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Diagnostic Performance of ^{18}F -Fluciclovine in Detection of Prostate Cancer Bone Metastases

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Abstract

Purpose— ^{18}F -fluciclovine is a synthetic amino acid radiotracer that has recently been approved in Europe and the United States for positron emission tomography (PET) imaging in men with biochemical recurrence (BCR) of prostate cancer following prior definitive treatment. Accurate identification of the sites of disease in patients presenting with BCR of prostate cancer is important in determining the appropriate treatment. Bone is the most frequent site of metastatic disease in patients with prostate cancer.

Methods—We conducted a comprehensive review of the available preclinical and clinical data on the diagnostic performance of ^{18}F -fluciclovine PET-computed tomography (PET/CT) in an attempt to draw practical and general conclusions on the utility and limitations of ^{18}F -fluciclovine PET/CT in localization of osseous metastatic disease in prostate cancer.

Results—The cumulative preclinical data and results of some retrospective and two prospective clinical studies suggest that ^{18}F -fluciclovine can detect early bone marrow involvement in patients with BCR of prostate cancer and negative prior bone specific imaging findings.

Conclusions— ^{18}F -Fluciclovine PET/CT appears to offer useful information for early detection of bone metastases in men with BCR of prostate cancer. Additional investigations will be needed to compare the diagnostic performance of ^{18}F -fluciclovine PET/CT to other standard and novel imaging methods in initial staging, BCR and castrate-resistant phases of disease.

Keywords

Fluciclovine; Prostate; Cancer; Bone; Metastasis

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Introduction

Epidemiology of Bone Metastases in Prostate Cancer

Most patients who are diagnosed with prostate cancer have clinically localized disease, which may be due to prostate-specific antigen (PSA) screening practice in the United States (1). Despite curative-intent treatments (e.g. radical prostatectomy, external beam radiation therapy), recurrence defined by rising levels of PSA (biochemical recurrence or BCR) occurs in 20–40% of patients (2–4). This relatively high rate of recurrence after curative-intent treatment may be due to biological factors (e.g. aggressiveness of the primary tumor, early dissemination and cellular escape), or inadequate initial staging with standard-of-care imaging methods. Accurate localization of disease sites (e.g. local recurrence in the treated prostate bed, distant oligo- and poly-metastatic disease) has major ramifications on subsequent treatment strategy. Salvage therapy (e.g. radiation to treated prostate bed, pelvic nodal dissection) may be an option for limited local recurrence or regional nodal disease, while oligometastatic (< 5 lesions) disease may be amenable to lesion-directed therapy (e.g. excision, radiation) and poly-metastatic disease is treated with systemic therapy (e.g. androgen deprivation therapy [ADT], chemotherapy).

Metastases of prostate cancer typically spread first to regional and distant lymph nodes, and ultimately to the skeleton and soft tissue organs (5–7). While bone metastases are initially asymptomatic, they can become painful and result in pathologic fractures or spinal cord compression (8). Among patients with prostate cancer, but no bone metastases, and rising PSA levels despite ADT, 33% will develop one or more bone metastases within 2 years, with a median bone metastasis-free survival of 32 months (9).

Imaging of Bone Metastases

The development of BCR represents a critical juncture in the progression of prostate cancer and might be considered the last opportunity for curative therapy. To determine the most appropriate therapy, accurate determination of the extent of disease is essential. Current standard-of-care imaging typically includes bone scintigraphy, contrast-enhanced CT of the chest, abdomen and pelvis and, increasingly, the use of multiparametric magnetic resonance imaging (mpMRI) of the pelvis. Detection of distant metastatic disease, including bone metastases, precludes potential curative salvage radiotherapy of the prostate bed, although localized treatment (e.g. with stereotactic body radiotherapy) may also be considered in patients with oligometastatic bone lesions.

Bone Scintigraphy

Currently, bone scanning (bone scintigraphy, typically with ^{99m}Technetium-methylene diphosphonate [MDP]) is the most widely used method for evaluating bone metastases of prostate cancer and is recommended for staging in those considered to have intermediate–high risk disease, and in all patients who are symptomatic (10, 11). Imaging is facilitated through adsorption of labeled MDP to the hydroxyapatite mineral of bone osteoblasts during normal bone growth and turnover, allowing local bone metabolism to be visualized (12). Thus, while osteoblastic bone metastases can be detected with relatively high sensitivity, the

indirect detection of osteoblastic processes, rather than direct assessment of tumor proliferation, can result in false positive findings from non-malignant causes or false negative outcomes for osteolytic metastases where an osteoclastic process is the biological feature (13, 14).

Suboptimal specificity (15, 16) and limited spatial resolution can also hinder bone lesion localization and characterization (14). Also associated with bone scanning is the osteoblastic flare, whereby bone regeneration following successful treatment of a bone metastasis can result in visualization of marrow lesions with a sclerotic rim around an initially lytic lesion or sclerosis of lesions that were previously undetected. This lesion healing is sometimes misinterpreted as progressive disease (13, 17).

Given these limitations, a need exists for an imaging method to be used either independently, or in combination with bone scintigraphy, to reliably locate or exclude potential bone metastases in patients with prostate cancer.

MRI

MRI is currently a favored option for the detection of metastases in the bone marrow cavity owing to its excellent soft tissue resolution (13, 14). A meta-analysis by Shen *et al* comparing the diagnostic performance of ^{11}C - or ^{18}F -choline positron emission tomography/computed tomography (PET/CT), MRI, and bone scintigraphy across 27 studies of patients with prostate cancer showed that at a subject level, the sensitivity and specificity of MRI (0.97, 95% Confidence Interval [CI]: 0.91–0.99 and 0.95, 95% CI: 0.90–0.97, respectively) were superior to bone scanning (0.79 [95% CI: 0.73–0.83] and 0.82 [95% CI: 0.78–0.85], respectively) and were similar to ^{11}C - or ^{18}F -choline (0.91 [95% CI: 0.83–0.96] and 0.99 [95% CI: 0.93–1.00], respectively) (18). Similar conclusions regarding performance were drawn from a meta-analysis of MRI, bone scanning and ^{18}F -fluorodeoxyglucose (FDG) PET/CT for the evaluation of bone metastases in the prostate cancer setting (19).

PET

Most studies of the potential role of PET tracers in the detection of prostate cancer bone metastases have focused on ^{18}F -sodium fluoride (^{18}F -NaF) and ^{11}C - or ^{18}F -choline PET/CT.

Before the introduction of $^{99\text{m}}\text{Tc}$ -labeled phosphonates, ^{18}F -NaF PET was available for skeletal imaging, but was of limited clinical utility owing to inadequate accessibility to PET scanners, challenges with radiotracer availability, and the relatively high cost of the procedure (20, 21). However, several studies have shown that ^{18}F -NaF PET or PET/CT has superior diagnostic performance to $^{99\text{m}}\text{Tc}$ -based bone scanning for the detection of bone metastases (20, 22, 23). A meta-analysis by Shen *et al* showed that, in comparison to $^{99\text{m}}\text{Tc}$ -MDP bone scintigraphy, ^{18}F -NaF PET or PET/CT had both higher sensitivity (0.96 vs. 0.88, $P = 0.002$) and specificity (0.91 vs. 0.80, $P = 0.001$) (24). It is of note that treatment flare may also affect ^{18}F -NaF PET/CT, similar to $^{99\text{m}}\text{Tc}$ -based bone scintigraphy.

Pooled data from the 2014 meta-analysis by Shen *et al* are unclear as to whether or not choline PET/CT is more sensitive than bone scanning (0.91; 95% CI: 0.83–0.86 for choline

PET/CT vs. 0.79; 95% CI: 0.73–0.83 for bone scanning), but choline PET/CT was shown to have higher specificity (0.99; 95% CI: 0.93–1.00 vs. 0.82; 95% CI: 0.78–0.85, respectively) with fewer indeterminate bone lesions (18).

Other metabolic (e.g. FDG) or targeted PET radiotracers (e.g. agents targeted to prostate-specific membrane antigen) also accumulate in metastatic bone lesions. However, as with choline, more studies are needed to decipher their role in relation to bone scanning and to understand the modulatory effect of various treatments on radiotracer localization in metastatic bone lesions.

¹⁸F-fluciclovine

¹⁸F-fluciclovine is a synthetic amino acid PET tracer recently approved in Europe and the USA for use in patients with suspected BCR of prostate cancer for localization of prostatic and extraprostatic lesions (28–31). Given the need for a reliable bone imaging method to improve the diagnostic performance of current standard-of-care, here we review the evidence to date concerning the detection of metastatic prostate cancer in bone using ¹⁸F-fluciclovine PET/CT.

Preclinical Data

Oka *et al* investigated the potential of ¹⁸F-fluciclovine to aid visualization of bone metastases by comparing the performance of ¹⁴C-fluciclovine with that of ³H-FDG, ³H-choline and ^{99m}Tc-hydroxymethylene diphosphonate (HMDP) using triple-tracer autoradiography in rat models of osteolytic bone metastases (derived from breast cancer) and osteoblastic bone metastases (derived from prostate cancer) (32). Histological verification confirmed that ¹⁴C-fluciclovine accumulated in areas of metastatic invasion in both the osteoclastic and the osteoblastic models. The distribution patterns of ¹⁴C-fluciclovine, ³H-FDG, and ³H-choline, were similar in both models, but ^{99m}Tc-HMDP was found to accumulate predominantly in osteoblastic lesions. ¹⁴C-fluciclovine visualized osteolytic lesions as early as day 6 and was also shown to accumulate particularly in early-stage, osteoblastic bone metastatic lesions with abundant malignant cells. ¹⁴C-fluciclovine was superior to ³H-choline in all aspects evaluated in the study. Despite having a target/background ratio in the osteolytic model that was lower than that of ³H-FDG, ¹⁴C-fluciclovine localized the osteoblastic lesions more clearly.

Of note, fluciclovine, in contrast to ^{99m}Tc-HMDP, did not accumulate in areas of new bone formation following bone damage, suggesting a reduced potential for false positive findings due to non-malignant bone disease, a known confounder in patients undergoing bone scanning. The authors concluded that fluciclovine PET can visualize true osteolytic and osteoblastic bone metastases, suggesting it could be useful in the detection of bone metastases from many types of cancer, including breast and prostate cancer.

A further study from the same group investigated the impact of fasting prior to fluciclovine-PET using triple-tracer autoradiography with ¹⁴C-fluciclovine, ³H-FDG, and ^{99m}Tc-HMDP in a rat model of breast cancer with mixed osteolytic/osteoblastic bone metastases in which the animals fasted overnight (33). Their results suggest that fasting, as is currently standard

procedure before clinical ^{18}F -fluciclovine PET/CT, improves the contrast between osteolytic and osteoblastic bone metastases and background.

Clinical Data

Suzuki *et al* (34) investigated the concordance between ^{18}F -fluciclovine PET/CT and both whole body contrast-enhanced CT and $^{99\text{m}}\text{Tc}$ -HMDP/ $^{99\text{m}}\text{Tc}$ -MDP bone scans performed within 28 days preceding the ^{18}F -fluciclovine PET/CT scan. In total, 68 patients with biopsy-proven prostate cancer scheduled either to undergo radical prostatectomy and extended lymphadenectomy ($n = 44$) or to be treated with ADT ($n = 24$) because of the presence of metastases, were enrolled. A total of 14 bone metastases were identified by bone scan/contrast-enhanced CT. Following the administration of ^{18}F -fluciclovine, PET/CT images were acquired within 30 minutes yielding a positive predictive value (PPV), negative predictive value (NPV), sensitivity and specificity of 0.61, 0.92, 0.73, and 0.86, respectively, for detection of bone metastases (34,35).

Bone metastases were evaluated by comparative diagnosis using integrated findings of bone scintigraphy and whole-body contrast-enhanced CT; the concordance rate for diagnosis of bone metastasis by ^{18}F -fluciclovine PET/CT and that based on the combined conventional imaging in the 66 patients who were evaluated for bone metastases was 0.83 (95% CI, 0.72–0.91) with an associated κ coefficient of 0.557 (95% CI, 0.326–0.788) that suggested moderate concordance. ^{18}F -fluciclovine PET/CT identified seven cases of bone metastases that were not identified by either bone scintigraphy or whole-body CT, probably because of the ability to visualize early marrow involvement with ^{18}F -fluciclovine. Four cases were deemed positive based on whole-body contrast-enhanced CT findings, but were negative according to the ^{18}F -fluciclovine PET/CT. The authors attributed this discordance to benign bone islands and not metastases.

A large, multicenter, retrospective study (BED001, NCT02443571) reported efficacy and safety data from 596 patients who underwent a total of 610 ^{18}F -fluciclovine scans for suspected BCR of prostate cancer (28). Data from this study, initially presented at American Society for Radiation Oncology (ASTRO) 2016, revealed a low detection rate (9%) for bone metastases across all participating centers with ^{18}F -fluciclovine PET/CT (36,37).

Data from BED001 that compared ^{18}F -fluciclovine PET/CT with other imaging methods are presented in Table 1 (37). These include bone single-photon emission computed tomography (SPECT) findings from one site (Emory University), which required all patients to have had a negative planar bone scan prior to ^{18}F -fluciclovine PET/CT. ^{18}F -fluciclovine PET/CT identified bone lesions in two patients, which were missed by conventional bone SPECT imaging. The first patient had multiple areas of uptake in the bony pelvis and the second had uptake in the femur and several lumbar vertebrae within 40 and 30 days, respectively, of a negative bone SPECT (37).

Two other patients had positive bone SPECT following a negative ^{18}F -fluciclovine PET/CT; one had a suspected lesion in L5 vertebra within the month following the negative ^{18}F -fluciclovine PET/CT, while the other had a positive bone SPECT (10th rib) within 2 months. The investigators suggested that in the latter case the rib was not visible on ^{18}F -fluciclovine

PET/CT, because their image capture protocol limited the field of view to the abdomino-pelvic region that excluded the area of rib involvement.

Five of 7 (71%) patients from the various centers who had a positive planar bone scan also showed a positive result with ^{18}F -fluciclovine PET/CT, as did 3/4 (75%) patients with bone lesions detected on MRI and 4/4 patients (100%) with lesions visible on contrast-enhanced CT. Similar high concordance was demonstrated between scan methods with respect to negative findings. When compared with MRI findings as a standard of truth, the PPV, NPV, sensitivity and specificity of ^{18}F -fluciclovine in detecting bone lesions were 0.75, 0.99, 0.75 and 0.99, respectively (37).

Nanni *et al* reported data from Bologna University that was included in BED001. This study was a prospective, intra-patient comparison of ^{18}F -fluciclovine with ^{11}C -choline PET for the detection of bone lesions in patients with BCR of prostate cancer (30). Overall, seven patients had bone lesions – four of these had identical positive findings with ^{11}C -choline and ^{18}F -fluciclovine, two were positive with ^{11}C -choline but negative with ^{18}F -fluciclovine, of which one was subsequently found to be a false positive ^{11}C -choline result and the final patient had a positive finding with ^{18}F -fluciclovine which was initially negative with ^{11}C -choline PET/CT, but eventually positive on follow up. Among this population, the PPV for bone lesions was shown to be higher for ^{18}F -fluciclovine (1.00) than for ^{11}C -choline (0.83) (30). Three illustrative clinical cases are shown in Figures 1–3.

Ongoing Trials – FALCON (NCT02578940) and LOCATE (NCT02680041)

Two open-label multisite studies are currently underway to establish the impact of ^{18}F -fluciclovine PET/CT on the management of patients with BCR of prostate cancer following primary treatment. FALCON (NCT02578940) is based in the UK and recently terminated recruitment early owing to overwhelming efficacy (38, 39). Interim data from FALCON show the ^{18}F -fluciclovine detection rate for bone lesions in patients with BCR of prostate cancer to be 9/85 (11%) (38). LOCATE (NCT02680041), a similar trial based in the USA, shows a similar bone lesion detection rate of 23/213 (11%) (37). It is noteworthy that all subjects in LOCATE were required to have a negative bone scan or ^{18}F -NaF PET/CT prior to their enrolment.

Conclusions

^{18}F -Fluciclovine PET/CT has been shown to detect bone involvement in patients with negative prior bone specific imaging. Superiority of ^{18}F -fluciclovine PET/CT over $^{99\text{m}}\text{Tc}$ -bone scintigraphy is probably related to their respective mechanisms of action – visualizing early initiation of a cancer lesion in the marrow compared with later, secondary effects of bone reaction to the presence of growing cancer lesions. Furthermore, ^{18}F -fluciclovine has been demonstrated to have strong concordance with MRI or ^{11}C -choline imaging of bone lesions, however there are cases where ^{18}F -fluciclovine findings may be negative – in particular, in small sclerotic lesions on CT.

Based on the relatively limited data available at this time, it is reasonable to conclude that ^{18}F -fluciclovine PET/CT can detect areas of early metastatic disease in bone and might offer

complementary localization of bone metastases in patients with prostate cancer when used with standard bone-specific imaging modalities. In cases of negative ^{18}F -fluciclovine findings and continuing clinical suspicion of bone involvement, additional imaging may be warranted.

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Figure 1.

67-year-old man with biochemical recurrence of prostate cancer s/p prostatectomy and serum PSA level of 6.44 ng/mL. Sagittal fused ^{18}F -fluciclovine PET and CT at bone window level (A) shows 2 sclerotic metastatic lesions at T7 (SUVmax 4.2) and T8 (SUVmax 2.9) (arrows). Mean blood pool SUV and mean L3 marrow SUVs were 1.2 and 2.2, respectively. Sagittal fused ^{18}F -NaF PET and CT at bone window level (B) show increased activity of T7 lesion (upper arrow); T8 sclerotic lesion (lower arrow) is not active. Axial fused PET/CT with ^{18}F -fluciclovine also demonstrated abnormal increased activity involving a 1.1 cm right external iliac node (circled) (C).

Figure 2.

63-year-old man with biochemical recurrence of prostate cancer s/p prostatectomy and serum PSA level of 0.50 ng/mL. Axial fused ¹⁸F-fluciclovine PET and CT at bone window level (A) with no definite abnormality on CT at bone window level (B) show focal increased activity at left anterior ilium (SUVmax 3.2) (circled) compatible with early bone marrow metastasis. Mean blood pool and mean L3 marrow SUVs were 1.1 and 2.4, respectively.

Figure 3.

67-year-old man with biochemical recurrence of prostate cancer s/p radical prostatectomy and serum PSA level of 88.08 ng/mL. Axial fused ^{18}F -fluciclovine PET and CT at bone window level (**A**) with sclerosis on CT at bone window level (**B**) shows abnormal focal increased activity in right inferior sacrum corresponding to mild sclerosis (SUVmax 4.5) (arrow). There was a dense inactive sclerotic lesion at L3 and active retroperitoneal lymphadenopathy (not shown). Mean blood pool SUV was 1.2.

Table 1

Bone lesion detection by ¹⁸F-fluciclovine PET/CT compared with other imaging methods (study BED001)

¹⁸ F-Fluciclovine	SPECT			Total	PLANAR			Total	MRI			Total	Contrast Enhanced CT			Total	Unenhanced CT			Total
	Positive	Negative	Indeterminate		Positive	Negative	Indeterminate		Positive	Negative	Indeterminate		Positive	Negative	Indeterminate		Positive	Negative	Indeterminate	
Positive	0	2	0	2	5	1	1	7	3	1	2	6	4	0	0	4	0	1	0	1
Negative	2	11	0	13	2	23	8	33	1	98	4	103	0	21	0	21	1	14	0	15
Indeterminate	0	0	0	0	0	2	0	2	0	2	0	2	1	1	0	2	0	0	0	0
Total	2	13	0	15	7	26	9	42	4	101	6	111	5	22	0	27	1	15	0	16