Clinical Significance of Incidental Focal ^{18}F -FDG Uptake in the Spinal Cord of Patients with Cancer

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Abstract

Purpose We investigated the incidence, location, and clinical significance of focal ^{18}F -FDG uptake of the spinal cord in patients with cancer.

Methods We reviewed the medical records of 22,937 consecutive adult patients with known or suspicious malignancy who underwent ^{18}F -FDG PET/CT. PET/CT scans with incidental focal spinal cord uptake were selected and retrospectively reviewed to determine the presence, location, number, and maximum standardized uptake value (SUV_{max}) of any focal hypermetabolic lesions of the spinal cord. In subjects with focal spinal uptake, clinical characteristics and clinical follow-up results, including follow-up PET/CT, were reviewed.

Results Incidental focal spinal cord uptake was observed in 69 of 22,937 adult patients (incidence = 0.3%; M:F = 31:38; age, 55.8 ± 14.7 years). Seventy-eight focal hypermetabolic lesions on spinal cord in the PET/CT scans of the 69 study subjects were analyzed. The most common sites of focal spinal cord uptake were the T12 vertebra (47/78; 60.3%) and L1 vertebra (20/78; 25.6%). Multifocal cord uptake was found in 8 of 69 patients (11.6%). The average SUV_{max} for cord uptake was 2.5 ± 0.5 (range, 1.4–3.9). There was no clinical or imaging evidence of abnormalities in the spinal cord, both at the time of PET/CT and during clinical follow-up.

Conclusions Although incidental focal ^{18}F -FDG uptake of the spinal cord is rare in patients with cancer, it may be

physiological or benign, but it should not be considered as malignant involvement. Common sites for the uptake were in the T12 and L1 spine levels.

Keywords Spinal cord · ^{18}F -FDG · PET/CT · Cancer · Differential diagnosis

Abbreviations

PET/CT	Positron emission tomography/computed tomography
ISCMs	Intramedullary spinal cord metastases
FDG	^{18}F -fluorodeoxyglucose
SUV	Standardized uptake value
SUV_{max}	Maximum SUV
SUV_{avg}	Average SUV
CTL	Cord-to-liver ratio

Introduction

Focal uptake incidentally detected in some organs in ^{18}F -fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F -FDG PET/CT) can be clinically significant [1, 2]. When incidental focal uptake is found in ^{18}F -FDG PET/CT, it is important to determine the malignant risk of the lesion and to manage it properly. However, some sites, such as the ovary and stomach, have normal physiologic uptake, which makes interpretation difficult and can lead to unnecessary, additional tests. Recently, a few studies have reported normal physiologic uptake by the spinal cord and highlighted the need to avoid misdiagnosis of malignant involvement for ^{18}F -FDG cord uptake [3–5]. However, such reports have investigated only spinal cord uptake without evidence of spinal cord malignancy or metastasis.

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In patients with underlying malignancy, focal ^{18}F -FDG uptake of the spinal cord may indicate intramedullary spinal cord metastases (ISCMs). ISCMs are rare, but they cause fatal neurologic manifestations, such as sensory loss, urinary incontinence, and Brown-Séquard syndrome. Early detection of the lesion is important because treatment may slow neurologic deterioration [6]. However, ISCMs can be asymptomatic at early stages, and they are difficult to detect with CT imaging that is generally used for metastasis work-up [7]. Recent studies have reported that ^{18}F -FDG PET/CT has become the standard method for evaluating cancer and may be the first imaging technique prior to spine MRI to show ISCMs [8, 9].

Focal ^{18}F -FDG uptake of the spinal cord can be incidentally found, but its clinical significance is not well understood, and further investigation is needed for accurate interpretation of the lesion. Studies of patients with underlying malignancy can shed light on ways to distinguish ISCMs from incidental focal uptake. Thus, we investigated the incidence, location, and malignant risk of spinal cord focal uptake found incidentally in patients with cancer.

Materials and Methods

Study Population

We retrospectively reviewed the medical records of 22,937 consecutive adult patients with known or suspicious malignancy who underwent ^{18}F -FDG PET/CT between Jan 2013 and May 2014. Of the 22,937 patients, 94 with PET/CT scans showing spinal cord uptake were selected. We excluded PET/CT scans of 25 patients who had a history of radiation therapy of the spinal cord or organs adjacent to the spinal cord, or known spinal cord malignancy, which might cause ^{18}F -FDG uptake. Thus, a total of 69 subjects with incidental focal spinal cord uptake were finally included for analysis. This retrospective study was approved by our institutional review board, and the requirement for written consent was waived.

FDG PET/CT Imaging

All patients fasted for at least 6 h and had blood glucose levels < 200 mg at the time of PET/CT. Imaging was performed 60 min after injection of 5 MBq/kg ^{18}F -FDG without intravenous or oral contrast on a Discovery LS or a Discovery STe PET/CT scanner (GE Healthcare, Milwaukee, MI). Whole-body CT was performed with a continuous spiral technique with an 8-slice helical CT (140 keV; 40–120 mA; section width, 5 mm; Discovery LS) or a 16-slice helical CT (140 keV; 30–170 mA; section width, 3.75 mm; Discovery STe). After the CT scan, an emission scan was obtained from head to thigh for 4 min per frame in 2-D mode with

reconstruction of attenuation-corrected PET images ($4.3 \times 4.3 \times 3.9$ mm) by using an ordered-subset expectation maximization algorithm (28 subsets, two iterations; Discovery LS), or for 2.5 min per frame in 3-D mode with reconstruction of attenuation-corrected PET images ($3.9 \times 3.9 \times 3.3$ mm) by using a 3-D ordered-subset expectation maximization algorithm (20 subsets, two iterations; Discovery STe).

Analyses of PET/CT

^{18}F -FDG uptake of the spinal cord was measured on fused transaxial PET/CT slices by positioning the center of a circular region of interest in the center of the spinal canal. Maximum standardized uptake values (SUV_{max}) were measured. Sagittal fused PET/CT images were used to identify the accurate level of spinal cord uptake and to exclude diffuse ^{18}F -FDG uptake.

The change in spinal cord uptake was also analyzed in patients with follow-up PET/CT scans. In patients with two or more follow-up PET/CT scans, the latest PET/CT scan was used for the analysis. Average standardized uptake values of the liver (SUV_{avg}) measured by using a spherical volume-of-interest (VOI) with a 20-mm diameter in the center of segment 8 were used for reference organ uptake to correctly compare quantification of ^{18}F -FDG cord uptake. From these data, the cord-to-liver ratio ($\text{CTL} = \text{SUV}_{\text{max}}$ of the hypermetabolic cord lesion/ SUV_{avg} of the liver VOI) was calculated for each focal hypermetabolic lesion on spinal cord.

Imaging and Clinical Follow-Up

The presence or absence of malignancy in focal spinal cord uptake lesions of patients without follow-up PET/CT scans was established by magnetic resonance imaging (MRI) findings ($n = 3$ lesions/3 patients), and follow-up CT imaging ($n = 31$ lesions/28 patients; 29.0 ± 8.9 months; range, 10 to 44). Focal spinal cord uptake lesions which show no significant anatomical change during follow-up period were not considered as malignant lesions. In the case of patients without follow-up diagnostic imaging for cord lesions, they were not treated as malignant lesions if they did not cause problems during clinical follow-up period ($n = 8$ lesions/5 patients; 20.0 ± 8.1 months; range, 12 to 30). The others ($n = 7$ lesions/5 patients) who had follow-up less than 12 months were not included for final analyses because they were difficult to decide malignant risk.

Statistical Analysis

Statistical analyses were performed with commercial software (SPSS version 20.0, IBM). The Kolmogorov-Smirnov test was first used to assess the normality of continuous variables. On the basis of those results, nonparametric tests were used for this study. The Wilcoxon signed rank test was used to

compare SUV_{max} and CTL for each focal hypermetabolic lesion on spinal cord between the first and second PET/CT scans. P-values less than 0.05 were considered statistically significant.

Results

Characteristics of Study Subjects

Incidental focal spinal cord uptake was observed in 69 of 22,937 patients (0.3%). Characteristics of the study group ($n = 69$) are summarized in Table 1. Mean age was 55.8 ± 14.7 years (range: 18–87 years), and the underlying malignancy was lung cancer ($n = 20$), breast cancer ($n = 11$), colorectal cancer ($n = 6$), stomach cancer ($n = 5$), lymphoma ($n = 4$), and others. Although 20 patients received radiation therapy prior to PET/CT scan, treatment did not cover the spinal cord area. There were no signs or symptoms suggesting a cord abnormality in any subjects.

Characteristics of ^{18}F -FDG Cord Uptake

There were 78 focal hypermetabolic lesions on spinal cord in the PET/CT scans of the 69 study subjects. Multifocal uptake was found in eight of 69 patients (11.6%). The most common site of focal spinal cord uptake was the 12th thoracic vertebra (47/78; 60.3%). The second most common site was the first lumbar vertebra (20/78; 25.6%). Other locations included the cord at the fourth cervical vertebra; the fourth, seventh, tenth, and 11th thoracic vertebra; and the fourth lumbar vertebra (Table 2). The average SUV_{max} for cord uptake was 2.5 ± 0.5 (range, 1.4–3.9).

Malignant risk of ^{18}F -FDG Cord Uptake

Follow-up PET/CT was performed for 29 focal hypermetabolic lesions on spinal cord in 28 patients at 15.3 ± 9.7 months (range, 3–43 months) after the previous PET/CT. In 15 of the 29 focal hypermetabolic lesions on spinal cord (51.7%), the uptake had completely disappeared. In the remaining 11 focal hypermetabolic lesions on spinal cord (37.9%), the uptake was unchanged (within $\pm 10\%$ change in SUV_{max}) or reduced (Fig. 1). The CTL of each spinal cord uptake was also significantly decreased at the follow-up scan (Tables 3 and 4).

Forty-two focal hypermetabolic lesions on spinal cord in the 36 patients had MRI, CT, and clinical follow-up of more than 12 months. Mean duration of follow-up was 27.2 ± 9.4 months (range: 10–44 months). There was no evidence of abnormalities suggesting spinal cord malignancy or other benign cord disease at those sites.

Discussion

In this study, we investigated the incidence, location, and malignant risk of focal uptake of the spinal cord found incidentally in patients with known or suspected cancer. Incidental spinal cord uptake was seldom observed. Uptake occurred most frequently at T12 and L1. Malignancy or other benign disease was not found in the spinal cords, either at the time of PET/CT or during clinical follow-up.

No previous studies have reported the prevalence of incidental focal ^{18}F -FDG uptake of the spinal cord. In our study, incidental focal ^{18}F -FDG uptake of the spinal cord rarely occurred in patients with cancer. However, because spinal cord metastasis or malignancy was found in only a minority of patients, the interpreter may have been less alert to the possibility of ^{18}F -FDG uptake [8]. Thus, the low clinical identification we documented may be an underestimate.

Several reports have characterized the pattern of spinal cord uptake in patients with cancer. Do et al. reported a significant increase in cord uptake at the T11–T12 vertebral body levels [4]. Greenspan et al. analyzed the physiologic uptake of the T11–L1 spinal cord in subjects without spinal cord metastasis and reported that the highest maximal SUV was 3.7 [3]. Our study also revealed that T12 and L1 were the most common sites of ^{18}F -FDG cord uptake, consistent with previous studies. Most cases of ^{18}F -FDG cord uptake disappeared or decreased during follow up and caused no clinical problems. This suggests that ^{18}F -FDG cord uptake at T12–L1 may be a transient physiological finding. A few studies have suggested that the distal spinal cord is characterized by a high amount of gray matter and is involved in neurologic transmission for the

Table 1 Characteristics of the study population

	Total ($n = 69$)
Age (years)	
Range	18–87
Mean $\pm$ SD	55.8 ± 14.7
Sex	
Male	31 (44.9%)
Female	38 (55.1%)
Therapeutic history	
Chemotherapy	33 (47.8%)
Radiotherapy	20 (29.0%)
Surgery	39 (56.5%)
Cancer history	
Lung cancer	20 (29.0%)
Breast cancer	11 (15.9%)
Colorectal cancer	6 (8.7%)
Stomach cancer	5 (7.3%)
Lymphoma	4 (5.8%)

SD standard deviation

Table 2 Distribution and SUV_{max} of ^{18}F -FDG cord uptake by level ($n = 78$)

Cord uptake level	n (%)
T12	47 (60.3%)
L1	20 (25.6%)
T11	6 (7.7%)
L4	2 (2.6%)
C4	1 (1.3%)
T4	1 (1.3%)
T7	1 (1.3%)
SUV_{max}	
Range	1.4–3.9
Mean $\pm$ SD	2.5 $\pm$ 0.5

SUV_{max} maximum standard uptake value, SD standard deviation

upper and distal extremities, which leads to higher glycolytic metabolism of the neural tissue of these functionally more active spinal cord regions [5]. One study found that patients with disc herniation of the thoracolumbar junction (T11–T12, T12–L1 level) had lower extremity weakness and bladder and

Table 3 Change in SUV_{max} of the cord lesion during PET/CT follow-up ($n = 29$)

Transition	SUV_{max}	CTL
Disappearance	15 (51.7%)	15 (51.7%)
Decrease	11 (37.9%)	12 (41.4%)
No significant change	3 (10.4%)	2 (6.9%)

SUV_{max} maximum standard uptake value, CTL cord-to-liver ratio

bowel dysfunction [10]. As such, the cord uptake in our study subjects may be related to hyperactivity in the lower extremity, bladder, and bowel, compared with other sites. However, further studies are needed to clarify this association.

Only one study has analyzed the character of ^{18}F -FDG uptake for ISCM lesions in PET/CT. A few studies have assessed physiologic spinal cord uptake without malignant risk in PET/CT. Unlike previous studies, we included cases of spinal cord uptake for which it had not been determined whether uptake was a malignant lesion or physiologic uptake, allowing us to focus on malignant risk. We found no evidence

Fig. 1 Follow-up PET/CT images of a 63-year-old male patient with rectal cancer. In the initial PET/CT scan, there was focal uptake in the spinal cord at the T12 spine level ($SUV_{max} = 3.5$) (A, B, C). In the follow-up PET/CT after 3 months, spinal cord uptake was reduced ($SUV_{max} = 2.5$) (D, E, F). There was no evidence of abnormalities suggesting spinal cord malignancy or benign cord disease for that site over the clinical follow-up of 3 years

Table 4 SUV_{max} and CTL of the cord lesion on PET/CT scan from baseline to follow-up

	Initial scan	Follow-up scan	P value
Lesion (<i>n</i> = 29)	2.5 ± 0.6 (1.4–3.5)	0.9 ± 1.0 (0–2.4)	<0.001
Liver (<i>n</i> = 29)	2.8 ± 0.4 (2.0–3.5)	2.8 ± 0.4 (1.8–3.4)	0.971
CTL (<i>n</i> = 29)	0.9 ± 0.2 (0.5–1.6)	0.3 ± 0.4 (0–1.2)	<0.001

SUV_{max} maximum standard uptake value, CTL cord-to-liver ratio

of malignancy after clinical and imaging follow-up or follow-up PET/CT of the spinal cord lesions. A recent study by Gilardi et al. reported that high focal ¹⁸F-FDG uptake of SUV_{max} 4.1 and 4.7 at T12 and L1, respectively, indicated intramedullary metastases from breast cancer [11]. Another report of ¹⁸F-FDG uptake for ten ISCMs found that the average SUV_{max} was 6.7 (range, 3.3–9.9) [8]. In part, our findings may be explained by low ¹⁸F-FDG uptake in our cases (SUV_{max} up to 3.9).

In a previous study, Amin et al. demonstrated a change in spinal cord uptake on follow-up ¹⁸F-FDG PET/CT studies over 3–6 months; the uptake disappeared completely in most subjects, and the degree of uptake was unchanged or reduced in the remaining subjects [12]. However, because absolute SUV can vary according to factors such as the patient's glucose level, it is important to use a reference organ for comparison [13]. We used the liver as the reference organ, allowing us to quantify change more accurately.

This study had several limitations. First, the study had a retrospective design, which could have caused bias during selection and exclusion of study subjects. Second, all spinal cord lesions showed low ¹⁸F-FDG uptake. Although there were no malignant lesions, it is possible that incidentally found spinal cord lesions with high ¹⁸F-FDG uptake have malignant risk. Third, there were no pathologically confirmed lesions to evaluate abnormalities in the spinal cord lesions, which may suggest relatively weak power to prove the relationship between ¹⁸F-FDG uptake and malignant risk. However, it is not ethical and evidence-based to perform such an invasive pathological confirmation as biopsy for the spinal cord in patients without typical symptom or sign suggesting abnormality in the spinal cord, just based on the focal ¹⁸F-FDG uptake. This is the first investigation of the relationship between incidental focal uptake of the spinal cord and malignant risk, and the results may aid in the interpretation of ¹⁸F-FDG PET/CT scans showing incidental focal ¹⁸F-FDG uptake of the spinal cord.

Conclusions

Incidental focal ¹⁸F-FDG uptake of the spinal cord is rare in patients with cancer. It may be physiological or benign and should not be considered as malignant involvement. The most common site of uptake occurred at T12 and L1. Further

studies of incidental high focal ¹⁸F-FDG uptake of the spinal cord are warranted.

Compliance with Ethical Standards

Conflicts of Interest Chae Hong Lim, Seung Hyup Hyun, Seung Hwan Moon, Young Seok Cho, Yeam Seong Choe, Kyung-Han Lee, Byung-Tae Kim, and Joon Young Choi declare that they have no conflicts of interest related to this manuscript.

Ethical Approval This study was performed in accordance with the ethical standards of the institutional and/or national research committees and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent The institutional review board at our institute approved this retrospective study, and the requirement to obtain informed consent was waived.

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