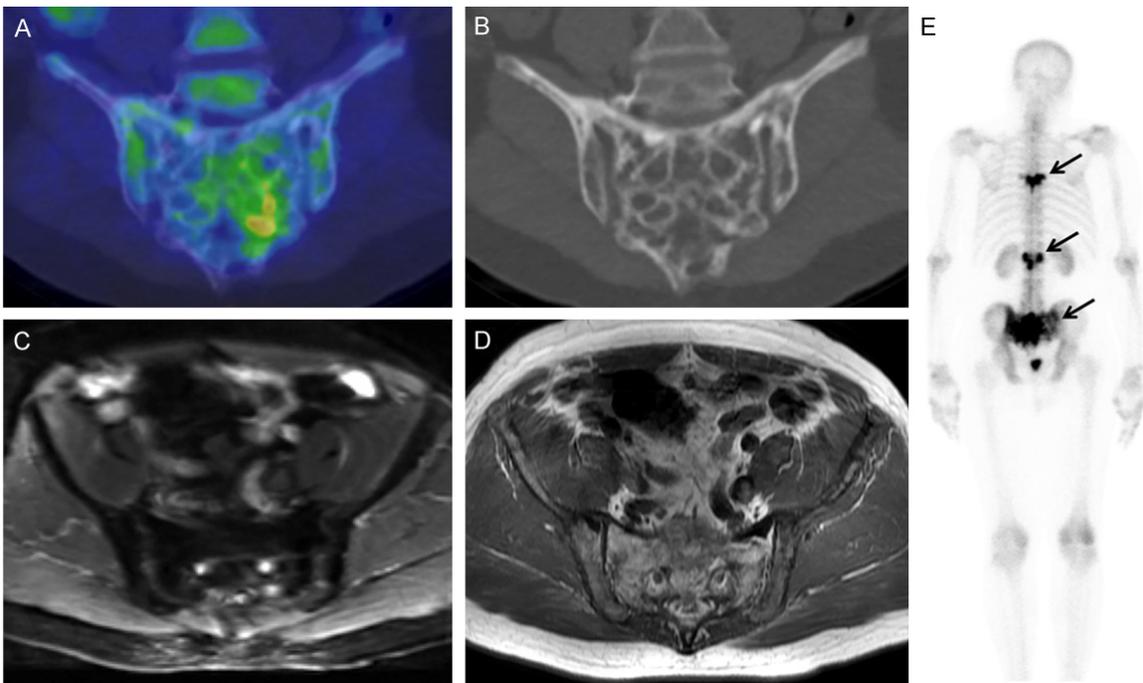


Figure 2. 68-year-old man with history of recurrent metastatic prostate cancer status post prostatectomy and androgen deprivation therapy. Coronal oblique fused ^{11}C choline PET/CT (A) and CT (B) images demonstrate changes of Paget's disease in the sacrum and both iliac bones with moderate choline activity (SUV_{max} 4.1). Axial DWI (C) and T1-weighted MRI (D) images demonstrate no diffusion restriction and normal T1 marrow fat signal. (E) Posterior planar $^{99\text{m}}\text{Tc}$ MDP bone scintigraphy image shows intense sacral uptake (arrow), only mild iliac bone uptake, and multiple additional sites of Paget's disease in the thoracolumbar spine (arrows). His ALP level was 225 IU/L.

ing the innominate bone, sacrum, humerus, femur, scapula, and T1, T6, T12, L2, L3, and L5

vertebral bodies. Seven patients had more than one ^{11}C choline PET/CT. In total, 58 af-

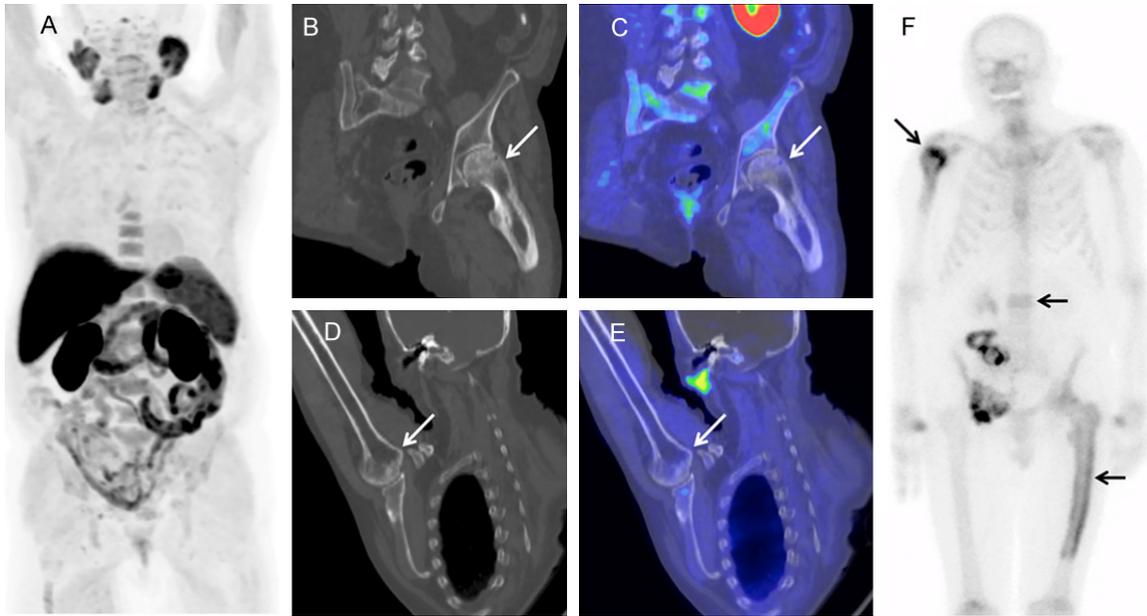


Figure 3. 81-year-old man with history of prostate cancer status post prostatectomy. ^{11}C choline PET MIP (A), CT (B, D), and fused PET/CT (C, E) images demonstrate typical CT findings of Paget's disease in the proximal right humerus and left femur without choline uptake (SUV_{max} 1.7). In contrast, anterior planar $^{99\text{m}}\text{Tc}$ MDP bone scintigraphy (F) demonstrates intense right humeral uptake, moderate left femoral uptake, and an additional site of Paget's disease in the lumbar spine (arrows). His ALP level was 203 IU/L.

affected bones were evaluated on 25 ^{11}C choline PET/CT examinations. Bone scan and serum ALP levels were each available in 9 out of 10 patients. In total, 29 pagetic bones evaluated by ^{11}C choline PET/CT had an ALP and correlative bone scintigraphy within 3 months of the exam. The mean lesion SUV_{max} was 2.6 ± 0.89 (range 1.0-4.4), $\text{SUV}_{\text{max}}/\text{Liver SUV}_{\text{mean}}$ was 0.33 ± 0.13 (range 0.12-0.61), $\text{SUV}_{\text{max}}/\text{Liver SUV}_{\text{max}}$ was 0.29 ± 0.11 (range 0.10-0.52), $\text{SUV}_{\text{max}}/\text{BP SUV}_{\text{mean}}$ was 2.47 ± 0.86 (range 0.91-4.22), and $\text{SUV}_{\text{max}}/\text{BP SUV}_{\text{max}}$ was 1.92 ± 0.71 (range 0.68-3.45). There was no significant correlation between serum ALP level and lesion SUV_{max} ($r = 0.09$), $\text{SUV}_{\text{max}}/\text{Liver SUV}_{\text{mean}}$ ($r = -0.10$), $\text{SUV}_{\text{max}}/\text{Liver SUV}_{\text{max}}$ ($r = -0.05$), $\text{SUV}_{\text{max}}/\text{BP SUV}_{\text{mean}}$ ($r = 0.07$), or $\text{SUV}_{\text{max}}/\text{BP SUV}_{\text{max}}$ ($r = 0.14$). All affected bones had a typical appearance on CT images characterized by cortical thickening, trabecular coarsening, fat attenuation of internal bone marrow, and whole bone involvement or involvement extending to the end of a long bone (**Figure 1**). Bone scan uptake was marked in 41 affected bones (**Figure 2**), moderate in nine bones, and mild in six. There was no significant correlation between lesion SUV_{max} and degree of uptake on bone scan ($p = 0.26$).

Discussion

This study is the largest of its kind to detail the appearance of Paget's disease on ^{11}C choline PET/CT. We found wide variability of choline uptake in PD and considerable overlap with levels of uptake seen in osseous prostate cancer metastases [24]. We also found that the level of ^{11}C choline uptake in PD did not correlate with the degree of bone scan uptake or serum ALP levels, and therefore these markers are not helpful in differentiating PD from prostate cancer metastases when the two are being considered as causes of increased uptake on ^{11}C choline PET/CT.

Prostate cancer is the second most common cancer in men and affects just over 1 million men worldwide [25] with 180,000 new cases and 26,000 deaths estimated within the United States in 2016 [26]. Although radical prostatectomy and/or radiation therapy is curative in intent, 20-40% of these patients will eventually develop biochemical recurrence [27]. Autopsy results show that over 80% of men who die from prostate cancer develop osseous metastasis [28]. Given the frequency of osseous metastases in prostate cancer, it is imperative to be aware of potential cases of false positives for osseous metastatic disease.

It is clear that PD may show uptake on PET with several different radiopharmaceuticals, including ^{18}F FDG [7, 9-15, 29], ^{68}Ga PSMA [16], ^{18}F NaF [30, 31], ^{18}F fluorocholine [19] and ^{11}C choline PET/CT [23]. As ^{11}C choline is important in cell membrane synthesis, we believe that the increased rate of osseous turnover, and therefore cell formation, underlies the mechanism by which bones affected by PD take up ^{11}C choline. It is unclear why choline uptake varies so widely and is apparently unrelated to the stage of disease activity, given the lack of association with serum ALP level. However, similar variability has been reported on ^{18}F FDG PET/CT [7, 9, 13-15, 29-31]. It is evident that the level of choline uptake is not linked to the rate of osteoblastic activity, given the lack of correlation between uptake on ^{11}C choline PET/CT and $^{99\text{m}}\text{Tc}$ MDP skeletal scintigraphy (Figure 3) in our study cohort.

Although there is overlap in levels of ^{11}C choline uptake between PD and osseous prostate cancer metastases, the characteristic appearance of PD on the CT images or comparison imaging should allow confident differentiation from prostate cancer osseous metastases. In our study, all affected bones had typical PD appearance on CT, characterized by cortical thickening, trabecular coarsening, preserved bone marrow fat attenuation, and whole bone involvement, which allowed for confident diagnosis despite increased ^{11}C choline uptake. Indeed, the CT appearance is often diagnostic, obviating the need for biopsy [6]. This reinforces the importance of evaluating the CT portion of a PET/CT study to assess the morphological features of an osseous lesion demonstrating increased tracer uptake. Not only can the diagnosis of PD be made, but also other sources of false positive findings including fractures or benign osseous lesions such as fibrous dysplasia can be identified [32].

Our study was limited by the small size and its retrospective nature. One of our patients had no comparison bone scan, and one had no available serum ALP value. However, given the polyostotic nature of the disease and patients with multiple PET/CTs in our cohort, there were still 29 pagetic bones evaluated on ^{11}C choline PET/CT with both correlative bone scans and AP values. The diagnosis of Paget's disease was also not pathologically proven, but as discussed previously, biopsy is often obviated by the typical imaging appearance.

Conclusions

Paget's disease on ^{11}C choline PET/CT demonstrates mild to moderate activity, which does not correlate with bone scan uptake or alkaline phosphatase level. It is important to recognize Paget's disease as a potential pitfall on ^{11}C choline PET/CT. However, the characteristic appearance on the CT portion of PET/CT examinations should allow confident diagnosis and differentiation from prostate cancer osseous metastases.

Disclosure of conflict of interest

None.

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