Am J Nucl Med Mol Imaging 2023;13(1):1-10
www.ajnmmi.us /ISSN:2160-8407/ajnmmi0149137

Original Article

Comparison of PSMA-based ^{18}F-DCFPyL PET/CT and Tc-99m MDP bone scan in detection of bone metastasis in prostate cancer

Zenus J Wilson[1,2], Guofan Xu[1], Sanjit O Tewari[1], Yang Lu[1]

[1]Department of Nuclear Medicine, Division of Diagnostic Imaging, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA; [2]Department of Diagnostic and Interventional Imaging, UT Health Houston McGovern Medical School, Houston, TX 77030, USA

Received January 14, 2023; Accepted February 14, 2023; Epub February 15, 2023; Published February 28, 2023

Abstract: While Tc-99m MDP bone scan (BS) remains the conventional standard for detection of bone metastasis in prostate cancer, newly FDA-approved imaging with PSMA-based ^{18}F-DCFPyL PET/CT has shown promise for early detection of metastatic disease. However, a paucity of data remains in the diagnostic accuracy of PSMA PET/CT in detecting bone metastasis compared to BS. This retrospective study included 91 patients who received both BS and PSMA PET/CT within a 3-month interval from August 2021 to February 2022. Separate concurrent primary cancer, interval PSA levels greater than a 2-fold difference (or absolute difference >1 ng/ml) between the two studies were excluded. All abnormal bone lesions on either scan were compared. The findings were verified by pathological findings and/or 6-month clinical follow-up. High concordance (78%) was found between modalities with discordant findings (20/91, 22%) demonstrating more false positives (4/20, 20%) and false negatives (3/20, 15%) on BS compared to PET/CT. Additionally, more bone metastases were detected on PSMA PET/CT (13/20, 65%) with all true positive BS lesions also detected PET/CT. The sensitivity, specificity, PPV and NPV for BS were 89%, 91%, 80%, and 95% respectively; and 100%, 97%, 93%, and 100% for ^{18}F-DCFPyL PET/CT respectively. Our results demonstrate that ^{18}F-DCFPyL PET/CT identified more bone metastases while also identifying all bone metastases identified on BS. With the added diagnostic value of detecting primary tumor and soft tissue metastasis, ^{18}F-DCFPyL PET/CT may render BS unnecessary to investigate bone metastases in patients with prostate cancer.

Keywords: Prostate cancer, bone metastasis, ^{18}F-DCFPyL, PET/CT, PSMA, bone scan

Introduction

Prostate cancer is the most common cancer worldwide and United States and is the second leading cause of cancer death in the United States [1, 2]. The mainstay of prostate cancer screening is based on clinical suspicion with shared decision making with or without digital rectal exam and prostate specific antigen (PSA) testing. The diagnosis is typically made histologically after prostate biopsy. Due to the highly variable biological behavior and clinical course of prostate cancer, ranging from indolent intraprostatic tumor to aggressive oligometastatic disease, imaging continues to play a critical aspect in prostate cancer management [3]. Additionally, while the 5-year relative survival of metastatic prostate cancer (mPC) is approximately 31%, local/regional disease is close to 100%. Thus, appropriate identification of disease sites, including intra-prostatic, intra-pelvic metastasis, and extra-pelvic metastasis, is relevant to determining subsequent therapy and prognosis. Imaging also provides clinical utility in biochemical recurrence (BCR) after initial treatment with curative intent, defined as PSA rise of >0.2 ng/mL after radical prostatectomy or rise of >2 ng/mL above nadir PSA following radiation therapy, where early detection of disease recurrence may support treatment with salvage therapy [4, 5]. Conventional imaging of abdominopelvic CT/MRI (with or without multiparametric prostate MRI) and Tc-99m methylene diphosphonate bone scan (BS) is currently the standard of practice in initial prostate cancer diagnosis, staging, and monitoring for dis-

ease progression. However, substantial advances in imaging demonstrates superior detection in intermediate and high risk disease [6-9].

Bone metastasis is the second most common site of metastasis in prostate cancer after lymph nodes and will develop in about 90% of advanced prostate cancer [10-12]. BS is the current standard imaging modality to evaluate for osseous metastatic disease in prostate cancer. However, it has suboptimal performance attributable partly to difficulty in discerning benign versus malignant bone lesions [13]. BS detected metastasis in only 5% of cases of BCR with PSA levels >7 ng/mL [5, 14, 15] with a recent meta-analysis suggesting bone scan provides only modest accuracy with a sensitivity of 71-83% and specificity of 62-87% for bone metastasis in prostate cancer [16, 17].

Recently approved prostate-specific membrane antigen (PSMA)-based PET/CT has been increasingly used in prostate cancers for initial staging and restaging of the extent of disease [6]. The latest updates to the National Comprehensive Cancer Network guidelines recognize the benefit of PSMA-based PET tracers in providing high detection of micro-metastatic disease and is now regarded as the preferred full body imaging in BCR [https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf]. PSMA is a transmembrane protein that is highly expressed in prostate cancer and weakly expressed in normal prostatic tissue [18]. The level of PSMA expression appears to correlate with Gleason grade and is overexpressed in castration resistant prostate cancer (CRPC) [19, 20]. Currently, there are only 2 FDA approved PSMA-based PET/CT tracer for patients with prostate cancer: ^{68}Ga-PSMA-11 and ^{18}F-DCFPyL (PYLARIFY). It has been postulated that the superior sensitivity of detecting lytic and intra-marrow bone metastases in prostate cancer with ^{68}Ga-PSMA-11 and PET/CT may replace BS altogether in prostate cancer staging [21]. ^{68}Ga-PSMA-11 and ^{18}F-DCFPyL share similar characteristics and excellent detection of metastatic disease and are both renally excreted. In BCR patients, ^{18}F-DCFPyL demonstrated higher SUV uptake and tumor-to-background ratio compared to ^{68}Ga-PSMA-11 [22]. Compared to ^{68}Ga-PSMA-11 and, ^{18}F-DCFPyL provides some distinct advantages including longer half-life which improves portability and de-centralizes production, and easier commercial availability. As a result, ^{18}F-DCFPyL has quickly gained significant popularity in routine clinical use for prostate cancer patients.

There is limited data regarding the detection of bone metastasis on PSMA-based ^{18}F-DCFPyL PET/CT. A 2016 case report suggested PSMA-based ^{18}F-DCFPyL PET/CT may provide improved sensitivity to early or subtle bone metastasis compared to BS or ^{18}F-NaF PET/CT [23]. Bodar et al. recently compared the diagnostic performance of ^{18}F-PSMA PET/CT with bone scan in newly diagnosed high risk prostate cancer patients with improved detection of bone metastasis, however the findings were limited by use of several ^{18}F-PSMA tracers, variable imaging protocols, and no direct statistical analysis of diagnostic accuracy [24]. Our study is a retrospective, single-institution review of men with history of prostate cancer undergoing evaluation for bone metastasis with both ^{18}F-DCFPyL PET/CT and conventional BS.

Methods

Patient selection

This retrospective study was approved by our institutional review board and included prostate cancer patients who underwent ^{18}F-DCFPyL PET/CT and BS at our institution from 8/1/2021 and 2/28/2022 within a 3-month interval. Exclusion criteria were intervening treatment (androgen deprivation therapy, radiation therapy or prostatectomy) between the PET and BS exams, interval PSA change of more than 50% between exams, absolute change in PSA level of more than 1 ng/ml, or concurrent history of other malignancy.

^{18}F-DCFPyL PET/CT protocol

The ^{18}F-DCFPyL PET/CT protocol at our institution conforms to the OSPREY trial and FDA approved PYLARIFY package insert [7]. In brief, patients were injected with approximately 333 MBq (9 mCi) of ^{18}F-DCFPyL with subsequent PET/CT imaging performed 60-90 minutes post-injection from the skull to the mid-thigh. All PET/CT were performed on either on a Siemens 64-slice Biograph mCT PET/CT scanner (Siemens Medical Systems, Erlangen, Germany), GE 64-slice Discovery 710 PET/CT scanner, or a

Table 1. Demographics and clinical characteristics (n = 91)

Age (years)	
Median	69
IQR	63-75
Total Gleason Score	n (%)
10	3 (3%)
9	37 (41%)
8	21 (23%)
7	25 (27%)
6	2 (2%)
Unknown	1 (1%)
PSA at PET (ng/ml)	
Median	5.4
IQR	1.85-16.45

IQR, interquartile range; PET, positron emission topography; PSA, prostate specific antigen.

GE discovery MI 64slice PETCT (GE Healthcare, Waukesha, Wisconsin, USA) per standard institutional protocol. In some cases, a low-dose, tube-current modulated CT was performed with intravenous contrast.

Technetium 99m MDP bone scintigraphy protocol

Per our institutional standard protocol, whole body delayed imaged with a dual head 16 slice SPECT/CT gamma camera were acquired 2-3 hours after injection of approximately 740 MBq (20 mCi) of Tc-99m methylene diphosphonate (MDP). This was achieved with either a Symbia T16 or Symbia Intevo Bold SPECT/CT scanner (Siemens Medical Systems). The whole-body images are reviewed by a board-certified nuclear medicine physician with additional SPECT/CT or spot images obtained at their discretion.

Imaging interpretation

BS and ^{18}F-DCFPyL PET/CT were independently re-reviewed by two investigators who were blinded to the original reports generated by a group of 10 board-certified nuclear medicine physicians and classified as positive, negative, or equivocal for bone metastasis. The two investigators are board-certified nuclear medicine physicians with 11 and 6 years of post-residency/fellowship experience in BS and PET/CT interpretation. The discrepancies between investigators, re-reviewed results and original reports, were discussed and reconciled with consensus. The reclassification of findings was determined with the assistance of all relevant imaging (X-ray, CT, MRI) within 30 days of the paired BS-PET/CT and minimal 6 months clinical follow up information up to the present (October 22, 2022). Patient tumor characteristics, biopsy results, PSA levels and treatment history from the electronic medical record within 30 days of the paired BS-PET/CT studies were recorded.

Statistical analysis

Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV), for ^{18}F-DCFPyL PET/CT and BS were calculated on a per lesion basis. An exact McNemar's test was performed to determine statistical significance of diagnostic accuracy between ^{18}F-DCFPyL PET/CT and BS. Analysis was performed using Microsoft® Excel® for Microsoft 365 MSO (Version 2202 Build 16.0.14931.20704) 64-bit.

Results

A total of 91 patients met inclusion for the study with demographics and clinical characteristics as described in **Table 1**. The median age of the 91 patients was 69 years (IQR 63-75 years). The median PSA at the time of the PET was 5.4 ng/ml (IQR 1.85-16.45 ng/ml).

The concordance between ^{18}F-DCFPyL PET/CT and BS was high (71/91, 78.0%) including 81.7% (58/71) concordant negative studies and 18.3% (13/71) concordant positive studies. 20/91 (22.0%) studies had discordant findings between ^{18}F-DCFPyL PET/CT and BS with results summarized in **Figure 1**. All bone metastasis identified on BS was also identified on ^{18}F-DCFPyL PET/CT.

The 58 patients with concordant negative findings demonstrated PSA levels with IQR of 1.575-13.975 ng/ml with a median of 4.85 ng/ml at time of ^{18}F-DCFPyL PET/CT. Gleason scores ranged from 7 to 10 with a median of 8. Additional soft tissue findings were identified in 34/58 patients (58.6%) which were confirmed on follow-up ^{18}F-DCFPyL PET/CT or MRI images. One patient showed soft tissue PSMA activity that was suggestive of possible treated disease. 23 patients had neither soft tissue nor

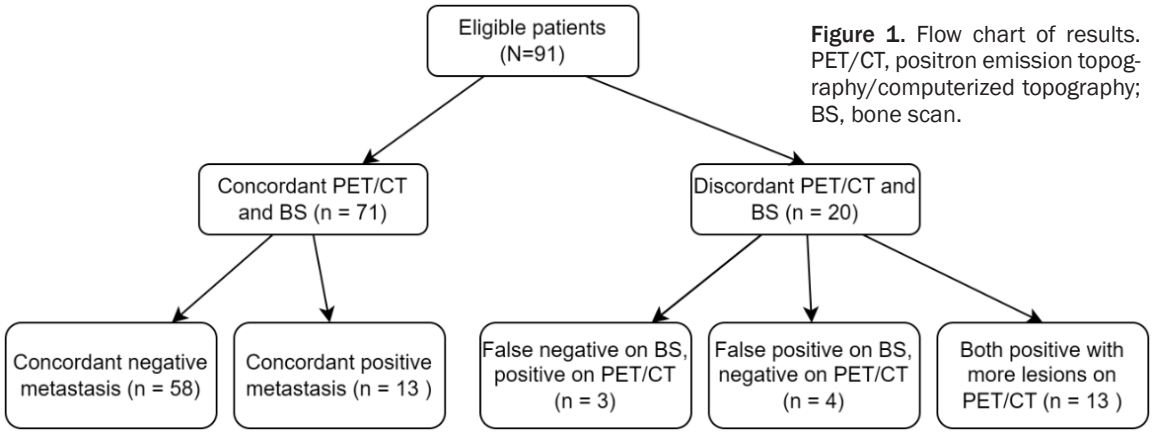

Figure 1. Flow chart of results. PET/CT, positron emission topography/computerized topography; BS, bone scan.

bone metastasis discovered on BS or ^{18}F-DCFPyL PET/CT.

The 13 patients with concordant positive findings demonstrated PSA levels with IQR of 2.7-6.575 ng/ml with a median of 4.90 at time of ^{18}F-DCFPyL PET/CT. Gleason scores ranged from 6 to 10 with a median of 9 with one patient having Gleason score unassigned due to variable treatment-related changes on pathology. Additional soft tissue findings were identified in 5/13 (38.5%) which were confirmed on follow-up ^{18}F-DCFPyL PET/CT or MRI images. 2/13 patients (15.4%) with concordant positive findings were determined to be false positives due to benign/posttraumatic changes after review of all relevant imaging and clinical information in the electronic medical record. One of the false positive paired studies demonstrated positive PSMA avid primary tumor and pelvic lymph nodes. Except for the two false positive results, these patients were all treated clinically as having bone metastasis.

20/91 patients had discordant findings as described below.

PET/CT positive, bone scan false negative

3/20 patients had osseous metastasis on ^{18}F-DCFPyL PET/CT with no lesion identified on BS. The first patient demonstrated three new PSMA-avid osseous lesions that were suspicious for new bone metastases and a new PSMA-avid supraclavicular lymph node. A follow-up biopsy two weeks later of the avid lymph node confirmed prostate metastasis. However, no biopsy was pursued for the osseous lesions which were presumed to be metastases and treated with focused site radiation. The second patient demonstrated innumerable PSMA-avid bone metastases without MDP-avid osseous lesions on BS (**Figure 2**) and had additional avid soft tissue uptake in multiple lymph nodes, pelvis, and the right lung. The bone metastases were previously identified on CT/MRI and confirmed with biopsy. The third patient demonstrated three bone metastases on ^{18}F-DCFPyL PET/CT that were previously identified on CT/MRI in addition to soft tissue uptake in the primary tumor, and pelvic lymph nodes. The bone lesions were not biopsy confirmed, but were presumptively managed as bone metastases.

PET/CT negative, bone scan-false positive

4/20 patients had positive findings on BS but were negative on ^{18}F-DCFPyL PET/CT. False positive findings were determined to represent treated metastasis or benign lesions including inflammatory/degenerative changes, posttraumatic changes, and dystrophic calcifications that were confirmed on follow up imaging (**Figure 3**). Of note, one patient demonstrated multifocal osseous lesions on BS that were not significantly PSMA-avid on ^{18}F-DCFPyL PET/CT and were subsequently determined to represent Paget's disease.

Higher bone metastasis detection on PET/CT than bone scan

13/20 patients found more osseous metastases on ^{18}F-DCFPyL PET/CT than BS. When accounting for the BS false negatives (excluding outlier case of innumerable bone metastasis on PET/CT, non-MDP avid on BS) ^{18}F-DCFPyL PET/CT detected 48 more bone metastases

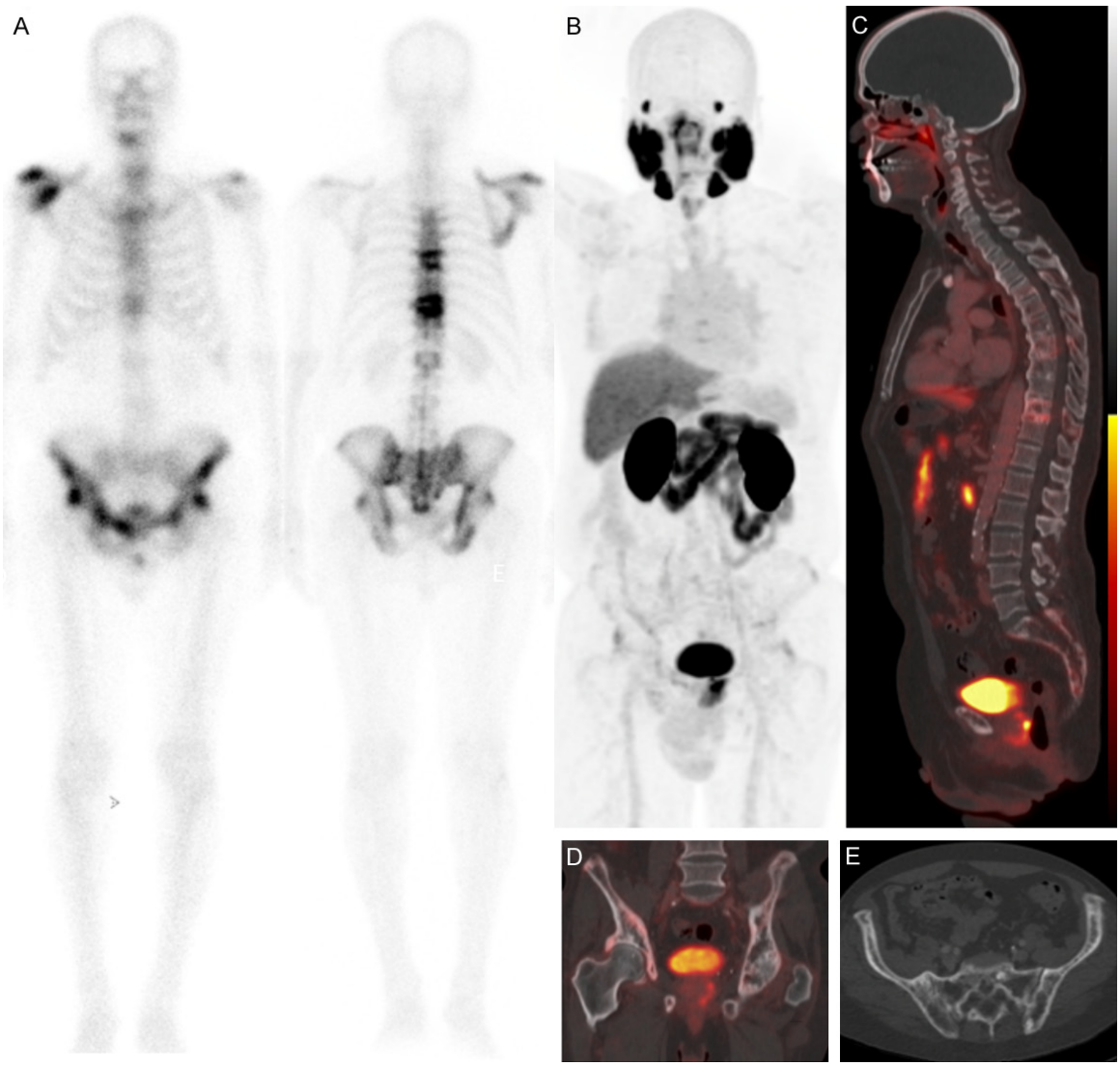

Figure 2. BS false positive, PSMA-based ^{18}F-DCFPyL PET/CT negative osseous lesions. A 75-year-old man with newly diagnosed prostate adenocarcinoma (Gleason score 9) with PSA of 4.6 ng/ml. Anterior and posterior views of BS with MDP-avid osseous lesions to right scapula, thoracic spine, and pelvis (A). ^{18}F-DCFPyL PET/CT 1 month later demonstrated PSMA-avid prostate, activity consistent with degenerative disc disease, and otherwise without suspicious osseous PSMA activity (B-D). CT component of PET/CT demonstrated mixed lucent/sclerotic lesions consistent with Paget's disease (E). BS, bone scan; PSMA, prostate-specific membrane antigen; PSA, prostate-specific antigen.

(average difference of 3.7 lesions in discordant findings, 0.6 lesions overall) than BS.

Diagnostic performance of BS and ^{18}F-DCFPyL PET/CT are described in **Table 2**. BS had a sensitivity of 89%, specificity of 91%, PPV of 80% and NPV of 95%. ^{18}F-DCFPyL PET/CT had a sensitivity of 100%, specificity of 97%, PPV of 93%, and NPV of 100%. As seen in **Table 3**, changes in sensitivity and specificity between modalities were not statistically significant by Exact McNemar's test (*P* value = 0.248 and 0.134 respectively).

Discussion

Prostate cancer bone metastasis confers a high level of morbidity and mortality with an associated median survival of 40 months and resulting in symptomatic treatment in 30% of men with metastatic CRPC [25, 26]. These treatments include systemic therapy, treatment of pathologic fractures, and palliative radiation. In addition, PSMA-based ^{18}F-DCFPyL PET/CT can be a screening modality for potential candidates for targeted radionuclide therapy such as ^{177}Lu-PSMA, which shows survival

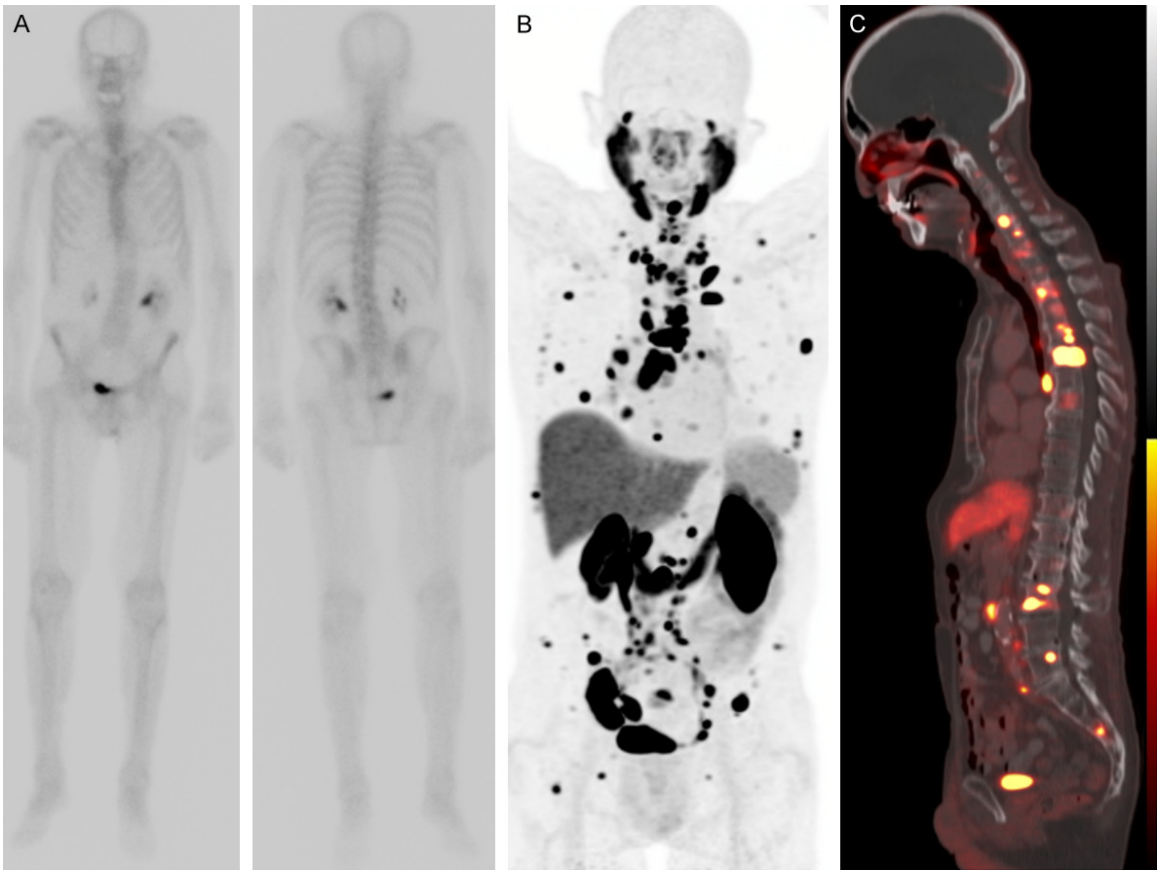

Figure 3. BS false negative, PSMA-based ^{18}F-DCFPyL PET/CT positive osseous lesions. An 80-year-old man with mCRPC (Gleason score 10) with PSA of 258.7 ng/ml status post androgen deprivation therapy. BS with no MDP-avid osseous lesions (A). ^{18}F-DCFPyL PET/CT 3 weeks earlier shows innumerable PSMA-avid skeletal metastasis, supra/infra-diaphragmatic lymph nodes, right lung metastasis and local metastasis (B, C). Biopsy of right iliac bone confirmed metastasis with CKD12 mutation. Additional lesions were presumed based on persistent activity on serial imaging and 6+ month clinical follow-up. BS, bone scan; PSMA, prostate-specific membrane antigen; PSA, prostate-specific antigen; mCRPC, metastatic castration resistant prostate cancer.

Table 2. PET/CT and bone scan diagnostic performance

	Bone metastases +		Bone metastases -	
	BS+	BS-	BS+	BS-
PET/CT+	24	3	2	0
PET/CT-	0	0	4	58

PET/CT, positron emission topography/computerized topography; BS, bone scan.

benefit for metastatic prostate cancer patients with better progression-free survival data [27]. Therefore, early recognition of osseous metastases is critical in the clinical management of mPC. The recently FDA-approved ^{18}F-DCFPyL PET/CT has a growing volume of clinical data supporting its effectiveness in detection of micro-metastatic disease, especially in prostate cancer with BCR. However, there is a paucity of clinical data available for bone metastasis. Rowe et al. noted higher detection of bone lesions with ^{18}F-DCFPyL PET/CT compared to bone scan in a case series of 8 patients with relatively low inter-modality agreement [28]. Wondergem et al. found bone metastasis in 31% of patients in their series of men with high-risk prostate cancer, of which 27/160 patients had no prior bone lesions detected on conventional imaging however diagnostic performance was not analyzed [29]. Rousseau et al. investigated ^{18}F-DCFPyL PET/CT in 130 prostate cancer patients with BCR at a single institution, demonstrating detection of bone metastasis in 20% of patients, however diagnostic performance was not analyzed [30]. In the landmark OSPREY study, ^{18}F-DCFPyL PET/CT demonstrat-

Table 3. Diagnostic performance comparison

	PET	BS
Sensitivity	100%	89%
Specificity	97%	91%
PPV	93%	80%
NPV	100%	95%

Exact McNemar's test of the paired modalities did not show statistical significance for sensitivity or specificity (*P* value = 0.248 and 0.134 respectively). PET, positron emission tomography; BS, bone scan; PPV, positive predictive value; NPV, negative predictive value.

ed sensitivity and positive predictive value of 96.8% and 81.6% respectively in detection of bone metastasis from patients with known radiological evidence of recurrence or mPC, however the study did not compute additional diagnostic performance metrics or compare its performance against conventional imaging modalities [7].

Our institution's oncological practice routinely requests ^{18}F-DCFPyL PET/CT in patients with clinical concern for progressive mPC or laboratory evidence of BCR as previously described. This resulted in several patients with paired studies eligible for this study. Our patient population is overall representative of the common prostate cancer demographics. 10 patients were excluded from the study who had hormone-sensitive prostate cancer or received intervening treatment. In our study PET/CT and BS was generally highly concordant at 78% (71/91 patients) with discordance at 22% (20/91 patients). ^{18}F-DCFPyL PET/CT sensitivity and PPV were 100% and 93% for bone metastasis respectively which is comparable to the OSPREY study with slightly higher PPV. Only 2/91 patients were determined to have false positive findings on ^{18}F-DCFPyL PET/CT which had concordant false positive results on BS. Of our discordant findings, ^{18}F-DCFPyL PET/CT identified 3/20 patients with bone metastases not identified on BS. ^{18}F-DCFPyL PET/CT identified false positive lesions on BS in 4/20 patients. ^{18}F-DCFPyL PET/CT detected more bone lesions than BS in 14/91 patients with an average difference of 3.7 more lesions in the discordant group and 0.6 more lesions overall.

False positive findings in this study were low in ^{18}F-DCFPyL PET/CT, which only demonstrated benign bone lesions and posttraumatic changes in 2/91 patients that were confirmed on follow-up imaging. False positives in BS ranged from posttraumatic changes, degenerative changes, treated metastasis, benign bone lesions, and Paget's disease. Interestingly, the patient with Paget's disease did not demonstrate any suspicious osseous PSMA activity (**Figure 3**), a previously described diagnostic pitfall potential with ^{18}F-DCFPyL PET/CT [31]. The diagnosis was identified by our image reviewers and subsequently confirmed on relevant imaging. One contributing factor to fewer false positives in ^{18}F-DCFPyL PET/CT is attributable to the hybrid cross sectional CT to better characterize bone lesions. While SPECT/CT which is often utilized concurrently with BS at our institution, Simsek et al. found the addition of SPECT/CT only modestly improves sensitivity and specificity to 59.2% and 87.6% respectively [32]. Differences in PPV compared to the OSPREY study may be insignificant given differences in sample size and patient clinical characteristics but may be attributable to fewer false positives from our image reviewers due to increased experience in interpreting PSMA-based ^{18}F-DCFPyL PET/CT.

Thirteen patients had more bone metastases identified on ^{18}F-DCFPyL PET/CT than BS, consistent with higher sensitivity noted in the OSPREY study. No bone metastasis was identified on BS that was not also identified on ^{18}F-DCFPyL PET/CT in our study. However, 3 patients had bone lesions on ^{18}F-DCFPyL PET/CT that were not identified on BS. Of these patients, two had bone metastases identified on PET/CT ranging from 3-4 lesions. The third patient had innumerable bone metastasis on PET/CT not seen on BS (**Figure 3**). This patient's clinical history indicated that they had a *CKD12* mutation resulting in aggressive, treatment resistant mPC with PSA level of 187.0 at time of ^{18}F-DCFPyL PET/CT. Higher detection of PET/CT in these cases is likely attributable to both the improved lesion characterization with the cross-sectional component as well as the advantageous detection of PSMA avidity from malignant prostate tissue.

Ultimately our study failed to demonstrate statistically significant differences in the diagnostic performance of ^{18}F-DCFPyL PET/CT over BS for bone metastasis. Possible contributions include lower sample size, patient clinical char-

acteristics, and reader expertise with lower detection of false positives on BS. However, our study suggests that ^{18}F-DCFPyL PET/CT increases detection of bone metastasis compared to BS and could sufficiently replace BS for bone metastases evaluation. While not the purpose of this study, soft tissue lesions (either primary tumor or nodal metastasis) on ^{18}F-DCFPyL PET/CT were identified in 48/91 patients, including 36 patients for which there were no bone metastasis identified on ^{18}F-DCFPyL PET/CT. This suggests ^{18}F-DCFPyL PET/CT as a complete whole body imaging modality for mPC evaluation. The higher diagnostic performance of ^{18}F-DCFPyL PET/CT by an experienced nuclear medicine-trained physician may reduce time and complexity of interpretation (i.e., fewer studies/imaging modalities compared, fewer interobserver variability as a single reader) for assessment of disease burden and improve early detection and treatment of osseous metastatic disease. Additional considerations for universal adoption should include cost analysis/insurance coverage of ^{18}F-DCFPyL PET/CT over BS however is outside the scope of this study.

Despite being well presented and written, this study has some limitations including its retrospective review, single-institution design and losing histopathologic confirmation. Additionally, our cohort is limited to patients who had ^{18}F-DCFPyL PET/CT ordered by their cancer treatment team (oncologists or urologists) which resulted in a population of intermediate-to-high risk patients or patients with BCR. Further prospective studies including low risk patients may offer more evidence on the overall performance of ^{18}F-DCFPyL PET/CT versus BS. There is selection bias of the radiotracer itself as ^{18}F-DCFPyL is relatively new and not collectively utilized or familiar by all clinicians. Another selection bias pertains to the ordering clinicians as bone metastasis may have already been suspected or undiagnosed when ordered. And finally, a possible limitation could be nuclear medicine reader experience during the study which may impact performance of ^{18}F-DCFPyL PET/CT relative to peers.

Conclusion

Our review is the largest paired study comparing the diagnostic performance of ^{18}F-DCFPyL PET/CT to BS for prostate cancer bone metastasis. Our study demonstrated a high concordance between the imaging modalities with ^{18}F-DCFPyL PET/CT displaying improved detection of false positive and false negative results compared to BS. Additionally, all bone metastases identified on BS were seen on ^{18}F-DCFPyL PET/CT. Recent updates from the NCCN recommending the use of ^{18}F-DCFPyL PET/CT herald its growing clinical value. Though further studies and experience are warranted for widespread adoption, with the added benefit of identifying soft tissue lesions ^{18}F-DCFPyL PET/CT may replace BS as a comprehensive whole body imaging modality for prostate cancer metastatic evaluation.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Yang Lu, Department of Nuclear Medicine, Division of Diagnostic Imaging, The University of Texas MD Anderson Cancer Center, 1400 Pressler St. Unit 1483, Houston, TX 77030, USA. E-mail: ylu10@mdanderson.org

References

[1] Global Burden of Disease Cancer Collaboration; Fitzmaurice C, Allen C, Barber RM, Barregard L, Bhutta ZA, Brenner H, Dicker DJ, Chimed-Orchir O, Dandona R, Dandona L, Fleming T, Forouzanfar MH, Hancock J, Hay RJ, Hunter-Merrill R, Huynh C, Hosgood HD, Johnson CO, Jonas JB, Khubchandani J, Kumar GA, Kutz M, Lan Q, Larson HJ, Liang X, Lim SS, Lopez AD, MacIntyre MF, Marczak L, Marquez N, Mokdad AH, Pinho C, Pourmalek F, Salomon JA, Sanabria JR, Sandar L, Sartorius B, Schwartz SM, Shackelford KA, Shibuya K, Stanaway J, Steiner C, Sun J, Takahashi K, Vollset SE, Vos T, Wagner JA, Wang H, Westerman R, Zeeb H, Zoeckler L, Abd-Allah F, Ahmed MB, Alabed S, Alam NK, Aldhahri SF, Alem G, Alemayohu MA, Ali R, Al-Raddadi R, Amare A, Amoako Y, Artaman A, Asayesh H, Atnafu N, Awasthi A, Saleem HB, Barac A, Bedi N, Bensenor I, Berhane A, Bernabe E, Betsu B, Binagwaho A, Boneya D, Campos-Nonato I, Castaneda-Orjuela C, Catala-Lopez F, Chiang P, Chibueze C, Chitheer A, Choi JY, Cowie B, Damtew S, das Neves J, Dey S, Dharmaratne S, Dhillon P, Ding E, Driscoll T, Ekwueme D, Endries AY, Farvid M, Farzadfar F, Fernandes J, Fischer F, G/Hiwot TT, Gebru A, Gopalani S, Hailu A, Horino M, Horita N, Husseini A, Huybrechts I, Inoue M, Islami F, Jakovljevic M, James S, Javanbakht

M, Jee SH, Kasaeian A, Kedir MS, Khader YS, Khang YH, Kim D, Leigh J, Linn S, Lunevicius R, El Razek HMA, Malekzadeh R, Malta DC, Marcenes W, Markos D, Melaku YA, Meles KG, Mendoza W, Mengiste DT, Meretoja TJ, Miller TR, Mohammad KA, Mohammadi A, Mohammed S, Moradi-Lakeh M, Nagel G, Nand D, Le Nguyen Q, Nolte S, Ogbo FA, Oladimeji KE, Oren E, Pa M, Park EK, Pereira DM, Plass D, Qorbani M, Radfar A, Rafay A, Rahman M, Rana SM, Soreide K, Satpathy M, Sawhney M, Sepanlou SG, Shaikh MA, She J, Shiue I, Shore HR, Shrime MG, So S, Soneji S, Stathopoulou V, Stroumpoulis K, Sufiyan MB, Sykes BL, Tabares-Seisdedos R, Tadese F, Tedla BA, Tessema GA, Thakur JS, Tran BX, Ukwaja KN, Uzochukwu BSC, Vlassov VV, Weiderpass E, Wubshet Terefe M, Yebyo HG, Yimam HH, Yonemoto N, Younis MZ, Yu C, Zaidi Z, Zaki MES, Zenebe ZM, Murray CJL and Naghavi M. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 32 cancer groups, 1990 to 2015: a systematic analysis for the global burden of disease study. JAMA Oncol 2017; 3: 524-548.

[2] Siegel RL, Miller KD, Fuchs HE and Jemal A. Cancer statistics, 2022. CA Cancer J Clin 2022; 72: 7-33.

[3] Lindenberg L, Choyke P and Dahut W. Prostate cancer imaging with novel PET tracers. Curr Urol Rep 2016; 17: 18.

[4] Roach M 3rd, Hanks G, Thames H Jr, Schellhammer P, Shipley WU, Sokol GH and Sandler H. Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: recommendations of the RTOG-ASTRO phoenix consensus conference. Int J Radiat Oncol Biol Phys 2006; 65: 965-974.

[5] Beresford MJ, Gillatt D, Benson RJ and Ajithkumar T. A systematic review of the role of imaging before salvage radiotherapy for post-prostatectomy biochemical recurrence. Clin Oncol (R Coll Radiol) 2010; 22: 46-55.

[6] Hofman MS, Lawrentschuk N, Francis RJ, Tang C, Vela I, Thomas P, Rutherford N, Martin JM, Frydenberg M, Shakher R, Wong LM, Taubman K, Ting Lee S, Hsiao E, Roach P, Nottage M, Kirkwood I, Hayne D, Link E, Marusic P, Matera A, Herschtal A, Iravani A, Hicks RJ, Williams S and Murphy DG; proPSMA Study Group Collaborators. 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. Lancet 2020; 395: 1208-1216.

[7] Pienta KJ, Gorin MA, Rowe SP, Carroll PR, Pouliot F, Probst S, Saperstein L, Preston MA, Alva AS, Patnaik A, Durack JC, Stambler N, Lin T, Jensen J, Wong V, Siegel BA and Morris MJ. A phase 2/3 prospective multicenter study of the diagnostic accuracy of prostate specific membrane antigen PET/CT with ^{18}F-DCFPyL in prostate cancer patients (OSPREY). J Urol 2021; 206: 52-61.

[8] Beheshti M, Imamovic L, Broinger G, Vali R, Waldenberger P, Stoiber F, Nader M, Gruy B, Janetschek G and Langsteger W. 18F choline PET/CT in the preoperative staging of prostate cancer in patients with intermediate or high risk of extracapsular disease: a prospective study of 130 patients. Radiology 2010; 254: 925-933.

[9] von Below C, Daouacher G, Wassberg C, Grzegorek R, Gestblom C, Sorensen J, Ahlstrom H and Walden M. Validation of 3 T MRI including diffusion-weighted imaging for nodal staging of newly diagnosed intermediate- and high-risk prostate cancer. Clin Radiol 2016; 71: 328-334.

[10] Azad GK, Taylor B, Rubello D, Colletti PM, Goh V and Cook GJ. Molecular and functional imaging of bone metastases in breast and prostate cancers: an overview. Clin Nucl Med 2016; 41: e44-50.

[11] Beheshti M, Langsteger W and Fogelman I. Prostate cancer: role of SPECT and PET in imaging bone metastases. Semin Nucl Med 2009; 39: 396-407.

[12] Bubendorf L, Schopfer A, Wagner U, Sauter G, Moch H, Willi N, Gasser TC and Mihatsch MJ. Metastatic patterns of prostate cancer: an autopsy study of 1,589 patients. Hum Pathol 2000; 31: 578-583.

[13] Nozaki T, Yasuda K, Akashi T and Fuse H. Usefulness of single photon emission computed tomography imaging in the detection of lumbar vertebral metastases from prostate cancer. Int J Urol 2008; 15: 516-519.

[14] Gomez P, Manoharan M, Kim SS and Soloway MS. Radionuclide bone scintigraphy in patients with biochemical recurrence after radical prostatectomy: when is it indicated? BJU Int 2004; 94: 299-302.

[15] Dotan ZA, Bianco FJ Jr, Rabbani F, Eastham JA, Fearn P, Scher HI, Kelly KW, Chen HN, Schoder H, Hricak H, Scardino PT and Kattan MW. Pattern of prostate-specific antigen (PSA) failure dictates the probability of a positive bone scan in patients with an increasing PSA after radical prostatectomy. J Clin Oncol 2005; 23: 1962-1968.

[16] Zhou J, Gou Z, Wu R, Yuan Y, Yu G and Zhao Y. Comparison of PSMA-PET/CT, choline-PET/CT, NaF-PET/CT, MRI, and bone scintigraphy in the

diagnosis of bone metastases in patients with prostate cancer: a systematic review and meta-analysis. Skeletal Radiol 2019; 48: 1915-1924.

[17] Sheikhbahaei S, Jones KM, Werner RA, Salas-Fragomeni RA, Marcus CV, Higuchi T, Rowe SP, Solnes LB and Javadi MS. ^{18}F-NaF-PET/CT for the detection of bone metastasis in prostate cancer: a meta-analysis of diagnostic accuracy studies. Ann Nucl Med 2019; 33: 351-361.

[18] Wright GL Jr, Haley C, Beckett ML and Schellhammer PF. Expression of prostate-specific membrane antigen in normal, benign, and malignant prostate tissues. Urol Oncol 1995; 1: 18-28.

[19] Bostwick DG, Pacelli A, Blute M, Roche P and Murphy GP. Prostate specific membrane antigen expression in prostatic intraepithelial neoplasia and adenocarcinoma: a study of 184 cases. Cancer 1998; 82: 2256-2261.

[20] Denmeade SR, Sokoll LJ, Dalrymple S, Rosen DM, Gady AM, Bruzek D, Ricklis RM and Isaacs JT. Dissociation between androgen responsiveness for malignant growth vs. expression of prostate specific differentiation markers PSA, hK2, and PSMA in human prostate cancer models. Prostate 2003; 54: 249-257.

[21] Lengana T, Lawal IO, Boshomane TG, Popoola GO, Mokoala KMG, Moshokoa E, Maes A, Mokgoro NP, Van de Wiele C, Vorster M and Sathekge MM. ^{68}Ga-PSMA PET/CT replacing bone scan in the initial staging of skeletal metastasis in prostate cancer: a fait accompli? Clin Genitourin Cancer 2018; 16: 392-401.

[22] Dietlein M, Kobe C, Kuhnert G, Stockter S, Fischer T, Schomacker K, Schmidt M, Dietlein F, Zlatopolskiy BD, Krapf P, Richarz R, Neubauer S, Drzezga A and Neumaier B. Comparison of [(18)F]DCFPyL and [(68)Ga]Ga-PSMA-HBED-CC for PSMA-PET imaging in patients with relapsed prostate cancer. Mol Imaging Biol 2015; 17: 575-584.

[23] Rowe SP, Mana-Ay M, Javadi MS, Szabo Z, Leal JP, Pomper MG, Pienta KJ, Ross AE and Gorin MA. PSMA-based detection of prostate cancer bone lesions with (1)(8)F-DCFPyL PET/CT: a sensitive alternative to (^{99}m)Tc-MDP bone scan and Na^{18}F PET/CT? Clin Genitourin Cancer 2016; 14: e115-118.

[24] Bodar YJL, Luining WI, Keizer B, Meijer D, Vellekoop A, Schaaf M, Hendrikse NH, Van Moorselaar RJA, Oprea-Lager DE and Vis AN. A prospective, multicenter head-to-head comparative study in patients with primary high-risk prostate cancer investigating the bone lesion detection of conventional imaging and ^{18}F-PSMA-PET/CT. Urol Oncol 2022; [Epub ahead of print].

[25] Sturge J, Caley MP and Waxman J. Bone metastasis in prostate cancer: emerging therapeutic strategies. Nat Rev Clin Oncol 2011; 8: 357-368.

[26] Smith MR, Brown GA and Saad F. New opportunities in the management of prostate cancer-related bone complications. Urologic Oncology: Seminars and Original Investigations 2009; 27: S1-S20.

[27] Sartor O, de Bono J, Chi KN, Fizazi K, Herrmann K, Rahbar K, Tagawa ST, Nordquist LT, Vaishampayan N, El-Haddad G, Park CH, Beer TM, Armour A, Perez-Contreras WJ, DeSilvio M, Kpamegan E, Gericke G, Messmann RA, Morris MJ and Krause BJ; VISION Investigators. Lutetium-177-PSMA-617 for metastatic castration-resistant prostate cancer. N Engl J Med 2021; 385: 1091-1103.

[28] Rowe SP, Macura KJ, Mena E, Blackford AL, Nadal R, Antonarakis ES, Eisenberger M, Carducci M, Fan H, Dannals RF, Chen Y, Mease RC, Szabo Z, Pomper MG and Cho SY. PSMA-based [(18)F]DCFPyL PET/CT is superior to conventional imaging for lesion detection in patients with metastatic prostate cancer. Mol Imaging Biol 2016; 18: 411-419.

[29] Wondergem M, van der Zant FM, Broos WAM and Knol RJJ. Matched-pair comparison of (18)F-DCFPyL PET/CT and (18)F-PSMA-1007 PET/CT in 240 prostate cancer patients: inter-reader agreement and lesion detection rate of suspected lesions. J Nucl Med 2021; 62: 1422-1429.

[30] Rousseau E, Wilson D, Lacroix-Poisson F, Krauze A, Chi K, Gleave M, McKenzie M, Tyldesley S, Goldenberg SL and Benard F. A prospective study on (18)F-DCFPyL PSMA PET/CT imaging in biochemical recurrence of prostate cancer. J Nucl Med 2019; 60: 1587-1593.

[31] Rowe SP, Deville C, Paller C, Cho SY, Fishman EK, Pomper MG, Ross AE and Gorin MA. Uptake of (18)F-DCFPyL in Paget's disease of bone, an important potential pitfall in clinical interpretation of PSMA PET studies. Tomography 2015; 1: 81-84.

[32] Simsek DH, Sanli Y, Civan C, Engin MN, Isik EG, Ozkan ZG and Kuyumcu S. Does bone scintigraphy still have a role in the era of 68 Ga-PSMA PET/CT in prostate cancer? Ann Nucl Med 2020; 34: 476-485.