

Diagnostic performance of ¹¹C-choline PET/CT and bone scintigraphy in the detection of bone metastases in patients with prostate cancer

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ABSTRACT

The aim of this study was to compare ¹¹C-choline PET/CT and bone scintigraphy (BS) for detection of bone metastases in patients with prostate cancer. Twenty-one patients with histologically proven prostate cancer underwent ¹¹C-choline PET/CT and BS before (n = 4) or after (n = 17) treatment. Patient-, region-, and lesion-based diagnostic performances of bone metastasis of both ¹¹C-choline PET/CT and BS were evaluated using a five-point scale by two experienced readers. Bone metastases were present in 11 (52.4%) of 21 patients and 48 (32.7%) of 147 regions; 111 lesions were found to have bone metastases. Region-based analysis showed that the sensitivity, specificity, accuracy, and area under the receiver-operating-characteristic curves (AUC) of ¹¹C-choline PET/CT were 97.9%, 99.0%, 98.6%, and 0.9989, respectively; those of BS were 72.9%, 99.0%, 90.5%, and 0.8386, respectively. Sensitivity, accuracy, and AUC significantly differed between the two methods (McNemar test, p = 0.0015, p = 0.0015, and p < 0.0001, respectively). ¹¹C-choline PET/CT detected 110/111 metastatic lesions (99.1%); BS detected 85 (76.6%) (p < 0.0001). According to the CT morphological type, the visualization rates of ¹¹C-choline-PET/BS were 100%/90.3% for the blastic type, 91.7%/8.3% for the lytic type, 100%/100% for the mixed type, and 100%/53.3% for the invisible type, respectively. Significant differences in blastic, lytic, and invisible types were observed between the two methods (p = 0.013, p = 0.0044, and p = 0.023, respectively). In conclusion, ¹¹C-choline PET/CT had greater sensitivity and accuracy than BS for detection of bone involvement in patients with prostate cancer.

Keywords: bone metastasis, bone scintigraphy, choline, FDG, PET, prostate cancer

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INTRODUCTION

In Western Europe and North America, prostate cancer is the most common tumor type in men and the second most frequent cause of death from cancer.¹⁾ Although prostate malignancy

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often develops slowly, it may present an aggressive pattern and involve bone metastases. The incidence of bone metastatic involvement depends on tumor stage and histology. However, bone involvement occurs in 65–75% of cases of advanced disease.²⁾ The axial skeleton is involved in 85% of patients who die from prostate cancer, and the presence and extent of bone metastases accurately reflect the prognosis for individual patients.³⁾

The early diagnosis of skeletal involvement in prostate cancer is crucial for appropriate patient management. In particular, it is important for the proper selection of therapy and follow-up care, assessment of patient prognosis, and prevention of complications, such as pathological fracture and spinal cord compression, which may lead to considerable morbidity and reduced quality of life.

Bone scintigraphy (BS) is a low-cost, whole-body, clinical examination commonly used to detect skeletal involvement.⁴⁾ The tracer is chemisorbed onto the bone surface depending on local blood flow and osteoblastic activity. BS exhibits high sensitivity, but suffers from suboptimal specificity because of the non-specific tracer uptake in benign processes, including degenerative changes, fracture, trauma, and arthritis.^{5,6)}

Within the last decade, positron emission tomography/computed tomography (PET/CT) has emerged as the imaging method of choice for diagnosis, staging, restaging, and response evaluation in several cancers. However, the commonly used tracer ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG) appears to be less useful in prostate cancer due to the low metabolism of many prostate adenocarcinomas.⁷⁾ Therefore, new tracers, such as ¹¹C-choline, have been sought. Prostate cancer cells have up-regulated choline kinase, which induces an elevated uptake of choline for synthesis of phospholipids. Once inside the cell, choline is phosphorylated and trapped.⁸⁾

To our knowledge, there are few systematic studies comparing the ability of ¹¹C-choline PET/CT to detect bone metastases in prostate cancer. Pichhio *et al.* reported better sensitivity of BS relative to ¹¹C-choline PET/CT,⁹⁾ whereas several groups reported the superiority of choline PET/CT over BS.¹⁰⁻¹³⁾ The true advantage of ¹¹C-choline PET/CT is still controversial. The purpose of this prospective head-to-head trial was to clarify which method is preferable for the detection of bone metastases in patients with prostate cancer.

MATERIALS AND METHODS

Patients

The institutional review board approved this study. In total, 21 patients (age range 47–90 years, mean 71 years) were included. Patients had histopathologically proven prostate cancer and they underwent ¹¹C-choline PET/CT and BS, for suspected bone metastasis, within a maximum interval of 2 weeks at our institution between October 2015 and January 2017. Informed consent was obtained from each patient after the procedures were fully explained. The median free serum prostate-specific antigen (PSA) level of 4 patients who underwent these two examinations before the treatment was 59.9 ng/ml (range 3–5916 ng/ml); the mean PSA level of 17 patients who underwent the two examinations during or after treatment was 5.1 (range, 0.2–946 ng/ml). Fifteen of 21 patients (71.4%) were receiving androgen-deprivation therapy at the time of the two examinations. For analytical purposes, these 15 patients were considered hormone-resistant patients, as documented by PSA serum level increases during treatment. There was no change in the patients' therapeutic regimen between the two examinations. Further details of patient demographics are listed in Table 1.

¹¹C-choline PET/CT study

All ¹¹C-choline PET/CT examinations were performed using a PET/CT scanner (Gemini TF64;

Table 1 Patient characteristics

Characteristics	value
Age (years)	
Mean	70.6±10.8
Range	47~90
PSA (ng/mL)	
Patients without any previous treatments (n=4)	
Mean	1,509.7±2,937.9
Range	3~5916
Median	59.9
Patients with previous treatments (n=17)	
Mean	68.4±226.7
Range	0.2~946
Median	5.05
Previous treatment	
None	4
Surgery (Prostatectomy)	1
Radiotherapy	1
Radiotherapy + Hormonal therapy	6
Hormonal therapy	9

PSA: prostate specific antigen

Philips Medical Systems, Eindhoven, the Netherlands). Patients received an intravenous injection of 3.0 MBq/kg body weight ^{11}C -choline. The PET/CT scan began 5 min after the injection, and emission data were acquired from 7–8 bed positions proceeding from the proximal thighs to the base of the skull. Each position required 2 min and each scan was acquired in a 3-dimensional (3D) mode. PET images were corrected for random scatter and attenuation, and were reconstructed on a 144-image matrix using an ordered-subsets expectation maximization algorithm (3 iterations, 33 subsets). For attenuation correction and anatomic localization, helical CT scans from the top of the head to the mid-thigh were obtained using the following parameters: tube voltage, 120 kV; effective tube current auto-mA, up to 100 mA; gantry rotation speed, 0.5 s; detector configuration, 64 × 0.625 mm; slice thickness, 2 mm; and transverse field of view, 600 mm.

Bone scintigraphy study

Whole-body BS was performed using a dual-head gamma camera (Forte, Hitachi Ltd., Tokyo, Japan) after intravenous administration of approximately 555 MBq of $^{99\text{m}}\text{Tc}$ -methylene diphosphonate ($^{99\text{m}}\text{MDP}$). After injection, patients were orally hydrated and were asked to void their bladders frequently and immediately prior to the scan. Total body images were obtained approximately 3 h after administration of $^{99\text{m}}\text{MDP}$, with simultaneous anterior and posterior whole-body acquisition. Static additional acquisitions were also acquired. Single-photon emission computed tomography (SPECT) was not acquired.

Image analysis

Two experienced nuclear medicines (both readers with 9 years of experience in PET/CT and 15 years in BS), who had no knowledge of the other imaging results or the clinical data,

prospectively interpreted the ^{11}C -choline PET/CT and BS images in consensus per patient and per lesion using a 5-point scale (1: definitely absent, 2: probably absent, 3: indeterminate, 4: probably present, and 5: definitely present). Discordant readings by the 2 observers for each modality were resolved by subsequent consensus review.

Diagnostic ability was determined on a per-patient basis and based on 7 regions: 1) spine (cervical spine, thoracic spine, lumbar spine, and sacrum) and sternum; 2) right and 3) left clavicle, ribs, and scapula; 4) right and 5) left iliac bone, pubic bone, ischium, and acetabulum; and 6) right and 7) left upper and lower extremities. In patients who presented with diffuse spine metastases, a single unique lesion per cervical spine, thoracic spine, or lumbar spine was arbitrarily considered due to the impossibility of calculating the proper number of lesions.

CT images provided by ^{11}C -choline PET/CT integrated studies were used to: 1) correct PET images for attenuation, 2) establish the anatomical localization of ^{11}C -choline PET findings, and 3) define the morphological characteristics of ^{11}C -choline findings, in cases of either suspected or pathological uptake.

A lesion was defined as malignant (grade 4 or 5) on ^{11}C -choline PET/CT when a significant and focal pathological increase of ^{11}C -choline was found both in an intramedullary region, independently of the CT finding, or in an adjacent region corresponding to a lytic, sclerotic, and/or mixed lytic-sclerotic lesion on CT. On BS, a lesion was defined as malignant according to standard pathological criteria of intensity, localization, and extension of $^{99\text{m}}\text{MDP}$ uptake.

Each bone lesion was classified as the osteoblastic (osteoblastic pattern with bone formation and ossification), osteolytic (osteoclastic pattern with bone resorption), mixed (both osteolytic and osteoblastic), or invisible type based on CT findings. Semiquantitative analysis of the abnormal radiotracer uptake for each suspicious bony metastatic lesion was performed using the maximum standardized uptake value (SUVmax). The SUV was calculated as:

$$\text{SUV} = \frac{\text{volume of interest (VOI) radioactivity concentration (Bq/mL)}}{\text{[injected dose (Bq)/patient's weight (g)]}}.$$

The SUVmax, which was defined as the highest SUV in the pixel with the highest count, within the VOI, was measured and recorded for the focal areas of uptake.

Final assessment

The final diagnosis was obtained from the confirmation of the same lesion by subsequent magnetic resonance imaging (MRI), or clinical follow-up of on the basis of PSA level, computed tomography (CT), MRI, BS, or ^{11}C -choline PET/CT.

Statistical analysis

To estimate each imaging modality's utility, receiver-operating-characteristic (ROC) analysis was used. An ROC contrast estimation was used to compare the diagnostic capability of the two modalities on a per-patient and per-region basis. To determine whether the areas under the ROC curves (AUC) were different, the correlation of the testing methods was accounted for in the analysis. Tests for differences in sensitivity, specificity, and accuracy between imaging modalities were conducted with the McNemar test. To calculate the sensitivity and specificity of each modality, scores of 4 and 5 were considered positive. Sensitivity, specificity, and accuracy were also separately calculated in hormone-resistant patients and in those who did not receive anti-androgenic treatment.

We also examined whether there was a significant difference in mean SUVmax among the osteoblastic, osteolytic, mixed, and invisible types using single-factor analysis of variance and a

multiple comparison test for parametric data with a Bonferroni correction.

A P value of less than 0.05 was considered significant for all analyses. Statistical analyses were performed using SAS software (version 9.3; SAS Institute, Cary, NC, USA).

RESULTS

Patient-based analysis

Bone metastases were present in 11 (52.4%) of 21 patients. Patient-based analysis showed that the sensitivity, specificity, accuracy, and AUC of ^{11}C -choline PET/CT were 90.9% (10/11), 90% (9/10), 90.5% (19/21), and 0.9682, respectively, whereas those of BS were 81.8% (9/11), 90% (9/10), 85.7% (18/21), and 0.8227, respectively (Table 2). There were no significant differences between the two methods. One false-negative case by ^{11}C -choline PET/CT was a case of pre-treatment with a single bone metastasis of the scapula. One false-positive case by ^{11}C -choline PET/CT was a case of radiotherapy post-treatment, in which abnormal ^{11}C -choline uptake of the normal thoracic vertebra was observed. However, two false-negative cases by BS were both cases of radiotherapy post-treatment followed by hormone therapy. One false-positive case by BS showed strong uptake of the degenerative change of the lumbar vertebra.

Table 2 Patient-based diagnostic result of ^{11}C -choline PET/CT and bone scintigraphy

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)	AUC
	95%CI	95%CI	95%CI	95%CI	95%CI	95%CI
^{11}C -Choline PET/CT	90.9 (10/11) 73.9–100	90 (9/10) 71.4–100	90.9 (10/11) 73.9–100	90 (9/10) 71.4–100	90.5 (19/21) 77.9–100	0.9682 0.7783–0.9962
Bone scintigraphy	81.8 (9/11) 59.0–100	90 (9/10) 71.4–100	90 (9/10) 71.4–100	81.8 (9/11) 59.0–100	85.7 (18/21) 70.7–100	0.8227 0.4948–0.9565
p value	p=1				p=1	p=0.24

PPV: positive predictive value, NPV: negative predictive value, AUC: area under the receiver-operating-characteristic curves, CI: confidence interval

A major difference of diagnostic accuracy of ^{11}C -choline-PET/CT and BS was not observed between patients who did (n = 15/21) or who did not (n = 6/21) receive hormone therapy at the time of imaging (Table 3). The lesion-based detectability of ^{11}C -choline PET/CT did not significantly differ between hormone-resistant patients (100%) and those who did not receive anti-androgenic treatment (85.7%). However, the lesion-based detectability of BS did not significantly differ between hormone-resistant patients (76.9%) and those who did not receive anti-androgenic treatment (71.4%).

Region-based analysis

Seven region sites, including the 1) spine (cervical spine, thoracic spine, lumbar spine, and sacrum) and sternum; 2) right and 3) left clavicle, ribs, and scapula; 4) right and 5) left iliac bone, pubic, ischium, and acetabulum; and 6) right and 7) left upper and lower extremities of

Table 3 Comparison of diagnostic accuracy between patients who did and did not receive hormone therapy

	¹¹ C-choline PET/CT	Bone scintigraphy	p value
With HT			
Patient-based			
Sensitivity (%)	100 (8/8)	75 (6/8)	p=0.48
Specificity (%)	100 (7/7)	100 (7/7)	p=1
Accuracy (%)	100 (15/15)	86.7 (13/15)	p=0.48
Lesion-based			
Sensitivity (%)	100 (104/104)	76.9 (80/104)	p<0.0001
Without HT			
Patient-based			
Sensitivity (%)	66.7% (2/3)	100 (3/3)	p=1
Specificity (%)	66.7% (2/3)	66.7 (2/3)	p=1
Accuracy	66.7% (4/6)	83.3 (5/6)	p=1
Lesion-based			
Sensitivity (%)	85.7 (6/7)	71.4 (5/7)	p=1

HT: hormone therapy

Table 4 Region-based diagnostic result of ¹¹C-choline PET/CT and bone scintigraphy

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)	AUC
	95%CI	95%CI	95%CI	95%CI	95%CI	95%CI
¹¹ C-Choline PET/CT	97.9 (47/48)	99.0 (98/99)	97.9 (47/48)	99.0 (98/99)	98.6 (145/147)	0.9989
	93.9–100	97.0–100	93.9–100	97.0–100	96.8–100	0.9939–0.9998
Bone scintigraphy	72.9 (35/48)	99.0 (98/99)	97.2 (35/36)	88.3 (98/111)	90.5 (133/147)	0.8386
	60.3–85.5	97.0–100	91.9–100	82.3–94.3	85.7–95.2	0.7439–0.9029
p value	p=0.0015				p=0.0015	p<0.0001

PPV: positive predictive value, NPV: negative predictive value, AUC: area under the receiver-operating-characteristic curves, CI: confident interval

each patient were evaluated. There were 48 (32.7%) sites of bone metastatic lesions in 147 region sites: 8 in the spine (cervical spine, thoracic spine, lumbar spine, and sacrum) and sternum, 14 in the clavicle, ribs, and scapula; 18 in the iliac bone, pubic bone, ischium, and acetabulum; and 8 in the upper and lower extremities.

Region-based analysis showed that the sensitivity, specificity, accuracy, and AUC of ¹¹C-choline PET/CT were 97.9% (47/48), 99.0% (98/99), 98.6% (145/147), and 0.9989, respectively. Those of BS were 72.9% (35/48), 99.0% (98/99), 90.5% (133/147), and 0.8386, respectively (Table 4). The sensitivity, accuracy, and AUC of ¹¹C-choline PET/CT were significantly higher than those of BS (McNemar test, p = 0.0015, p = 0.0015, and p < 0.0001, respectively).

Lesion site-based analysis

A total of 111 lesions were found to be bone metastasis: 4 in the cervical spine, 8 in the thoracic spine, 8 in the lumbar spine, 5 in the sacrum, 4 in the sternum, 2 in the clavicle, 15 in the ribs, 9 in the scapula, 15 in the iliac bone, 9 in the pubic bone, 10 in the ischium, 11 in the acetabulum, 3 in the upper extremities, and 8 in the lower extremities (Table 5). ^{11}C -choline PET/CT could detect 110 lesions (99.1%); BS could detect 85 (76.6%) ($p < 0.0001$). One false-negative lesion site detected by ^{11}C -choline PET/CT was the scapula, whereas 26 false-negative lesion sites were detected by BS, including the cervical spine ($n = 2$), thoracic spine ($n = 4$), lumbar spine ($n = 2$), sacrum ($n = 2$), sternum ($n = 1$), ribs ($n = 5$), scapula ($n = 2$), iliac bone ($n = 4$), acetabulum ($n = 3$), and lower extremities ($n = 1$). In all locations, the visualization rate of ^{11}C -choline PET/CT was greater than or equal to that of BS without significant difference.

Among 111 metastatic bony lesions, 83 (74.8%) were osteoblastic, 12 (10.8%) were osteolytic, 1 (0.9%) was mixed, and 15 (13.5%) were invisible according to the CT morphological types (Table 6). The visualization rate of ^{11}C -choline-PET/BS was 100%/90.3% for the osteoblastic type, 91.7%/8.3% for the osteolytic type, 100%/100% for the mixed type, and 100%/53.3% for the invisible type. The sensitivities of ^{11}C -choline PET/CT were significantly higher than BS in the osteoblastic, osteolytic, and invisible types ($p = 0.013$, $p = 0.0044$, and $p = 0.023$, respectively). The mean SUVmax of the metastatic bony lesions was 4.53 ± 2.32 , 4.66 ± 2.64 , 9.92, and 5.27 ± 3.30 for the osteoblastic, osteolytic, mixed, and invisible types, respectively. SUVmax differed significantly among the four subgroups ($p = 0.023$). Moreover, a Bonferroni correction revealed significant differences in SUVmax between the osteoblastic and mixed types ($p = 0.0016$), and between the osteolytic and mixed types ($p = 0.02$). No significant difference in SUVmax was observed between the osteoblastic and osteolytic types.

Two representative cases are shown (Figures 1 and 2).

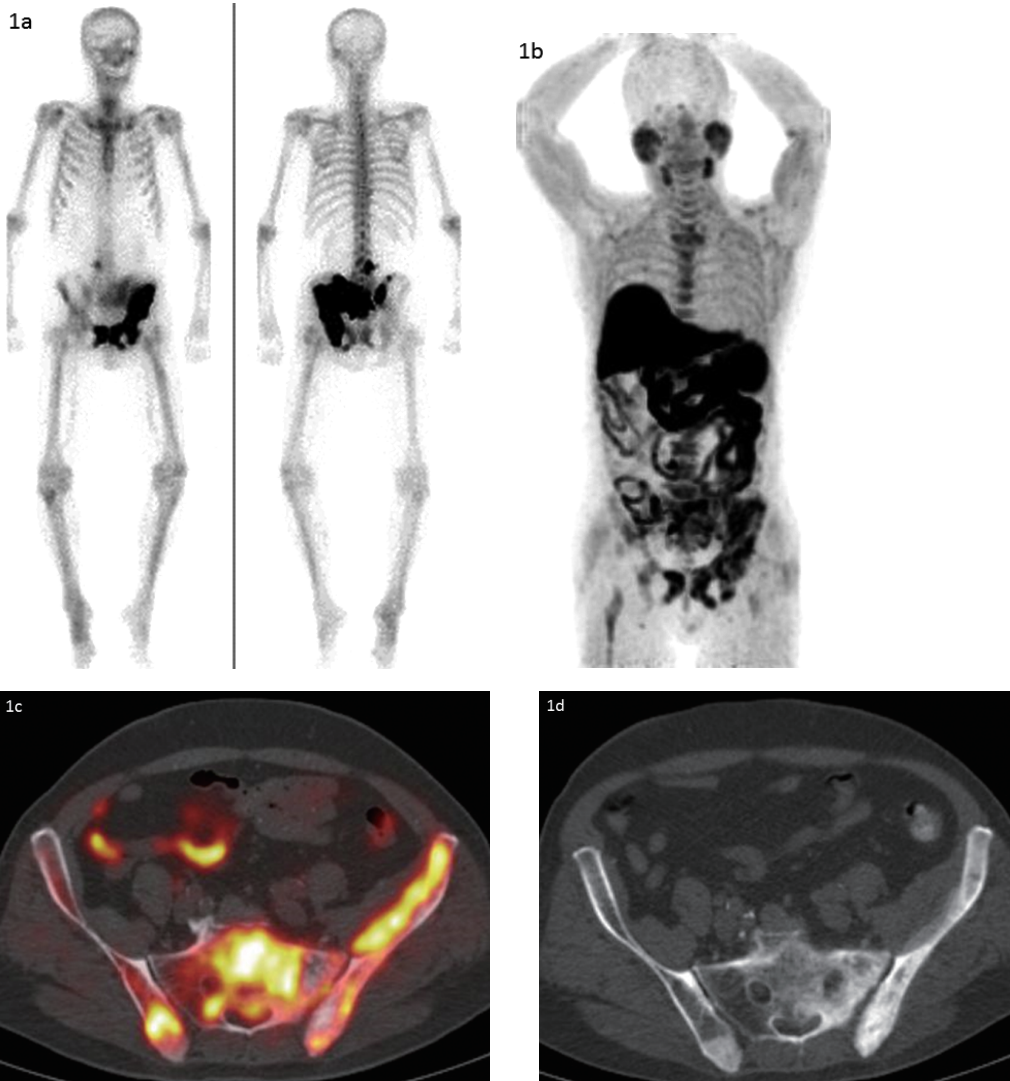
Table 5 Distribution and visualization rates of ^{11}C -choline PET/CT and bone scintigraphy

Location	Lesion no.	Sensitivity (%) of ^{11}C -choline PET/CT	Sensitivity (%) of Bone scintigraphy	p value
Cervical spine	4	100 (4/4)	50 (2/4)	p=0.48
Thoracic spine	8	100 (8/8)	50 (4/8)	p=0.13
Lumbar spine	8	100 (8/8)	75 (6/8)	p=0.48
Sacrum	5	100 (5/5)	60 (3/5)	p=0.48
Sternum	4	100 (4/4)	75 (3/4)	p=1
Clavicle	2	100 (2/2)	100 (2/2)	p=1
Ribs	15	100 (15/15)	66.7 (10/15)	p=0.074
Scapula	9	88.9 (8/9)	77.8 (7/9)	p=1
Iliac bone	15	100 (15/15)	73.3 (11/15)	p=0.13
Pubic	9	100 (9/9)	100 (9/9)	p=1
Ischium	10	100 (10/10)	100 (10/10)	p=1
Acetabulum	11	100 (11/11)	72.7 (8/11)	p=0.25
Upper extremities	3	100 (3/3)	100 (3/3)	p=1
Lower extremities	8	100 (8/8)	100 (7/8)	p=1
Total	111	99.1 (110/111)	76.6 (85/111)	p<0.0001

Table 6 The visualization rates of ^{11}C -choline PET/CT and bone scintigraphy for the different CT types of bone metastases

CT pattern	Lesion no. (%)	Sensitivity (%) of ^{11}C -choline PET/CT	Sensitivity (%) of Bone scintigraphy	p value	SUV max on ^{11}C -choline PET/CT
OsteoBlastic	83 (74.8)	100 (83/83)	90.3 (75/83)	p=0.013	4.53±2.32
OsteoLytic	12 (10.8)	91.7 (11/12)	8.3 (1/12)	p=0.0044	4.66±2.64
Mixed	1 (0.9)	100 (1/1)	100 (1/1)	p=1	9.92
Invisible	15 (13.5)	100 (15/15)	53.3 (8/15)	p=0.023	5.27±3.30
Total	111	99.1 (110/111)	76.6 (85/111)	P<0.0001	4.69±2.53

SUV: standardized uptake value



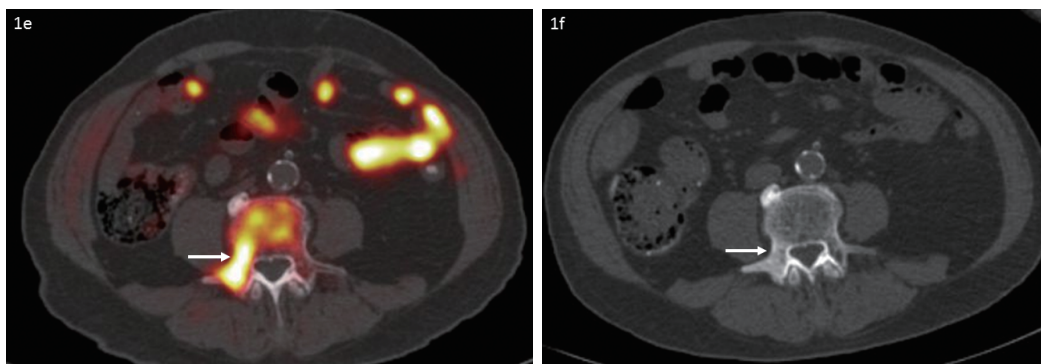


Fig. 1 A 67-year-old man with a PSA level of 49.9 ng/mL, receiving androgen-deprivation therapy for prostate cancer.

a) Anterior and posterior whole-body views of bone scintigraphy showed strong ^{99m}MDP uptake in the bilateral iliac bones, pubic bone, ischium, left acetabulum, sacrum, and lumbar spine (L4), with a score of 5 for diagnosing bone metastasis.

b) Maximum intensity projection of ^{11}C -choline PET shows multiple abnormal ^{11}C -choline uptakes in the bilateral iliac bones, pubic bone, ischium, left acetabulum, sacrum, and lumbar spine (L4), with a score of 5 for diagnosing bone metastasis.

c) The fused ^{11}C -choline PET/CT image and (d) CT image (bone image) show strong accumulation in the osteoblastic change of the bilateral iliac bones and sacrum. The SUVmax of the right and left bilateral iliac bones and sacrum were 6.16, 5.46, and 6.00, respectively.

e) The fused ^{11}C -choline PET/CT image and (f) CT image (bone image) show strong accumulation (SUVmax: 5.68) in the mild osteoblastic change of the right pedicle of L4 (arrow).



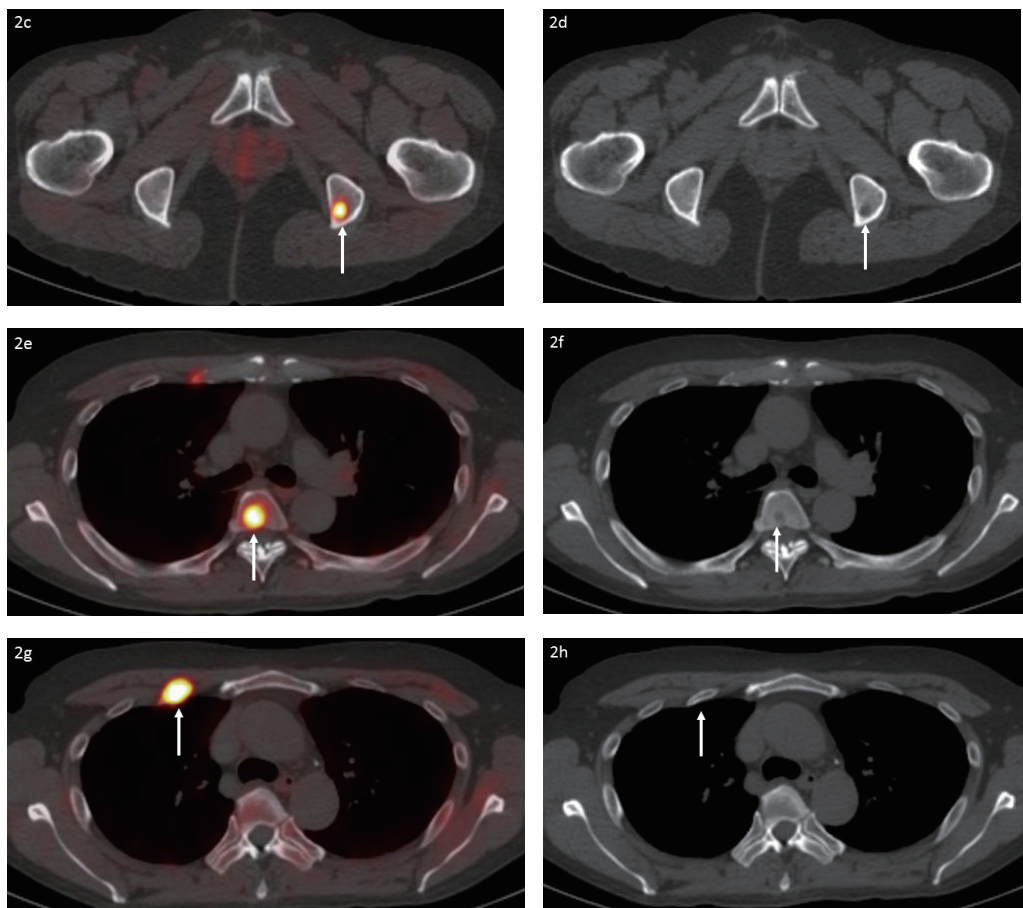


Fig. 2 A 57-year-old man with a PSA level of 19.9 ng/mL, who was treated with external-beam radiotherapy for prostate carcinoma 3 years earlier and then received androgen-deprivation therapy.

- a) Anterior and posterior whole-body views of bone scintigraphy were negative, with a score of 1 for diagnosis of bone metastasis (false negative).
- b) Maximum intensity projection of ^{11}C -choline PET shows multiple abnormal ^{11}C -choline uptakes in the left ischium, right iliac bone, lumbar spine (L5), bilateral ribs, cervical spine, and thoracic spine with a score of 5 for diagnosing of bone metastasis.
- c) The fused ^{11}C -choline PET/CT image and (d) CT image (bone image) show strong accumulation (SUVmax: 6.11) in the osteolytic change of the left ischium (arrow).
- e) The fused ^{11}C -choline PET/CT image and (f) CT image (bone image) show strong accumulation (SUVmax: 6.18) in the osteolytic change of the thoracic spine (Th5) (arrow).
- g) The fused ^{11}C -choline PET/CT image and (h) CT image (bone image) show strong accumulation (SUVmax: 8.17) in the osteolytic change of the right second rib (arrow).

Additional ^{11}C -choline PET/CT findings

In addition to bone metastasis, ^{11}C -choline PET/CT could detect primary prostate cancer or local recurrence (11 patients) and lymph nodal metastases (5 patients).

DISCUSSION

In our present study, we were able to prove that the region and lesion site-based sensitivities of ^{11}C -choline PET/CT, for detecting bone metastases in patients with prostate cancer, were significantly higher compared to those of BS, regardless of the use of hormone therapy or CT morphological pattern.

This superiority of ^{11}C -choline PET/CT is similar to several previous studies¹⁰⁻¹³) and one meta-analysis.¹⁴) A meta-analysis demonstrated that pooled sensitivity and specificity of ^{11}C -choline PET/CT were 0.91 (95% confidence interval (CI): 0.83–0.96) and 0.99 (95% CI: 0.93–1.00), and those figures for BS were 0.79 (95% CI: 0.73–0.83) and 0.82 (95% CI: 0.78–0.85).¹⁴) In our opinion the greater sensitivity of ^{11}C -choline PET/CT could be due to two reasons: 1) the uptake mechanism of $^{99\text{m}}\text{MDP}$ and ^{11}C -choline is different. $^{99\text{m}}\text{MDP}$ accumulates in the osteoblastic lesions and is an indirect sign of the presence of a metastatic lesion, but ^{11}C -choline directly accumulates in the metastasis itself, so it is reasonable to think that ^{11}C -choline could detect the lesion more accurately than $^{99\text{m}}\text{MDP}$, as soon as the metastasis is detectable by the PET scanner. 2) PET/CT image quality is much higher compared to BS, and the addition of high-quality CT imaging has greatly improved the diagnostic information provided by this hybrid method.

Although the visualization rate and SUVmax between osteoblastic and osteolytic types were most similar on ^{11}C -choline PET/CT in our series, it has been reported that osteoblastic lesions primarily show low choline uptake.^{15,16}) Beheshti *et al.* demonstrated that densely sclerotic malignant lesions (Hounsfield unit level greater than 825) showed no choline uptake and all lesions were observed in patients who were receiving hormone therapy.¹⁵)

The potential influence of anti-androgenic treatment in patients who undergo ^{11}C -choline studies is still controversial. A significant reduction of ^{11}C -choline uptake following treatment with the non-steroidal androgenic antagonist bicalutamide has been reported during the staging phase of prostate cancer patients.¹⁷) Conversely, in a large population of 358 prostatectomized patients with a PSA serum level increase, it was revealed that the presence of androgen deprivation therapy as a variable could significantly predict an increased risk of positive ^{11}C -choline PET/CT only when analyzed alone and not in comparison with other variables, primarily PSA-related values and Gleason score.¹⁸) Picchio *et al.* demonstrated that the accuracy for detecting bone metastasis of ^{11}C -choline PET/CT did not significantly differ between hormone-resistant patients (97%) and those who did not receive anti-androgenic treatment (95%) in a study similar to our series.⁹) Based on these results, the withdrawal of anti-androgenic treatment cannot be recommended for ^{11}C -choline PET/CT execution in hormone-resistant patients.

^{11}C -choline PET/CT showed increased sensitivity in the detection of bone lesions, but it is more expensive and less available than BS. However, the diagnostic accuracy of bone metastasis by ^{11}C -choline PET/CT has been reported to be equal to or inferior to that of MRI.^{14,19}) The clinical impact of the use of ^{11}C -choline PET/CT in prostate cancer patients remains to be assessed in larger prospective studies. A cost-effectiveness analysis is necessary to assess the best diagnostic flowchart in patients with prostate cancer.

This study had several limitations. First, the sample size of this single institution is too small to draw a definite conclusion. Therefore, a prospective, multicenter trial including a large cohort of patients would help better clarify the exact role of ^{11}C -choline PET/CT in clinical decision-making and long-term outcomes in this clinical setting. Second, the population of the enrolled patients was heterogeneous; treatment naïve patients, those with or without hormonal treatment. This sample heterogeneity will bring complicated confounding factors for analysis. Third, the gold standard for any analysis is the histological confirmation of the findings. However, clinical follow-up is a valid approach for evaluation of diagnostic accuracy and response to therapy, and

it would have been unethical to investigate all PET/CT-detected lesions using invasive procedures. Positive findings are easy to confirm, but negative findings only indicate that it has not been possible to acquire positive findings during follow-up, making it uncertain whether the findings are truly negative. Forth, in this study, SPECT/computed tomography (SPECT/CT) was not available for use. Presently, the use of hybrid imaging (SPECT/CT) could increase sensitivity and specificity of BS by identifying benign bone conditions with increases in bone turnover and whenever equivocal findings of planar bone imaging occur.²⁰⁾

CONCLUSIONS

¹¹C-choline PET/CT had better sensitivity and accuracy than bone scintigraphy for detection of bone involvement in patients with prostate cancer, especially for region- and lesion-based analysis. This finding was observed regardless of the use of hormone therapy and CT morphological pattern. The clinical impact of the use of ¹¹C-choline PET/CT for detecting bone metastasis in prostate cancer patients must be assessed in larger prospective studies.

CONFLICT OF INTEREST

All authors declare no actual or potential conflict of interest.

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