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^{18}F-FDG PET/CT for Diagnosis of Osteosclerotic and Osteolytic Vertebral Metastatic Lesions: Comparison with Bone Scintigraphy

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Study Design: A retrospective study.

Purpose: The aims of this study were to investigate the diagnostic value of ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) in PET/computed tomography (CT) in the evaluation of spinal metastatic lesions.

Overview of Literature: Recent studies described limitations regarding how many lesions with abnormal ^{18}F-FDG PET findings in the bone show corresponding morphologic abnormalities.

Methods: The subjects for this retrospective study were 227 patients with primary malignant tumors, who were suspected of having spinal metastases. They underwent combined whole-body ^{18}F-FDG PET/CT scanning for evaluation of known neoplasms in the whole spine. ^{99m}Tc-methylene diphosphonate bone scan was performed within 2 weeks following PET/CT examinations. The final diagnosis of spinal metastasis was established by histopathological examination regarding bone biopsy or magnetic resonance imaging (MRI) findings, and follow-up MRI, CT and ^{18}F-FDG PET for extensively wide lesions with subsequent progression.

Results: From a total of 504 spinal lesions in 227 patients, 224 lesions showed discordant image findings. For 122 metastatic lesions with confirmed diagnosis, the sensitivity/specificity of bone scan and FDG PET were 84%/21% and 89%/76%, respectively. In 102 true-positive metastatic lesions, the bone scan depicted predominantly osteosclerotic changes in 36% and osteolytic changes in 19%. In 109 true-positive lesions of FDG PET, osteolytic changes were depicted predominantly in 38% while osteosclerotic changes were portrayed in 15%.

Conclusions: ^{18}F-FDG PET in PET/CT could be used as a substitute for bone scan in the evaluation of spinal metastasis, especially for patients with spinal osteolytic lesions on CT.

Keywords: ^{18}F-fluorodeoxyglucose positron emission tomography; Technetium Tc 99m (Sn)methylenediphosphonate; Positron emission tomography and computed tomography; Spine; Metastasis

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Introduction

Very few factors can change the strategy for cancer treatment, including spine surgery, in such a radical way as the presence or absence of bone metastases assessed during the initial stage or during follow up. The vertebral column is the region of the skeleton most frequently affected by metastasis. The tumors that most commonly metastasize to the vertebrae are carcinomas of the breast in women and carcinomas of the lung and prostate in men; however, metastases are also frequently seen in patients with lymphoma and multiple myeloma [1,2]. It is well known that vertebral metastases represent hematogenous dissemination of the primary tumor, direct extension through the intervertebral foramina or invasion of the epidural space from adjacent vertebral segments. Metastatic lesions often cause compression of the adjacent neural structures such as the spinal cord, cauda equine and/or nerve roots and in the latter, they are often associated with radiculopathy [1]. In order to increase the chances of a favorable outcome, the most important issue remains avoiding the development of any permanent neurological or functional deficit through early diagnosis and treatment [3]. While in a selected group of patients a combined approach; including chemotherapy and surgery; may be plausible for the treatment of metastatic spinal tumors, radiation remains the primary choice [4].

The most commonly used imaging procedure for the assessment of bone metastases is ^{99m}Tc-methylene diphosphonate (MDP) bone scintigraphy, though it cannot detect accompanying soft-tissue abnormalities and lacks specificity, given the multiplicity of abnormal, but benign processes, that could affect bones, leading to false negative and positive results [5]. On the other hand, ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) is more sensitive than bone scintigraphy in patients with lung cancer and lymphoma, and can detect early bone marrow involvement including spinal metastasis before the appearance of cortical changes on bone scintigraphy [6,7]. With the increased use of whole-body ^{18}F-FDG PET for the staging and follow-up of malignant diseases, it is not uncommon to encounter vertebral metastases. Recent studies described limitations regarding how many lesions with abnormal ^{18}F-FDG PET findings in bone show corresponding morphologic abnormalities, even if they are not suspected of representing definite bone metastasis [8]. Other studies have reported false-positive ^{18}F-FDG PET results in patients suspected of bone metastases [9]. Due to these limitations, several clinical applications have become available for use with the recently released generation of combined PET/computed tomography (CT) scanners [10-12]; which can provide detailed anatomic information and abnormal findings beyond the capabilities of the PET scanner alone [13]. At present, detection of bone metastases on the PET is usually followed by the CT for assessment of the morphologic features regarding the lesions [14].

The present study was designed to retrospectively investigate the diagnostic values of ^{18}F-FDG PET in the evaluation of spinal metastases and to compare ^{18}F-FDG PET in PET/CT with the conventional ^{99m}Tc-MDP bone scan, and to assess the added value of CT in PET/CT studies in lesion detection and localization of vertebral lesions, and to correlate between the morphological changes detected on CT and the positive findings of ^{18}F-FDG PET findings or bone scan in spinal metastatic lesions.

Materials and Methods

1. Study cohort

The subjects of this retrospective study were 227 patients (121 men, 106 women; age range, 35–82 years; mean, 59.9) with primary malignant tumors in the lung (n=91), breast (n=43), gastrointestinal tract (n=33) (esophageal, gastric and colonic cancers), kidney (n=21), prostate (n=15), uterus or ovaries (n=10), lymph nodes (n=8, malignant lymphoma), head and neck (n=3), and bone and soft tissues (n=3), who were suspected of having spinal metastases. They underwent combined whole-body PET/CT scanning for evaluation of known neoplasms in the whole spine between January 2005 and December 2008. ^{99m}Tc-MDP bone scan was performed within 2 weeks after PET/CT examinations. The final diagnosis of spinal metastasis was established by a histopathological examination of the bone biopsy or MRI findings, and a follow-up MRI, CT, and ^{18}F-FDG PET of extensively wide lesions with subsequent progression.

2. ^{99m}Tc-MDP bone scans

Routine bone scans were obtained with a large field-of-view, dual-head gamma camera (E-CAM, Siemens Medical System, Hoffman Estates, IL, USA) with a low-energy

Table 1. Differences between morphological changes on CT with true-positive lesions on each bone scan or FDG PET

	Bone scan (n=102)	FDG PET (n=109)	*p*-value	SUV	
				Mean	Range
None	32 (31.4)	35 (32.1)	NS	-	-
Non-specific	14 (13.7)	17 (15.6)	NS	-	-
Osteolytic changes	19 (18.6)	41 (37.6)	<0.05	8.67	5.6–15.7
Osteosclerotic changes	37 (36.3)	16 (14.7)	<0.05	1.27	0.1–2.6

Values are presented as bone scan and FDG PET represent number of lesions.
Data in parentheses are percentages.
$p<0.05$; for "Bone scan" and "FDG PET" (by Mann-Whitney U-test).
CT, computed tomography; FDG, fluorodeoxyglucose; PET, positron emission tomography; SUV, standardized uptake value; NS, not significant.

high-resolution collimator. Anterior and posterior whole-body images were acquired 3 hours after an intravenous injection of approximately 740 MBq of ^{99m}Tc-MDP.

3. PET/CT scanning

^{18}F-FDG PET/CT was performed using a combined PET/CT scanner (Discovery LS, General Electric Medical Systems, Waukesha, WI, USA). For the PET/CT scanners, 35 transaxial images were acquired simultaneously per field of view with an interslice spacing of 4.25 mm. The PET/CT scanner incorporates an integrated 4-slice multidetector CT scanner, which was used for attenuation correction. The CT scanning parameters were as follows: Auto mA (upper limit, 40 mA; noise index, 20), 140 kV, 5-mm section thickness, 15-mm table feed, and pitch of 4. After at least 4 hours of fasting, the patient received an intravenous injection of 185 MBq of ^{18}F-FDG and image acquisition began 50 minutes after injection. A whole-body emission scan was performed from the head to the inguinal region with 2 minutes per bed position (7–8 bed positions). A transmission scan with CT was performed prior to the emission scan. CT images for attenuation correction were applied to the emission data and the attenuation-corrected emission images were reconstructed with an ordered-subset expectation maximization iterative reconstruction algorithm (2 iterations, 14 subsets).

4. Image analysis

Two experienced physicians (H.N., T.H.) identified the spinal lesions on bone scans as sites of increased MDP uptake relative to the surrounding normal bone activity. Whole-body FDG PET skeletal images were independently and visually analyzed by two experienced physicians (T.M., T.T.) on a high-resolution display to compare them with the corresponding ^{99m}Tc-MDP whole-body bone scan findings. A spinal lesion on ^{18}F-FDG PET was defined as a focus of increased ^{18}F-FDG uptake, above the intensity of the surrounding normal bone activity, excluding the physiologically increased ^{18}F-FDG uptake areas of renal pelvis, urinary bladder, bowel, myocardium, and brain. In order to examine the differences between morphological changes on the CT with the true-positive lesions at each bone scan or FDG PET, a region of interest (ROI; size, 20×20 mm) was placed by one author (T.M.) over all suspected lesions, and the maximal single pixel value was determined for each lesion on the whole spine. The standardized uptake value (SUV) was calculated using the following formula: $SUV=ROI_{RC}/(ID/BW)$; where ROI_{RC} is the radioactivity concentration within the region of interest (in becquerels per milliliter), ID is the injected dose of ^{18}F-FDG (in becquerels), and BW is body weight in grams.

The CT images were evaluated by two physicians (D.S., S.W.) using CT planes that corresponded to the planes in which the lesion appeared on the FDG PET. The physicians were aware of the positive spinal lesions on the PET, and they used a workstation to display the CT scans with the bone and soft-tissue windows. The CT analysis determined the presence or absence of spinal metastasis and the type of morphologic changes (nonspecific, osteolytic, osteosclerotic). Nonspecific changes represented abnormal CT findings that were neither neoplastic nor degenerative changes [14]. Lesions exhibiting both osteolytic and osteosclerotic changes were considered to be either

type based on the predominant change in that lesion.

5. Statistical analysis

The Mann-Whitney U-test was used to compare differences between the percentages of patients being evaluated through "Bone scan" and "FDG PET" (Table 1). A probability value less than 0.05 denoted statistical significance. All statistical analyses were conducted using SPSS software (ver. 15.0, SPSS, Chicago, IL, USA).

Results

A total of 504 spinal lesions in 227 patients found on either bone scans or FDG PETs were evaluated. Positive FDG PET as well as positive bone scan findings were identified in 280 spinal lesions. In the remaining 224 lesions with discordant findings, 68 had positive bone scan images, but negative FDG PETs, while 156 had negative bone scans but positive FDG PETs (Table 2). In 156 spinal lesions (cervical 25, thoracic 90, and lumbar 41), including 22 examined histopathologically, the final diagnosis

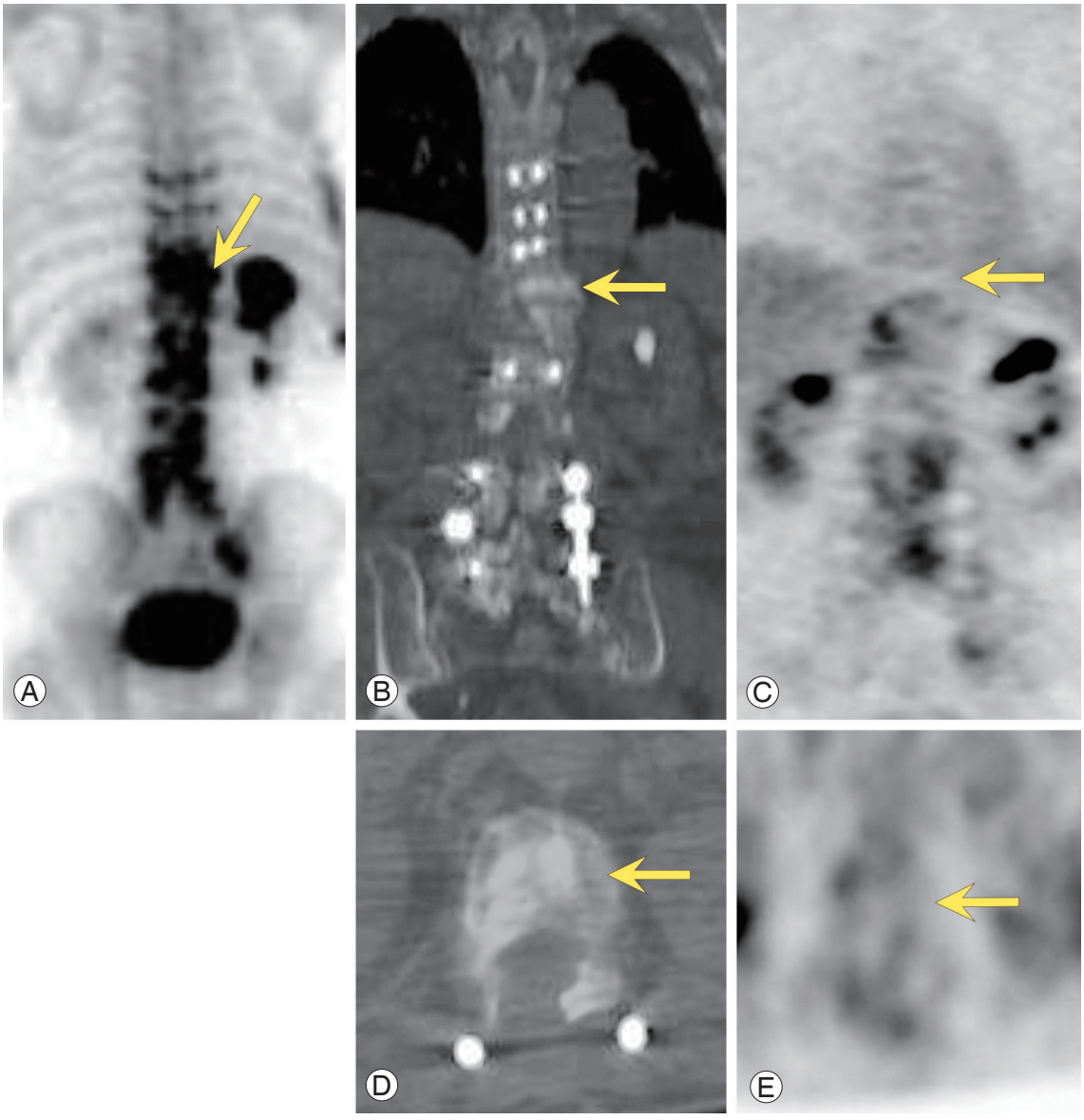

Fig. 1. Bone scan **(A)**, CT, **(B, D)** and FDG PET **(C, E)** images of a 77-year-old man with prostate carcinoma. Note the focal intense uptake of osteoblastic spine metastases (vertebral body of T11) on the bone scan only but not on the PET images (arrows). Axial and coronal CT images show ostesclerotic changes in the vertebral body **(B, D)** and no focal intense uptake on the PET images **(C, E)**. CT, computed tomography; FDG, fluorodeoxyglucose; PET, positron emission tomography.

was 122 spinal metastatic lesions and 34 benign lesions. Of the 122 metastatic lesions, positive bone scan findings were recorded in 102 lesions and negative findings were recorded in 20 lesions. Positive FDG PET findings were recorded in 109 lesions and negative findings were recorded in 13 lesions. The sensitivity with regards to bone scans and FDG PETs were 84% and 89%, respectively. In contrast, for the 34 benign lesions, the positive and negative bone scan findings were recorded in 27 and 7 lesions, respectively, whereas positive and negative FDG PET findings were recorded in 8 and 26 lesions, respectively (the specificity for bone scans and FDG PETs were 21% and 76%, respectively) (Table 3).

The morphological changes were determined for true-positive lesions on each bone scan (102 lesions) and FDG PET (109 lesions) (Table 1). No changes on CT were seen for bone scans in 32 lesions (31%), and on FDG PETs in 35 lesions (32%). Bone scans depicted predominantly sclerotic changes in 37 lesions (36%) and mainly osteolytic changes in 19 lesions (19%) (Fig. 1). On the other hand, FDG PETs depicted predominantly osteolytic changes in 41 lesions (38%) and mainly osteosclerotic changes in 16 lesions (15%) (Fig. 2).

Table 2. Distribution of bone scan and FDG PET findings in spinal lesions examined in present study

Bone scan	FDG PET	
	Positive	Negative
Positive	280	68
Negative	156	Undefined

Values are presented as number of lesions.
FDG, fluorodeoxyglucose; PET, positron emission tomography.

Table 3. Distribution of bone scan/FDG PET findings based on final diagnosis in all spinal lesions

	Bone metastatic (Bone scan/FDG PET)	Benign (Bone scan/FDG PET)
Positive	102/109	27/8
Negative	20/13	7/26

Values are presented as number of lesions.
FDG, fluorodeoxyglucose; PET, positron emission tomography.

Discussion

In the assessment of spine tumors, while evaluating the epidural extension or marrow involvement, the MRI remains as the gold standard [15-18]. However, when evaluating large numbers of screenings in suspected bone metastases cases, bone scintigraphy is the most common modality used due to its high sensitivity, availability, cost, and ease of surveying the entire skeleton. However, many patients with bone metastases do not show typical or specific patterns on these scans [5,19]. Several factors can influence the tracer uptake, such as degenerative joint disease and related benign bone diseases or osteocartilaginous abnormalities, such as previous skeletal trauma; all of which will finally limit the specificity of the bone scan. Since the conventional bone scan is sensitive enough to detect accelerated osteoblastic activities, which are nonspecific indicators of pathology; the image provided by a different modality such as tissue glucose utilization mapped with ^{18}F-FDG, would be expected to provide a different view of bone pathology. Tumor cells release a myriad of biologically active substances that could actively interfere with glycolysis, following tumor invasion. Therefore, not only the measurement of mineral turnover, as conventionally achieved in bone scans, but also the assessment of glucose metabolic processes, could be of great significance for differentiating benign from malignant bone lesions [20]. The present study was undertaken in order to evaluate the usefulness of ^{18}F-FDG PET in measuring glycolytic activity in bone marrow metastatic lesions in patients with suspected malignant spinal metastases, and to compare bone scans and FDG PETs in the detection of spinal metastases. Our results indicate that ^{18}F-FDG PET is potentially useful for the detection of vertebral metastatic lesions based on the analysis of 122 spinal lesions.

Several studies compared bone scans to FDG PETs in the detection of different types of cancers [21,22]. FDG PETs were superior to bone scans in the detection of breast cancer in patients with known skeletal metastases; with the exception of a subgroup of patients with osteoblastic metastases [23], though the bone scan had been reported to be superior than PET in detecting osteoblastic metastatic lesions [22]. Such data emphasize the complementary nature of bone scans and FDG PETs in the evaluation of skeletal metastases in breast cancer patients, as reported previously [24]; as well as in the staging of bone metastasis in breast cancer, where each modality cannot substitute the other. It has been reported already that the FDG PET is less sensitive than the bone scan in

prostate cancers [25]; where the FDG with a sensitivity of 65%, only identified 131 of 202 untreated metastases in a group of 22 patients [26]. Morris et al. [27] found that the bone scan was significantly more sensitive (94%) than the FDG (77%) in a series of 134 bone metastases. While the FDG appears to be quite useful in the detection of bone metastases from lung cancer, it is not so effective in prostate cancers due to the osteoblastic characteristics of the lesions [25]. A higher accuracy of PET in the detection of bone metastases, relative to the bone scan, was also reported [7]. Thus, it is clear that PETs and bone scans provide different diagnoses according to the type of the primary cancer, being an important limitation to our study, and implies the need for larger studies to examine each primary cancer.

In our research, among the lesions finally diagnosed as metastases using all the available resources; the CT characterized only 31% to 32% as probable or definite metastases whereas the remaining 68% to 69% of the lesions was undiagnosed. Furthermore, while morphologic changes were often identified using bone windows to display the CT images, only 50% of the lesions depicted

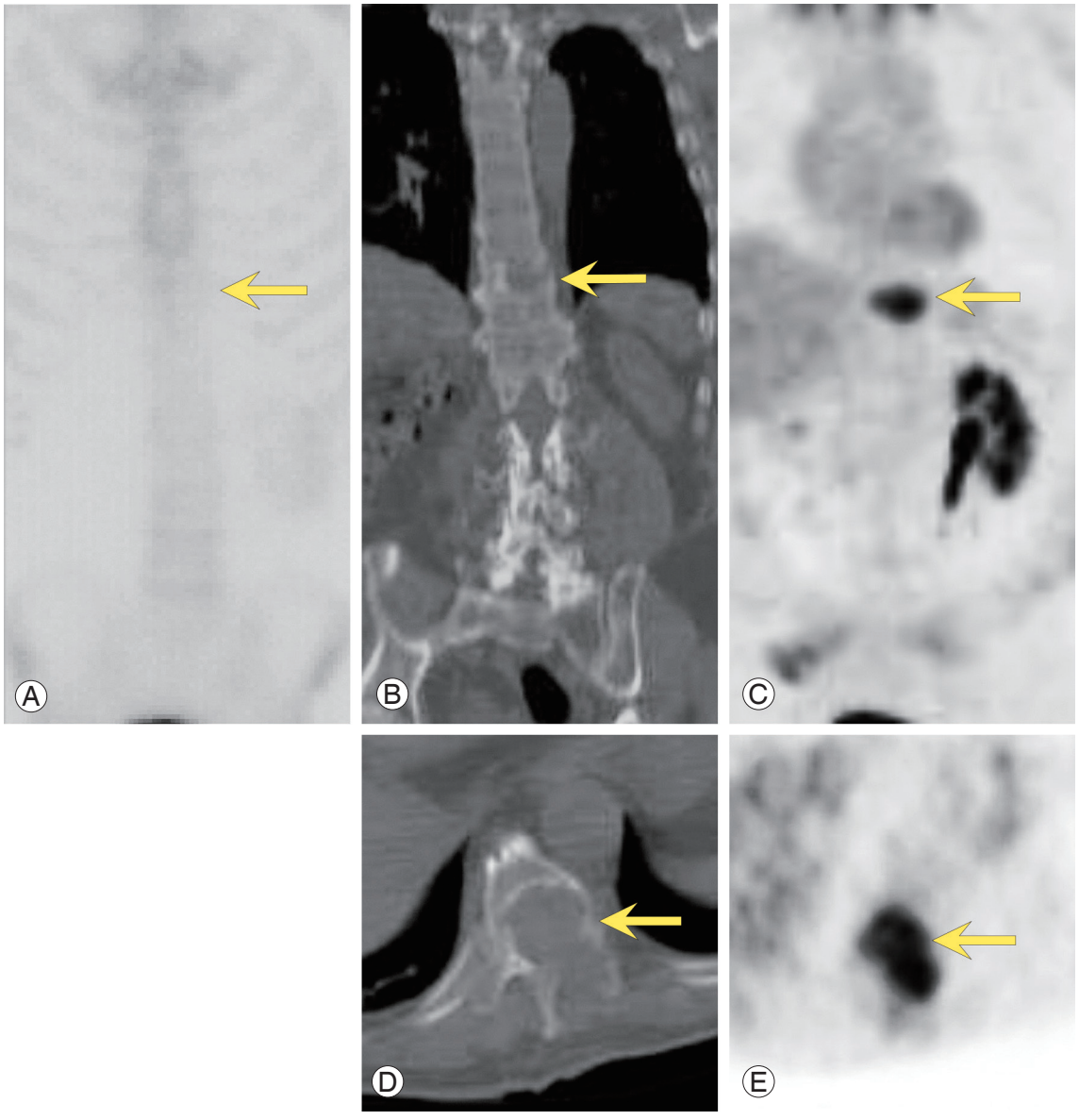

Fig. 2. Bone scan **(A)**, computed tomography (CT) **(B, D)** and fluorodeoxyglucose (FDG) positron emission tomography (PET) **(C, E)** images of a 69-year-old man with renal cell carcinoma. Note the focal intense uptake in osteolytic spine metastases (vertebral body of T10) on PET only but not on the bone scan (arrows). Axial and coronal CT images show osteolytic changes in the vertebral body **(B, D)** and focal intense uptake on the PET images **(C, E)**.

minimal and more marked osteolytic or osteoblastic changes. These findings emphasize the limitations of the CT in confirming or excluding bone metastases detected on bone scans or PETs.

Our results also demonstrated differences in the detection of osteolytic versus osteoblastic lesions; where FDG-PET showed a higher sensitivity in the detection of osteolytic lesions, but lower sensitivity, relative to bone scans, in osteoblastic metastases. Whether the greater avidity for ^{18}F-FDG in osteolytic metastases reflects a higher glycolytic rate in this type of lesion remains unknown; and since osteoblastic metastases are relatively acellular [28], the degree of ^{18}F-FDG uptake may be influenced by the lower volume of viable tumor tissue within the lesion. It is also important to take into consideration the hypoxic environment typically noted in osteolytic lesions, compared with osteoblastic lesions, which is caused by poor blood supply in these lesions due to their aggressive growth. Such behavior may be an additional factor that could influence the diagnosis, since hypoxia is known to increase ^{18}F-FDG uptake in some cell lines [29].

Conclusions

The present study showed a comparable diagnostic accuracy of spinal metastases by bone scan and FDG PET in PET/CT. Although the CT (as part of PET/CT) can provide detailed anatomic information, our data suggest that characterization of the spinal metastatic lesions is of limited value even when optimal CT window width and level were used. PET in PET/CT could be a substitute for bone scan regarding the evaluation of spinal metastasis, especially for patients with spinal osteolytic lesions identified on the CT. In contrast, osteoblastic metastases show lower metabolic activity and are frequently undetectable on the FDG PET. The biologic explanation for this observation remains to be elucidated.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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