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Comparison between ^{18}F-FDG PET/CT and ^{99m}Tc-MDP SPECT/CT for bone metastases from prostate cancer

Akito ITO [1], Kenichi KATO [2], Kazuhiro IWASAKI [1], Wataru OBARA [1] and Shigeru EHARA [2]

[1] Department of Urology, School of Medicine, Iwate Medical University, Morioka, Japan

[2] Department of Radiology, School of Medicine, Iwate Medical University, Morioka, Japan

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Abstract

The purpose of this study was to compare ^{18}F-FDG PET/CT and ^{99m}Tc-MDP SPECT/CT for the diagnosis of bone metastases from prostate cancer. This prospective study included 32 patients with high-risk prostate cancer who underwent examinations for staging or restaging. They underwent ^{18}F-FDG-PET/CT and ^{99m}Tc-MDP SPECT/CT within 4 weeks. All lesions were interpreted separately by two radiologists as benign (including subsets of benign or probably benign) or malignant (equivocal, probably malignant or malignant). These interpretations were compared with the diagnosis of bone metastases based on the clinical course and follow-up imaging by CT and MRI. We compared the two imaging modalities by McNemar test, and inter-observer agreements was calculated. In all the patients, sensitivity, specificity, positive predictive value, negative predictive value and accuracy were 53.1%, 99.3%, 96.3%, 86.2%, and 87.6%, respectively, for ^{18}F-FDG PET/CT, and 77.6%, 96.2%, 87.4%, 92.7% and 91.5%, respectively, for ^{99m}Tc-MDP SPECT/CT. ^{99m}Tc-MDP SPECT/CT is significantly superior in sensitivity to ^{18}F-FDG PET/CT ($p<0.01$). Inter-observer agreements for ^{18}F-FDG PET/CT and ^{99m}Tc-MDP SPECT/CT were 92.7% and 86.9%, respectively. ^{99m}Tc-MDP SPECT/CT is more useful than ^{18}F-FDG PET/CT in the clinical management of patients with high-risk prostate cancer.

Key words : ^{18}F-FDG PET/CT, ^{99m}Tc-MDP SPECT/CT, bone metastases, prostate cancer

I. Introduction

Bone metastases are reported to occur in 65–75% of prostate cancer cases and are associated with poor prognosis [1, 2]. Mette et al. [3] reported that the 1- and 5-year survival rates were 87% and 56% in patients with prostate cancer without bone metastasis, 47% and 3% in those with bone metastases, and 40% and <1% in those with bone metastases and skeletal-related events, respectively. Early detection of bone metastases potentially makes it possible to prevent intractable skeletal-related events by prompt palliative interventions. Bone scintigtraphy has long been used for the detection of bone metastases, especially with prostate cancer,

because the modality is highly sensitive to their sclerotic metastases[4]. However, its efficacy is also degraded by frequent detection of false-positive lesions. In recent years, technetium-99m methylene diphosphonate single photon emission computed tomography/computed tomography (^{99m}Tc- MDP SPECT/CT) has been used in clinical settings and has improved the precision of differentiating between true- and false-positive lesions [5]. It is reported that ^{99m}Tc-MDP SPECT/CT has higher detectability, sensitivity, and specificity than does bone scintigraphy[6]. Fluorine-18 fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET)/CT is also increasingly used for assessment of cancer in various phases of treatment such as staging, detection of residual disease or recurrence.

However, in prostate cancer, glucose metabolism and FDG accumulation tend to be poor and might not be useful in the detection of the primary tumor [7]. Indeed, in previous reports, ^{18}F-FDG PET/CT was reported to be ineffective for detecting primary prostate cancer lesions [8]. However, it was reported to be useful in detecting metastatic lymph nodes and distant organ metastases in prostate cancer [9]. To our knowledge, no previous studies have compared the abilities of ^{18}F-FDG PET/CT and ^{99m}Tc-SPECT/CT to detect bone metastases in prostate cancer. The purpose of this study is to compare the efficacy of these relatively new modalities in the detection of bone metastases from prostate cancer.

II. Materials and methods

1. Patient selection

This was a single-institution study that prospectively enrolled patients with prostate cancer undergoing imaging for staging or re-staging between January 2013 and April 2014. The inclusion criteria for staging were an initial diagnosis of prostate cancer with serum prostate-specific antigen (PSA) ≥ 10 ng / ml and a positive digital rectal examination or Gleason scores ≥8. The inclusion criteria for restaging were PSA failure (an increase in PSA of more than 25% from nadir and PSA ≥ 2 ng/ml), increased alkaline phosphatase levels (≥ 2.5 × the upper limit of normal), or bone metastatic symptoms after substantial period of PSA nadir by hormone therapy and/or chemotherapy. Exclusion criteria were current treatment for other cancers and surgery and/or chemotherapy in the 2 weeks preceding study entry. All patients were examined by ^{18}F-FDG PET/CT and ^{99m}Tc-MDP SPECT/CT with an interval of less than 4 weeks between them. This study was approved by the ethics committee of Iwate Medical University School of Medicine. Informed consent was obtained from all patients.

2. Imaging studies

1) ^{99m}Tc-MDP SPECT/CT

Bone scintigraphy was obtained approximately 3 hours following an intravenous injection of 555 MBq of ^{99m}Tc-MDP. All data were acquired with a combined SPECT/CT in-line system (Hawkeye 4 Infinia, General Electric, USA). SPECT/CT images from the cervical region to the proximal femur were obtained with a matrix size of 128 × 128, 180 ° in 60 projections, and 10 seconds per projection. Transverse, coronal, and sagittal SPECT images were generated. The SPECT/CT images were displayed as follows: the minimum of window width was set to the mean uptake of normal femoral head, and the

maximum of window width was not changed.

2) ^{18}F-FDG-PET/CT

The patients fasted for at least 4 hours before PET imaging, and a blood glucose level < 150 mg/dl was verified. Immediately prior to the scan acquisition, patients were asked to void urine. One hour after an intravenous administration of 170–340 MBq ^{18}F-FDG, PET/CT scans were performed with a whole-body PET/CT scanner (Discovery PET/CT 600 Motion scanner; General Electric Company Healthcare, USA). ^{18}F-FDG-PET/CT images were reconstructed by an iterative method (2 iterations and 8 subsets) using the OSEM (ordered subset expectation maximization method) algorithm.

3. Image interpretation

Two radiologists with more than 15 years of experience in radiology, and familiar with the interpretation of ^{18}F-FDG-PET/CT and ^{99m}Tc-MDP SPECT/CT images, reviewed whole anonymized images independently and in a random order. The radiologists were blinded to all clinical information except age, PSA level, Gleason score, and the presence or absence of treatment. All examinations were reported on a workstation with a Digital Imaging and Communication in Medicine (DICOM) viewer. Only fusion images were used, and they were analyzed according to the intensity and distribution of accumulation. Lesions were scored using the following 5-point scale: 0, normal; 1, probably normal; 2, equivocal; 3, probably malignant; and 4, malignant. This 5-point interpretation was applied to every lesion. Lesions with a score of 0 or 1 were categorized as benign, and those with scores of 2–4 were classified as malignant. In the case of disagreement between the two radiologists, consensus was reached by involvement of a third expert. The interval of interpretation for ^{99m}Tc-MDP SPECT/CT and ^{18}F-FDG-PET/CT images was over 2 weeks. The findings from ^{18}F-FDG PET/CT and ^{99m}Tc-MDP SPECT/CT were compared with the results of the "gold standard" analysis that was based on the clinical course and follow-up imaging, including CT and magnetic resonance imaging (MRI) findings. We divided bone metastases into three morphological categories (sclerotic, lytic, and mixed lesions) based on CT. The detectability of ^{18}F-FDG-PET/CT and ^{99m}Tc-MDP SPECT/CT was analyzed according to these 3 morphological categories.

4. Image analysis

We performed a lesion-based analysis of the skeletal system excluding the head. According to a lesion-based analysis, simple and fair evaluation was possible in cases of diffuse bone accumulation. The skeleton was subdivided into 14 parts as follows: 1) superior cervical vertebrae C1–C3, 2) inferior cervical vertebrae C4–C7, 3) superior thoracic vertebrae Th1–Th4, 4) middle thoracic vertebrae Th5–Th8, 5) inferior thoracic vertebrae Th9–Th12, 6) superior ribs T1–T4, 7) middle ribs, T5–T8, 8) inferior ribs T9–T12, 9) superior lumbar vertebrae L1–L3, 10) inferior lumbar vertebrae L4–L5, 11) bilateral ilea, 12) ischium, pubis, and sacrum, 13) acetabular cartilage and femurs, 14) arms (shoulder joints, humerus, and clavicles). In cases of different scores existing in the same region, the highest score was chosen for the final score.

5. Statistical analysis

We analyzed the sensitivity, specificity, positive predictive value (PPV), negative

predictive value (NPV), and accuracy of ^{18}F-FDG-PET/CT and ^{99m}Tc-MDP SPECT/CT for the detection of bone metastases in patients with prostate cancer. The McNemar test was performed to compare the results of ^{18}F-FDG-PET/CT and ^{99m}Tc-MDP SPECT/CT. Moreover, we examined inter-observer agreements and calculated kappa coefficients. Imaging modalities were tested with a confidence level of 95% ($p<0.05$ was considered significant). The statistical analysis was performed using JMP® 10 (SAS Institute Inc., Cary, NC, USA) and SPSS (PASW® Statistics 18, SPSS Inc., Chicago IL, USA).

Table 1. Patient characteristics

Age (years), Mean		72 (59-90)	
PSA (ng/ml), Mean		282 (0.01-4400)	
T	cT1c	1	3%
	cT2	17	53%
	cT3	8	25%
	cT4	6	19%
N	N0	24	75%
	N1	8	25%
M	M0	18	56%
	M1(Bone)	14	44%
Gleason Score	6	3	9%
	7	5	16%
	8/9/10	23	72%
	unknown	1	3%

III. Results

A total of 32 patients (20 staging and 12 restaging) were included. Table 1 lists the patient characteristics. The mean age of the patients was 72 years and age ranged from 59 to 90 years. The median follow-up period was 13.5 months (6–24 months). Thirty-one patients had a biopsy-proven adenocarcinoma, and 1 patient did not undergo biopsy because he was under anticoagulation therapy. In this patient, we made the diagnosis based on clinical findings, such as a high PSA value (296 ng/ml) and a positive digital rectal examination. The total number of analyzed regions was 388. In 6 patients, the range of the ^{99m}Tc-MDP SPECT/CT acquisitions was only from the abdomen to the pelvis, and from the chest to the abdomen in 1 patient. Fourteen patients (43.8%) had bone metastases based on CT/MRI findings and follow-up imaging.

The results of the image interpretations for ^{18}F-FDG PET/CT and ^{99m}Tc-MDP SPECT/CT are shown in Table 2. For all patients,

Table 2. Image interpretations of ^{18}F-FDG-PET/CT and ^{99m}Tc-MDP SPECT/CT.

	^{18}F-FDG-PET/CT				^{99m}Tc-SPECT/CT			
	Observer A		Observer B		Observer A		Observer B	
Score	Number	%	Number	%	Number	%	Number	%
0 (benign)	271	69.8%	290	74.7%	256	66.0%	251	64.7%
1 (probably benign)	40	10.3%	40	10.3%	23	5.9%	58	14.9%
2 (equivocal lesion)	25	6.4%	11	2.8%	28	7.2%	13	3.4%
3 (probably malignant)	11	2.8%	9	2.3%	21	5.4%	13	3.4%
4 (malignant)	41	10.6%	38	9.8%	60	15.5%	53	13.7%
total	388	100%	388	100%	388	100%	388	100%

Table 3. Sensitivity, specificity, PPV, NPV, and accuracy values of ^{18}F-FDG PET/CT and ^{99m}Tc-MDP SPECT/CT in a lesion-based analysis

Modality		Sensitivity	Specificity	PPV	NPV	Accuracy
^{18}F-FDG PET/CT	Number of the detection	52	288	52	288	340
	Total number	98	290	54	334	388
	%	53.1%	99.3%	96.3%	86.2%	87.6%
	95% CI	48.6-54.5%	97.8-99.8%	88.2-99.0%	84.9-86.7%	85.4-88.4%
^{99m}Tc-SPECT/CT	Number of the detection	76	279	76	279	355
	Total number	98	290	87	301	388
	%	77.6%	96.2%	87.4%	92.7%	91.5%
	95% CI	71.6-81.8%	94.2-97.7%	80.7-92.2%	90.8-94.1%	88.5-93.7%

PPV=positive predictive value NPV=negative predictive value
CI=Confidence interval

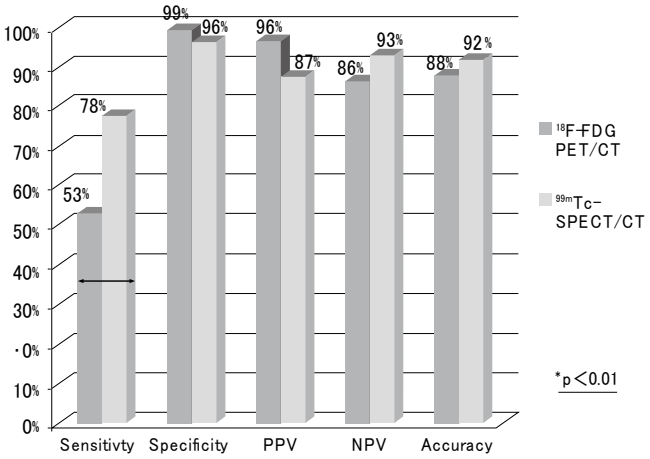

Fig. 1. Diagnostic accuracy of ^{18}F-FDG-PET/CT and ^{99m}Tc-MDP SPECT/CT.
The sensitivity, NPV, and accuracy were higher for ^{99m}Tc-MDP SPECT/CT than ^{18}F-FDG PET/CT. The sensitivity was significantly higher for 99mTc-MDP SPECT/CT ($p<0.01$). There were no significant differences in specificity among the modalities ($p=0.12$).
PPV=positive predictive value
NPV=negative predictive value

the sensitivity, specificity, PPV, NPV, and accuracy were 53.1%, 99.3%, 96.3%, 86.2%, and 87.6%, respectively, for ^{18}F-FDG PET/CT and 77.6%, 96.2%, 87.4%, 92.7% and 91.5%, respectively, for ^{99m}Tc-MDP SPECT/CT (Table 3 and Fig. 1). In this study, ^{99m}Tc-MDP SPECT/CT was found to be significantly superior in terms of sensitivity to ^{18}F-FDG PET/CT ($p < 0.01$).

Table 4. Inter-observer agreement

Modality	Inter-observer agreements ^{18}F-FDG-PET/CT	^{99m}Tc-SPECT/CT
Number of detection	373	337
Total number	388	388
%	92.7%	86.9%
κ value	0.84	0.785

Inter-observer agreements are presented in Table 4. Inter-observer agreements for ^{18}F-FDG PET/CT and ^{99m}Tc-MDP SPECT/CT were 92.7% and 86.9%, respectively. The concordance rate of ^{18}F-FDG-PET/CT was higher than that of ^{99m}Tc-MDP SPECT/CT. The changes in sensitivity and specificity according to the applied cutoff values are shown in Fig. 2.

Bone metastases were morphologically subdivided into sclerotic, lytic, and mixed types based on CT findings (Table 5). In total, metastatic bone lesions were present

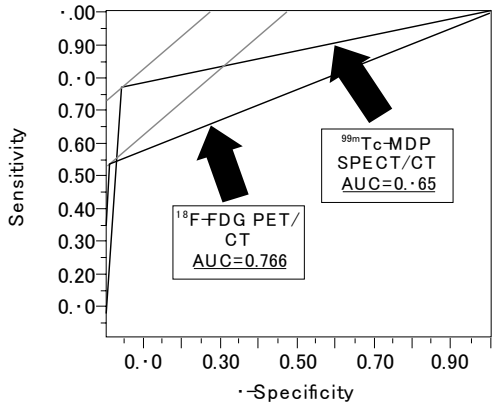

Fig. 2. ROC analysis for ^{18}F-FDG PET/CT and ^{99m}Tc-MDP SPECT/CT.
In the total patients group, the AUC of ^{99m}Tc-MDP SPECT/CT at 0.86 is highest (0.76 for ^{18}F-FDG PET/CT).
ROC=Receiver Operating Characteristic
AUC= Area Under the Curve

in 98 of 388 lesions (25.5%). In this study, 66 lesions were of the sclerotic type, 32 lesions were of the mixed type, and no lesions were of the lytic type. ^{99m}Tc-MDP SPECT/CT and ^{18}F-FDG PET/CT were able to detect 65.2% (43/66) and 43.9% (26/66) of the sclerotic-type metastases (Fig. 3), and 90.6% (29/32) and 78.1% (25/29) of the mixed-type metastases, respectively. The true-positive rate for ^{99m}Tc-MDP SPECT/CT in detecting sclerotic type lesions was significantly superior to that of ^{18}F-FDG PET/CT ($p < 0.01$).

IV. Discussion

We compared the efficacy of ^{18}F-FDG PET/CT and ^{99m}Tc-MDP SPECT/CT for detecting bone metastases of prostate cancer. Many researchers have reported the efficacy of these and other nuclear imaging modalities for detecting bone metastasis, such as ^{18}F-FDG PET/CT, ^{99m}Tc-MDP planar bone scintigraphy, ^{99m}Tc-MDP SPECT , and ^{99m}Tc-MDP SPECT/CT [6,10]. For example, Damle et al. [10] recently compared ^{18}F-FDG PET/CT, ^{18}F-fluoride PET/CT, and ^{99m}Tc-MDP bone scintigraphy and found that ^{18}F-fluoride PET/CT was the most reliable modality for ruling out bone metastases in prostate cancer. However, the availability of ^{18}F-fluoride PET/CT is limited in regular clinical settings. The authors also reported that ^{18}F-FDG PET/CT was superior to ^{99m}Tc-MDP bone scintigraphy in specificity, PPV, and accuracy in prostate cancer. In our study, ^{99m}Tc-MDP SPECT/CT was found to be superior to ^{18}F-FDG PET/CT in sensitivity for detecting bone metastasis in prostate cancer; however, the sensitivity was low compared to that reported in previous studies using ^{99m}Tc-MDP bone scintigraphy.

Most patients with prostate cancer are elderly and may have an accumulation of ^{99m}Tc-MDP due to degenerative spinal disease

Table 5. Bone metastases based on morphological type

Morphological type	Total number of metastatic lesions		^{18}F-FDG PET/CT	^{99m}Tc-SPECT/CT	p value
Sclerotic	66	Number of the detection True positive rate (%)	26 43.9%	43 65.2%	<0.01
Mixed	32	Number of the detection True positive rate (%)	25 78.1%	29 90.6%	0.07
Lytic	0	Number of the detection True positive rate (%)	0 0%	0 0%	-

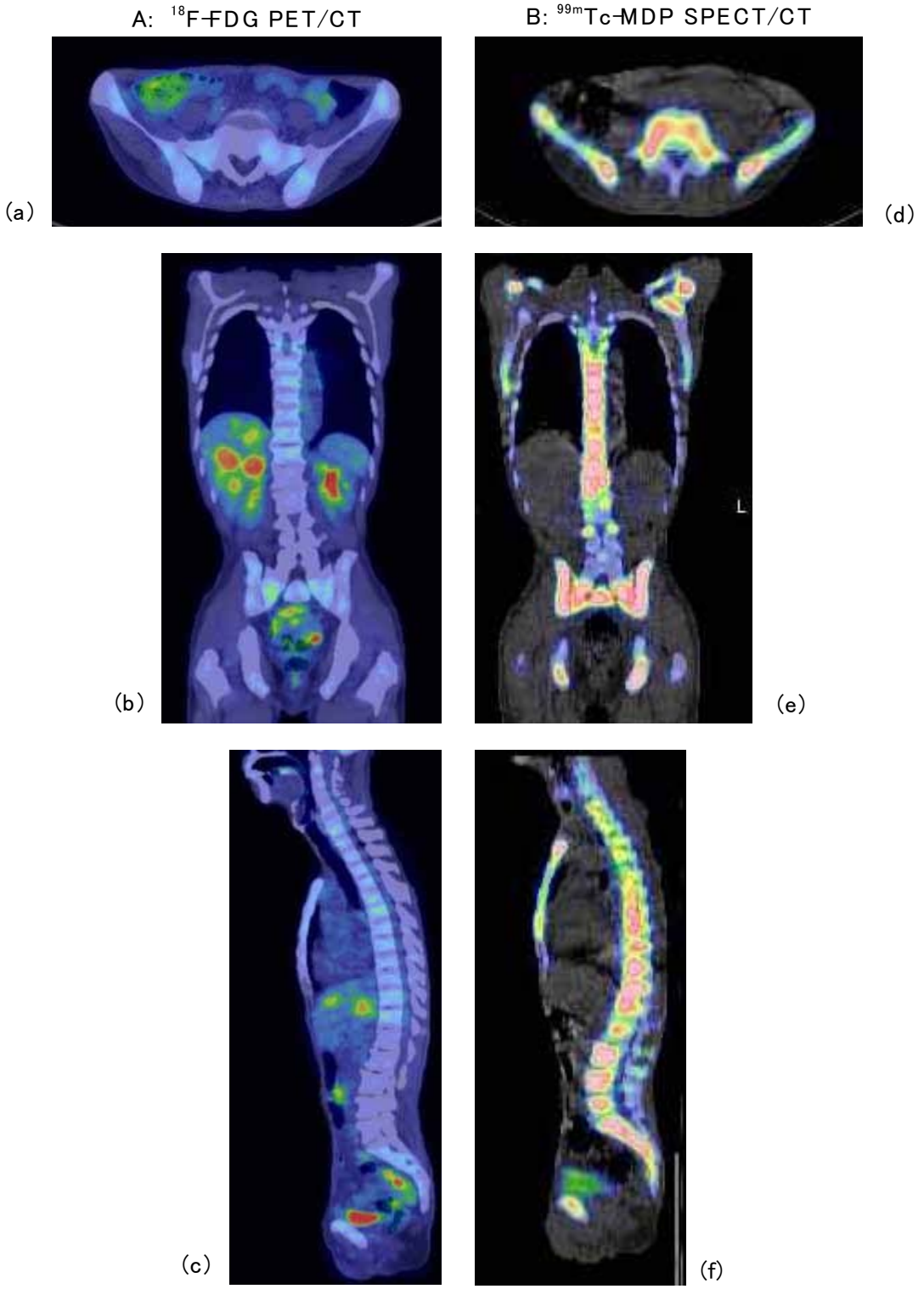

Fig 3. Diffuse sclerotic bone metastases of the castration-resistant prostate cancer.
A 73-year-old man was treated with hormonal therapy for high-risk prostate cancer (PSA, 1230 ng / ml; Gleason score, 5 + 5 = 10; cT4N1M1b) with multiple sclerotic bone metastases. ^{18}F-FDG PET/CT did not show abnormal accumulation in the skeletal system; however ^{99m}Tc-MDP SPECT/CT showed diffuse, abnormal accumulation in the skeletal system compatible with "super bone scan." Liver metastases were noted in ^{18}F-FDG PET/CT.
A: ^{18}F-FDG PET/CT (a) transverse (b) coronal (c) sagittal.
B: ^{99m}Tc-MDP SPECT/CT (d) transverse (e) coronal (f) sagittal

or inflamed joints, leading to a high false-positive rate. In particular, the detectability of 99mTc-MDP SPECT/CT is very high in these regions; thus, the incidence of false-positive lesions may be increased. Accordingly, we chose the mean uptake of normal femoral head as the minimum window width when displaying ^{99m}Tc-MDP SPECT/CT imaging to reduce the detection of false-positive lesions. Therefore, the minimum window width of ^{99m}Tc-MDP SPECT/CT imaging might be higher and the sensitivity of ^{99m}Tc-MDP SPECT/CT lower in our study than that in previous reports, especially for sclerotic bone metastases typically seen in prostate cancer.

More false-negative lesions in re-staging cases are thought to be related to reductions in ^{99m}Tc-MDP accumulation due to hormone therapy or chemotherapy. On the other hand, ^{18}F-FDG PET/CT did not demonstrate acceptable results in our study. Oyama et al. reported that the accumulation of FDG decreased after hormonal therapy[12], and FDG accumulation in restaging patients was thought to be decreased in our examinations. Moreover, image interpretation in this study was performed using only a fusion image, and severe sclerotic changes might have been interpreted as false-negative lesions.

Palmedo et al.[6] compared ^{99m}Tc-MDP bone scintigraphy, ^{99m}Tc-MDP SPECT, and ^{99m}Tc-MDP SPECT/CT, and reported that the specificity was significantly higher with ^{99m}Tc-MDP SPECT/CT ($p<0.01$). Furthermore, it is important to note that the specificity improved dramatically by creating a fusion image with CT. In our study, the true-positive rate for detecting sclerotic-type lesions was significantly superior with ^{99m}Tc-MDP SPECT/CT and this was equivalent for mixed-type lesions in the analysis according to lesion morphology. In prostate cancer, we believe that ^{99m}Tc-MDP SPECT/CT should be used continuously for detecting bone metastases.

Our study has some limitations. First, our prospective study included a small number of cases. Furthermore, the number of patients with bone metastases was limited in our prospective cohort, and cases without bone metastases were included in the same cohort. As a result, specificity and NPV might have been calculated to be high, and a significant difference was not observed. Second, ^{99m}Tc-MDP SPECT/CT lacks a standardized display and quantitative analysis compared to ^{18}F-FDG PET/CT. Third, we set the interval of both imaging modalities within 4 weeks. Therefore the lesion might be change during the interval of both imaging modalities.

In conclusion, the sensitivity of ^{99m}Tc-MDP SPECT/CT for detecting bone metastases was found to be superior to that of ^{18}F-FDG PET/CT in prostate cancer. As for sclerotic lesions, ^{99m}Tc-MDP SPECT/CT had a higher true-positive rate than ^{18}F-FDG PET/CT. We suggest that ^{99m}Tc-MDP SPECT/CT is a useful modality for continuous monitoring in prostate cancer management.

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Conflict of interest: The authors have no conflict of interest to declare.

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前立腺癌骨転移診断における ^{18}F-FDG PET/CT と ^{99m}Tc-MDP SPECT/CT の比較検討

伊藤明人[1)]，加藤健一[2)]，岩崎一洋[1)]，
小原　航[1)]，江原　茂[2)]

[1)] 岩手医科大学医学部，泌尿器科学講座
[2)] 岩手医科大学医学部，放射線医学講座

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要旨

前立腺癌骨転移診断における ^{18}F-FDG PET/CT と ^{99m}Tc-MDP SPECT/CT の有用性を比較するために前向き研究を実施した．Staging および re-staging 目的で検査が行われた 32 例の高リスク前立腺癌症例が登録された．両検査は 4 週間以内に施行され，すべての病変は 2 人の放射線科医によって独立下で良性もしくは悪性として読影が行われ，臨床経過およびフォローアップの CT/MRI 画像に基づいた骨転移診断と比較した．両検査はマクネマー検定によって比較し，読影者間一致割合を算出した．感度，特異度，陽性反応的中度，陰性反応的中度，正診率は ^{18}F-FDG PET/CT が 53.1%，99.3%，96.3%，86.2%，87.6% であったのに対し，^{99m}Tc-SPECT/CT は 77.6%，96.2%，87.4%，92.7%，91.5% であり，感度において ^{99m}Tc-SPECT/CT が有意差をもって優れていた ($p<0.01$)．評価者間一致割合は ^{18}F-FDG PET/CT が 92.7%，^{99m}Tc-MDP SPECT/CT が 86.9 % であった．^{99m}Tc-SPECT/CT は ^{18}F-FDG PET/CT と比べ高リスク前立腺癌患者における clinical management においてより有用であると考えられる．