RESEARCH ARTICLE

Incidental Abnormal FDG Uptake in the Prostate on 18-fluoro-2-Deoxyglucose Positron Emission Tomography-Computed Tomography Scans

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Abstract

18-fluoro-2-deoxyglucose positron emission tomography-computed tomography (^{18}F-FDG PET/CT) scans are commonly used for the staging and restaging of various malignancies, such as head and neck, breast, colorectal and gynecological cancers. However, the value of FDG PET/CT for detecting prostate cancer is unknown. The aim of this study was to evaluate the clinical value of incidental prostate ^{18}F-FDG uptake on PET/CT scans. We reviewed ^{18}F-FDG PET/CT scan reports from September 2009 to September 2013, and selected cases that reported focal/diffuse FDG uptake in the prostate. We analyzed the correlation between ^{18}F-FDG PET/CT scan findings and data collected during evaluations such as serum prostate-specific antigen (PSA) levels, digital rectal examination (DRE), transrectal ultrasound (TRUS), and/or biopsy to confirm prostate cancer. Of a total of 18,393 cases, 106 (0.6%) exhibited abnormal hypermetabolism in the prostate. Additional evaluations were performed in 66 patients. Serum PSA levels were not significantly correlated with maximum standardized uptake values (SUVmax) in all patients (rho 0.483, p=0.132). Prostate biopsies were performed in 15 patients, and prostate cancer was confirmed in 11. The median serum PSA level was 4.8 (0.55-7.06) ng/mL and 127.4 (1.06-495) ng/mL in the benign and prostate cancer groups, respectively. The median SUVmax was higher in the prostate cancer group (mean 10.1, range 3.8-24.5) than in the benign group (mean 4.3, range 3.1-8.8), but the difference was not statistically significant (p=0.078). There was no significant correlation between SUVmax and serum PSA, prostatic volume, or Gleason score. ^{18}F-FDG PET/CT scans did not reliably differentiate malignant or benign from abnormal uptake lesions in the prostate, and routine prostate biopsy was not usually recommended in patients with abnormal FDG uptake. Nevertheless, patients with incidental prostate uptake on ^{18}F-FDG PET/CT scans should not be ignored and should be undergo further clinical evaluations, such as PSA and DRE.

Keywords: Prostate cancer - positron emission tomography/computed tomography - prostate

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Introduction

18-Fluoro-2-deoxyglucose positron emission tomography-computed tomography (^{18}F-FDG PET/CT) scanning is a molecular imaging modality that provides images of physiological and metabolic processes (Bouchelouche and Oehr, 2008). FDG uptake depends on the cellular glucose metabolism via the GLUT transporter family; once taken up it is phosphorylated to form FDG-6-phosphate. The ^{18}F-FDG tracer is a glucose analog that is taken up preferentially and trapped inside malignant cells, including lung cancer, colorectal cancer, and malignant lymphomas, which are characterized by increased cellular proliferation and increased glucose consumption (Bouchelouche and Oehr, 2008). ^{18}F-FDG PET/CT scans have been used for the staging and restaging of various primary and metastatic cancers such as head and neck, breast, lung, colorectal, and gynecological cancers (Zhao et al., 2014).

To date, ^{18}F-FDG PET/CT scans have played only a limited role in the diagnosis or staging of urological malignancies including prostate, bladder, and kidney cancer because of the urinary excretion of ^{18}F-FDG and variable uptake in some urological cancers (Scher et al., 2007). The specific reasons for its limited use in the diagnosis of prostate cancer are as follows: *i*) glucose utilization is lower in prostate cancer than in other tumor types; *ii*) the urinary excretion of ^{18}F-FDG leads to high bladder activity, which can mask prostate uptake; and *iii*) the differences between FDG uptake in prostate cancer, benign prostate hyperplasia (BPH), and inflammation are small (Scher et al., 2007).

The main aim of this study was to investigate the frequency of incidental focal FDG uptake into the

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prostate on PET/CT scans performed for the evaluation of known cancer or as part of screening health check-ups. The second aim was to evaluate the association between maximum standardized uptake value (SUVmax) with the clinicopathological results of benign and malignant cases.

Materials and Methods

A total of 18, 393 patients underwent ^{18}F-FDG PET/CT scans from September 2009 to September 2013. After Institutional Review Board approval, we reviewed all 18F-FDG PET/CT scan reports, and enrolled all patients with abnormal uptake in the prostate gland. Patients were excluded if they had known prostate cancer.

^{18}F-FDG PET/CT

All patients fasted for at least 6h before ^{18}F-FDG administration. ^{18}F-FDG PET/CT imaging was performed 60 min after injection with approximately 370 MBq of ^{18}F-FDG using a dedicated PET/CT scanner (Discovery ST [DST] PET/CT, General Electric Medical System, Milwaukee, WI, USA). Non-contrast enhanced CT scans (helical, eight-slice, 120 Kvp, 10-130 mAs, and 3.79 slice thickness) were performed, followed by PET scans (3 min/bed, 6-8beds) The PET images were reconstructed using a full 3-D iterative algorithm (two integrations, 20 subsets, 128×128 matrix) after attenuation correction using the CT data.

Definition of abnormal hypermetabolism (interpretation)

Two nuclear medicine physicians reviewed the PET/CT images on a workstation containing fusion software (AW workstation, GE Milwaukee, WI, USA). Hypermetabolism of the prostate gland was defined as discrete FDG activity higher than that of the surrounding prostate gland on visual analysis (Figure 1). All axial, coronal, and sagittal images were analyzed carefully. Focal hypermetabolism was considered to be significant if evident asymmetrical placement was observed on one side of the prostate gland. The SUVmax of the prostate gland was measured on axial images.

Diagnostic methods

PET/CT findings were correlated with the results of serum prostate-specific antigen (PSA) levels, digital rectal examination (DRE), transrectal ultrasound (TRUS), and/or biopsy to confirm prostate cancer. Biopsies (≥ six cores) were performed in suspicious cases in males who had an abnormal palpable nodule on DRE or a serum PSA level >4.0 ng/dL.

Statistical analysis

Statistical analyses were performed using the SPSS software, version 18.0 (SPSS Inc., Chicago, IL, USA). Descriptive analyses were applied to evaluate the frequency of abnormal prostate hypermetabolism, whereas secondary evaluations were used to detect prostate cancer and the percent diagnosis with prostate cancer. The patients who underwent prostate biopsies were categorized into the benign or malignant groups. Clinical characteristics, including age, serum PSA levels, and SUVmax, were then compared between the two groups using Mann-Whitney U-tests and Chi-square tests. The correlations among SUVmax, serum PSA, and Gleason score were evaluated using Spearman's correlation coefficient. Significance was set at $p<0.05$.

Results

Of the 18,393 patients who underwent ^{18}F-FDG PET/CT scans, 106 cases (0.6%) exhibited incidental abnormal hypermetabolism of the prostate. The reasons for the 18F-FDG PET/CT scans are described in Table 1. Eight scans were performed for cancer screening (health check-up), and the remaining 98 were performed for staging or restaging of known non-prostatic malignancies.

Among the 106 cases with hypermetabolism of prostate, 66 patients underwent further evaluation by DRE, serum PSA, and TRUS (Table 2). Prostate biopsies were performed in 15 patients who had an abnormal palpable mass lesion (two patients) or a serum PSA level >4.0 ng/mL (13 patients). Prostate cancer was confirmed by biopsy in 11 patients (16.7% of the 66 patients who underwent further evaluation). There was one case of metastatic prostate carcinoma, and one case of metastatic lymphadenopathy. BPH was confirmed in the remaining four patients.

The clinical parameters of the benign and malignant groups were compared (Table 3). The median serum PSA levels were 4.8 ng/mL in the benign group, compared with 127.4 ng/mL in the malignant group. The SUVmax was higher in the malignant group than in the benign group, but the difference was not statistically significant (p=0.176). In addition, there was no significant correlation between serum PSA levels and Gleason score with SUVmax in

Table 1. Characteristics of 106 Patients with Incidental Hypermetabolism in Prostate

Reason for PET/CT	Number of patients
Colorectal cancer	36
Lung cancer	19
Gastric cancer	17
Cancer screening	8
Head and neck cancer	8
Unknown origin cancer	4
Hepatobiliary cancer	4
Urogenital cancer	4
Skin cancer	4
Bone tumor	2
Total	106

Table 2. Characteristics of 66 Patients with Incidental Hypermetabolism in Prostate Performed Further Evaluations

Characteristics		Value
Age (median, years)		68.2 (range 52-87)
Serum PSA level (ng/mL), median		27.4 (range 0.18-495.6)
SUVmax (median)		6.36 (range 2.1-24.5)
FDG uptake pattern	Discrete	60
	Diffuse	6
TRUS, volume (cc)		35.9

PSA: Prostate specific antigen, SUVmax: Maxumum standardized uptake value, FDG: Fluoro-2-deoxyglucose,TRUS: Transrectal ultrasonography

Table 3. Comparison between Benign and Malignant Groups

		Benign group (n= 4)	Malignant group (n=11)	p value
Age (median, years)		72 (range 64-81)	71.6 (range 61-87)	
Serum PSA level (ng/mL), median		4.8	127.4	0.04
	0-2.9	1	1	
	3.0-9.9	3	3	
	10.0-19.9	0	2	
	≥20.0	0	5	
SUV max (median)		4.3 (range 3.1-8.8)	10.1 (range 3.8-24.5)	0.078
FDG uptake pattern	Discrete	3	10	
	Diffuse	1	1	
Biopsy: Gleason score	6		0	
	7		3	
	≥8		8	
TRUS	volume (cc)	48	45	
	<30	2	3	
	≥30	2	8	
	calcification	4	8	

PSA: Prostate specific antigen, SUVmax: Maxumum standardized uptake value, FDG: Fluoro-2-deoxyglucose,TRUS: Transrectal ultrasonography

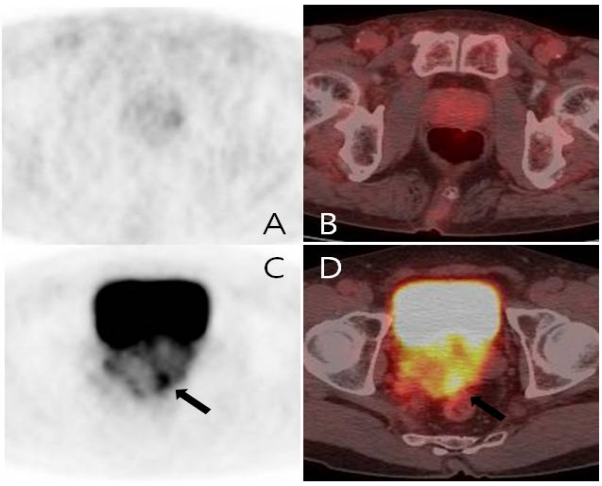

Figure 1. Hypermetabolism Pattern in a ^{18}FDG-PET/CT Scan of the Prostate. A diffuse uptake pattern on axial FDG PET images of the prostate and FDG PET/CT fusion images (A, B). A Discrete uptake pattern on axial FDG PET images of the prostate and FDG PET/CT fusion images (C, D)

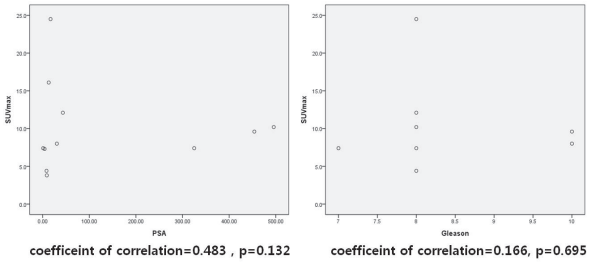

Figure 2. Correlation between Serum PSA, Gleason Score, and SUVmax in Patients with Malignancies according to Spearman's Correlation

all patients (r=0.483, p=0.132 and r=0.166, p=0.695, respectively) (Figure 2).

Discussion

PET/CT scans are a widely accepted tool for staging and assessing the response to cancer therapy, and 18F-FDG is the most widely using PET tracer in clinical oncology (Hasbek et al., 2014). It also can be useful for cancer screening and evaluating the whole body and detecting hypermetabolic malignant lesions. However, ^{18}F-FDG PET/CT scans do not play an important role in the primary diagnosis or staging of prostate cancer. This is because detecting prostate cancer using ^{18}F-FDG PET/CT scans is limited by urinary excretion of the radiotracer, as well as the low metabolic activity of prostate cancer (Powles et al., 2007). In addition, because the uptake of ^{18}F-FDG can result in a focal or diffuse pattern under benign conditions (prostatitis or BPH), it is difficult to distinguish malignant or benign lesions from abnormal prostatic uptake in ^{18}F-FDG PET/CT images (Hoh et al., 1998; Lawrentschuk et al., 2006; Kao et al., 2008).

When ^{18}F-FDG PET/CT scans detect incidental focal uptake in the prostate, it is unclear whether the patient should be further evaluated, the prostate should be biopsied, or no action should be taken. Several studies have addressed the incidental detection rate of prostate cancer (Han et al., 2010; Hwang et al., 2013). The incidence of abnormal focal hypermetabolism in the prostate gland in two previous studies was 1.2-1.5%. These studies reported that 3 of 55 patients (5.5%) and 23 of 120 (19.2%) were confirmed to have prostate cancer after further evaluation. In the current study, the incidence of abnormal hypermetabolism in the prostate was 0.6%, and 11 of 66 (16.7%) patients evaluated further were confirmed to have prostate cancer. The differences in the incidence of prostate cancer among studies could be attributable to the use of different confirmatory methods, and also to the fact that all patients with abnormal FDG uptake in the prostate underwent further evaluation using DRE, serum PSA and histologic confirmation.

The association between FDG uptake into lesions in the prostate and prostate cancer is controversial. In some reports, ^{18}F-FDG accumulation is correlated with malignancies rather than benign lesions because the increased FDG uptake is generally linked to elevated cell proliferation (Oyama et al., 1999; Minamimoto et al., 2011). Oyama et al. (1999) performed FDG-PET/CT imaging and assessed the time-activity curve of FDG accumulation (Kc). They reported that FDG-PET/CT could detect prostate cancer, and that the Kc value was higher than that of the Gleason score. Another study

performed in Japan reported that FDG-PET/CT scans could detect prostate cancer cases that had a high Gleason score (≥7). They performed a prospective study of 50 patients with high PSA scores who also underwent prostate biopsy, and revealed that the mean SUVmax was higher in true-positive cases (4.0±0.9) compared with false-positive cases (3.5±0.4) (Oyama et al., 1999).

In contrast, others reported that increased FDG uptake is generally not correlated with malignancy, consistent with the current study. Effert et al. performed FDG-PET on 48 patients with untreated prostate cancer, and concluded that it was not useful for differentiating prostate cancer from BPH (Effert et al., 1996). FDG accumulation in the prostate was positive visually in only 19% of patients with prostate cancer. Furthermore, they reported that FDG accumulation was not related to clinical stage or histological grade. The study by Effert et al. used continuous bladder irrigation with a Foley catheter to reduce the artifacts caused by residual urinary activity; however, this did not result in increased tumor uptake (Effert et al., 1996; Reinicke et al., 2012). This result could be explained by reports that prostate cancer uses hexoses other than glucose, such as fructose, preferentially. Glucose transport in human cells is mediated mostly by the mammalian faciliative hexose transporter GLUT family; FDG is taken up into cells by GLUT-1 (Godoy et al., 2006; Levi et al., 2007).

One study revealed that prostate cancer specimens express very low levels of GLUT-1. In BPH, GLUT-1 immunostaining was also detected at very low levels in the secretory/luminal epithelial cells, and was undetectable in stromal cells. In addition, GLUT-1 was undetectable in high-grade prostatic intraepithelial neoplasia and prostate cancer. These results suggest that carcinogenesis in prostate tissue is not associated with GLUT-1 expression, and therefore that glucose might not play an important role in maintaining prostate cancer cell metabolism (Reinicke et al., 2012). Consistent with this, an additional study examined resected prostate cancer tissues immunohistochemically using anti-GLUT-1 antibodies, and revealed only weak positive staining. These data also failed to show any correlation between GLUT-1 expression and Gleason score or cancer cell density (Minamimoto et al., 2011).

Consistent with the current study, several clinical reports revealed no significant difference in the ^{18}F-FDG activity of primary prostatic adenocarcinoma compared with BPH, and that the correlation coefficient between PSA levels and SUVmax was very low (Hofer et al., 1999; Shiiba et al., 2012).

Despite the lack of GLUT-1 transporter expression in the studies described above, it is possible that the increased FDG uptake into the prostate, which is related to increased glucose consumption, could be associated with elevated energy production from aerobic glycolysis, or that increased GLUT-1 expression is associated with neovascularization in response to hypoxia in the presence of adverse prognostic factors (Effert et al., 2004).

Because ^{18}F-FDG PET/CT is not sufficient to detect prostate cancer, many studies have assessed the use of non-FDG tracers, including ^{11}C-choline, ^{18}F-choline and ^{11}C-acetate (Hwang et al., 2013; Piccardo et al., 2014; Picchio et al., 2014). However, ^{11}C-acetate PET and ^{18}F-choline PET/MRI scans were useful only in prostate cancer patients with PSA recurrence, and not for detecting prostate cancer.

The current study had an important limitation. Not all patients underwent further evaluation, and histological confirmation was not performed in all cases of incidental abnormal FDG uptake. Therefore, the true incidence of prostate cancer could not obtained, and might be higher than reported here. Nevertheless, this study will facilitate determination of how incidentally abnormal uptake of ^{18}F-FDG PET/CT into the prostate should be interpreted. Although prostate hypermetabolism on ^{18}F-FDG PET/CT is not associated with prostate malignancy, such findings indicate that further clinical evaluations, such as PSA and DRE, should be performed.

In conclusions, ^{18}F-FDG PET/CT could not reliably differentiate malignant or benign tissues from abnormal uptake lesion in the prostate, and routine prostate biopsies are not usually recommended in all patients with abnormal FDG uptake. However, increased FDG uptake is generally linked to increased cellular proliferation. Therefore, these observations should not ignored, and the patient should undergo further clinical evaluations, such as PSA and DRE.

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