Differentiation of Tuberculous and Pyogenic Spondylitis Using Double Phase F-18 FDG PET

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Abstract: To assess the usefulness of double phase F-18 FDG PET in pyogenic spondylitis (PS) and tuberculous spondylitis (TS). Also, to investigate whether double phase F-18 FDG PET could improve the diagnostic accuracy for discrimination of PS from TS. Methods: Double phase F-18 FDG PET/CT was performed in a consecutive 23 patients (9 men, 14 women; mean age, 58.5±17.9 years, range, 19~81 years) suspected having spondylitis. PET/CT imaging was performed 60 and 120 minutes after injection of F-18 FDG.. Results: The SUV_{max1} of TS and PS showed no statistical differences (TS, 4.53±1.77; PS, 4.5±1.9, p=0.9515). The SUV_{max2} also showed no statistical differences between two groups (TS, 5.17±1.95; PS, 5.3±2.21, p=0.9321). The mean SUV of early and delayed F-18 FDG PET images revealed no statistical differences between TS and PS. The $\%\Delta SUV_{max}$ and $\%\Delta SUV_{mean}$ have no statistical differences between TS and PS ($\%\Delta SUV_{max}$, TS, 15.07±6.57%, PS, 18.79±10.48%, p=0.5109; $\%\Delta SUV_{mean}$, TS, 16.49±9.1%, PS, 16.88±6.72%, p=0.6524). Also, none of these quantitative indices could differentiate the TS from PS. Furthermore, none of these quantitative indices could predict the presence of TS. Conclusion: Based on the presented data, the quantitative indices of double phase F-18 FDG PET could not differentiate TS from PS despite of high sensitivity for the detection of spondylitis of F-18 FDG PET.

Keywords: Double phase, F-18 FDG PET, spondylitis.

INTRODUCTION

Infectious spondylitis is defined as an infection by a specific organism of one or more components of the spine, namely the vertebra, intervertebral discs, paraspinal soft tissues, and epidural space [1]. It represents 2~4% of all cases of osteomyelitis. Males are affected more frequently than females usually in the fifth to sixth decade, but it may appear in all age group [2].

Although infection can be caused by pyogenic, granulomatous, autoimmune, idiopathic, and iatrogenic conditions, pyogenic spondylitis is the most common spinal infection, and tuberculosis continues to be a major problem in developing countries and is resurgent in Western world with the onset of HIV [3].

The differentiation of pyogenic spondylitis (PS) and tuberculous spondylitis (TS) is important because the treatment is different and proper treatment of different types of spondylitis could reduce the rate of disability and functional impairment [3, 4]. Also, the delays in accurate diagnosis can lead to increased morbidity and mortality. However, the diagnosis of spinal infections could be difficult, because of the patient's history, subjective symptoms and physical findings are inconclusive.

Although magnetic resonance imaging (MRI) is the modality of choice for diagnosing spinal infection, whether it could be used for differentiation of PS from TS is still controversial [5, 6]. Some authors reported that TS has distinctive features on MRI and could be differentiated from PS [7, 8].

Fluorine-18 fluorodeoxyglucose positron emission tomography (F-18 FDG PET) has emerged as a significant molecular imaging technique in clinical oncology and cancer research [9-11]. Not only tumors but also infections and inflammatory processes show an increased F-18 FDG uptake. F-18 FDG PET has great potential in the evaluation of a variety of inflammatory and infectious disorders and possibly other benign disorders [12]. Although limited experiences in diagnosing spinal infection are available, recent preliminary study reported that F-18 FDG PET is a very sensitive imaging procedure in the detection of spondylodiscitis [13].

Recently, to better distinguish benign lesion from malignant diseases, some studies have made major findings using dual phase acquisition of F-18 FDG PET [14-16]. However, no other study has adopted the dual phase acquisition of F-18 FDG PET for the evaluation of infectious or inflammatory diseases including spondylitis.

A recent study showed relationship between F-18 FDG uptake in non-small cell lung caner and proliferating cell nuclear antigen (PCNA) [17]. PCNA is a 36-kDa nuclear protein that is produced in the late G1 and S phases in the cell cycle and acts as a co-protein of DNA polymerase δ. PCNA is regarded as a parameter for the proliferation ability of the tumor [18]. Also, PCNA has been implicated in autoimmunity. Approximately 3% of systemic lupus erythematosus patients express anti-PCNA autoantibodies [19]. A recent study reported that induction of PCNA in response to myco-

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bacterium tuberculosis may represent a pathogenically relevant mechanism in autoimmunity [20].

With these findings, we hypothesized that TS might represent different time course of F-18 FDG uptake compared to PS with dual phase acquisition of F-18 FDG PET. The current study was focused on assessment of double phase F-18 FDG PET findings in PS and TS. Also, we investigated whether double phase F-18 FDG PET could improve the diagnostic accuracy for discrimination of PS from TS.

METHODS

Patients

Double phase F-18 FDG PET/CT was performed in a consecutive 23 patients (9 men, 14 women; mean age, 58.5±17.9 years, range, 19~81 years) suspected having spondylitis on the basis of clinical symptomatology and imaging procedures such as radiography and bone scan. All 23 patients were operated and underwent histological confirmation.

F-18 FDG PET/CT

An F-18 FDG PET image was done with a dedicated PET/CT scanner (Gemini, Philips, Milpitas, CA, USA), consisting of a dedicated germanium oxyorthosilicate full-ring PET scanner and a dual slice helical CT scanner. Standard patient preparation included at least 8 hours fasting and a serum glucose level of less than 140 mg/dL before F-18 FDG administration. PET/CT imaging was performed 60 and 120 minutes after injection of F-18 FDG (mean dose, 383.7±47.4 MBq; range, 314.5~488.4 MBq). At 60 minutes (early images) after administration of F-18 FDG, low-dose CT (30 mAs, 120kV) covering area from the base of the skull to the proximal thighs was performed for the purpose of attenuation correction and precise anatomical localization. Thereafter, emission scan was conducted in the 3-dimensional mode. Emission scan time per bed position was 3 minutes; 9 bed positions were acquired. Delayed PET emission images of the affected spine were acquired at 120 min after administration of F-18 FDG, using 2 or 3 bed positions with a 3-min acquisition at each. This acquisition was immediately followed by a transmission scan of the same transverse planes, using a 2-min acquisition at each bed position. PET data were obtained using a high resolution whole body scanner with an axial field of view of 18 cm. The average axial resolution varied between 4.2 mm full width at half maximum (FWHM) in the center and 5.6 mm at 10 cm. The average total PET/CT examination time was 30 minutes. After scatter and decay correction, PET data were reconstructed iteratively with attenuation correction and reoriented in axial, sagittal, and coronal slices. The row action maximum-likelihood algorithm was used for 3-dimensional reconstruction.

F-18 FDG PET/CT Image Analysis

PET/CT data sets of early and delayed scans were evaluated by two nuclear medicine physicians with 11 years and 5 years of experience, respectively blinded to clinical and pathological results. Decisions concerning the analysis of F-18 FDG PET/CT data sets were reached by consensus. PET/CT data sets of early and delayed images were analyzed quantitatively by use of the SUV as index of F-18 FDG uptake. For quantitative analysis, all affected spine was evaluated by lesion-by-lesion analyses. Spherical regions of interest (ROIs) were placed over all affected spine lesions visible on PET images. The ROIs of lesions that were invisible on PET images were located by use of the corresponding CT images. ROIs were placed in the same area on the selected image for both of early and delayed images. The maximal SUV of early images (SUV_{max1}) and delayed images (SUV_{max2}) were calculated by manually drawing a region of interest (ROI) over the most intense slice of lesions visible on early and delayed PET images. Also, with these ROIs, mean SUV of early (SUV_{mean1}) and delayed images (SUV_{mean2}) calculated. From these quantitative indices, the % changes of SUV_{max} and SUV_{mean} were calculated as following equations:

% change of SUV_{max} ($\%\Delta SUV_{max}$)= (SUV_{max2}-SUV_{max1})/SUV_{max1} X 100

% change of SUV_{mean} ($\%\Delta SUV_{mean}$)= (SUV_{mean2}-SUV_{mean1})/SUV_{mean1} X 100

Statistical Analysis

All numerical results are reported as mean values with standard deviations. The association of PS and TS with various clinicopathologic features was evaluated using χ^2 test. Mann Whitney U test was used for statistical comparison of differences of quantitative indices between PS and TS. Receiver operating characteristic curve analysis (ROC) was used to determine optimal cut-off values of quantitative indices of double phase F-18 FDG PET for discrimination of PS and TS. The sensitivities, specificities, positive, and negative predictive values of double phase F-18 FDG PET according to quantitative indices were obtained and the standard errors, 95% confidence intervals and area under curves (AUCs) were also calculated. To determine the effect of quantitative indices of double phase F-18 FDG PET for the prediction of differentiation of PS and TS, logistic regression analyses were performed. Initially, univariate logistic regression was used to test for associations between variables estimated. After that, forward stepwise multiple logistic regressions were used to develop a prediction model. Variables were successively entered into the model if their effects were significant at $p < 0.05$. At each step, the variable with the lowest p value was included. Previously entered variables were excluded if their effects were no longer significant ($p > 0.1$) upon inclusion of a new variable. The final model was determined when no remaining variable had a significant effect ($p > 0.1$). Statistical significance was defined as $p < 0.05$.

RESULTS

Table **1** represents the individual data of affected spines of the patients including quantitative indices of double phase F-18 FDG PET, laboratory tests, and causative organisms. All of the patients had a histopathologically confirmed spondylitis as final diagnosis. A causative organism was found in 8 patients. Another 4 patients showed acid fast bacilli (AFB) stain positive results. In 10 patients with spondylitis, a causative organism was not found. Of these 10 patients, 3 had anti-tuberculous chemotherapy and 7 received antibiotic treatment before surgical intervention.

On visual assessment, all affected 43 spines revealed true positive findings in double phase F-18 FDG PET.

Table 1.

	Age	Sex	Dx	Location	SUV_{max1}	SUV_{max2}	$\%\Delta SUV_{max}$	SUV_{mean1}	SUV_{mean2}	$\%\Delta SUV_{mean}$	ESR	CRP	Culture
1	19	M	TB	L2	6	7.5	25.0	2.3	2.9	26.1	73	6.59	M.Tb
				L3	8.2	10	22.0	3.5	3.9	11.4			
				L4	5.4	6.3	16.7	2.2	2.7	22.7			
2	54	F	P	L3	7.4	8.6	16.2	2.7	3.4	25.9	96	18.64	E.coli
3	63	F		L4	2.3	2.6	13.0	1.2	1.5	25.0	120	19.45	
4	70	F	P	L2	3.1	4.3	38.7	2.3	2.8	21.7	99	0.96	No growth
5	75	F	P	L4	4	4.6	15.0	2.4	2.8	16.7	120	2.98	No growth
				L5	2.9	3.1	6.9	2.3	2.6	13.0			
6	34	M	TB	T8	5.4	5.9	9.3	3	3.3	10.0	67	2.2	No growth
				T9	4.3	4.9	14.0	2.8	3.4	21.4			
7	43	F	P	L4	4.1	5.2	26.8	1.8	2.2	22.2	26	5.64	Staphylococcus aureus
8	56	M	TB	L2	2.7	3.1	14.8	1.6	2.1	31.3	21	0.51	No growth
				L3	2.3	2.8	21.7	1.6	2.2	37.5			
9	34	F	TB	L2	3.8	4.7	23.7	2.4	2.7	12.5	95	3.19	M.Tb
				L3	2.8	3.3	17.9	1.4	1.7	21.4			
10	24	M	TB	L1	3.4	4.2	23.5	1.9	2.4	26.3	73	3.7	AFB(+)
11	81	F	TB	L2	4.8	5.2	8.3	2.5	2.6	4.0	82	2.4	AFB(+)
				L3	5.7	6.1	7.0	2.7	3	11.1			
12	75	F	P	L4	5.2	5.6	7.7	2.9	3.2	10.3	111	5.9	Streptococcus viridans
				L5	6.3	6.7	6.3	3.4	3.7	8.8			
13	78	F	P	T4	5	5.8	16.0	3.1	3.5	12.9	78	24.19	No growth
				T5	7.6	8.1	6.6	3.4	3.8	11.8			
14	73	M	TB	L3	2	2.3	15.0	1.4	1.7	21.4	81	11.8	No growth
15	65	M	P	L1	3.1	3.6	16.1	2.1	2.6	23.8	120	7.8	No growth
				L2	3.3	3.9	18.2	2.1	2.4	14.3			
				L3	2.9	3.3	13.8	2.3	2.7	17.4			
16	68	M	P	L4	3.4	4.1	20.6	2.4	2.7	12.5	27	0.44	No growth
17	76	F	TB	T12	7.1	7.3	2.8	3.8	4.3	13.2	102	4.18	M.Tb
				L1	7.2	7.3	1.4	3.1	3.2	3.2			
18	48	F	TB	T12	2.4	2.9	20.8	1.2	1.5	25.0	34	6.89	M.Tb
19	45	M	P	L2	3	4.1	36.7	1.7	2.1	23.5	48	3.6	No growth
20	59	F	TB	L1	5.8	6.8	17.2	3.3	3.5	6.1	NP	NP	AFB(+)
				L2	6.5	7.2	10.8	3.5	3.7	5.7			
21	69	F	TB	T7	2.7	3.1	14.8	2.1	2.4	14.3	50	4.91	AFB(+)
				T8	2.6	3.1	19.2	2.1	2.5	19.0			
				T12	4.6	5	8.7	2.5	2.7	8.0			
				L1	4.5	5.3	17.8	2.4	2.8	16.7			
				L2	4.2	4.8	14.3	2.7	3	11.1			
22	66	F	P	L2	5.5	5.9	7.3	2.9	3.1	6.9	120	6.74	No growth
				L3	9.4	11.8	25.5	4.3	4.6	7.0			
				L5	4.8	6.5	35.4	2	2.6	30.0			
23	72	M	P	L2	3.6	4.2	16.7	2.1	2.5	19.0	118	17.1	Staphylococcus aureus
				L3	3.1	4.1	32.3	2	2.3	15.0			

Comparison of Quantitative Indices of Double Phase F-18 FDG PET in TS and PS

Fig. (**1**) showed the differences of quantitative indices of double phase F-18 FDG PET between PS and TS. The SUV_{max1} of TS and PS showed no statistical differences (TS, 4.53±1.77; PS, 4.5±1.9, p=0.9515). The SUV_{max2} also showed no statistical differences between two groups (TS, 5.17±1.95; PS, 5.3±2.21, p=0.9321). The mean SUV of early and delayed F-18 FDG PET images revealed no statistical differences between TS and PS (SUV_{mean1}, TS, 2.43±0.72, PS, 2.47±0.7, p=0.8935; SUV_{mean2}, TS, 2.79±0.7, PS, 2.85±0.69, p=0.9321).

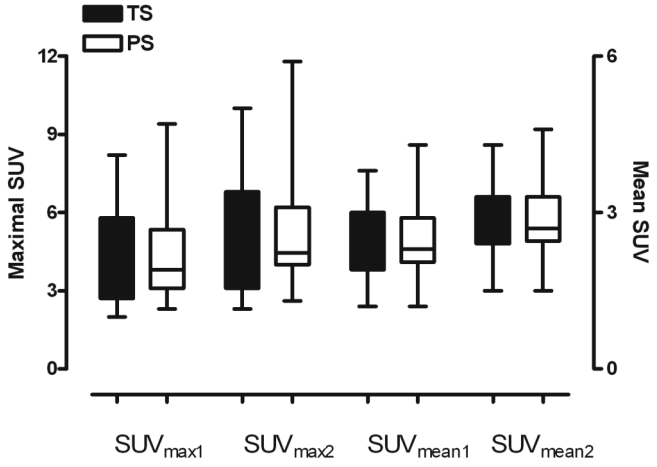

Fig. (1). The differences of SUV_{max} and SUV_{mean} between tuberculous and pyogenic spondylitis.

Fig. (**2**) represents the group differences of the $\%\Delta SUV_{max}$ and $\%\Delta SUV_{mean}$ between TS and PS. These quantitative indices have no statistical differences between TS and PS ($\%\Delta SUV_{max}$, TS, 15.07±6.57%, PS, 18.79±10.48%, p=0.5109; $\%\Delta SUV_{mean}$, TS, 16.49±9.1%, PS, 16.88±6.72%, p=0.6524).

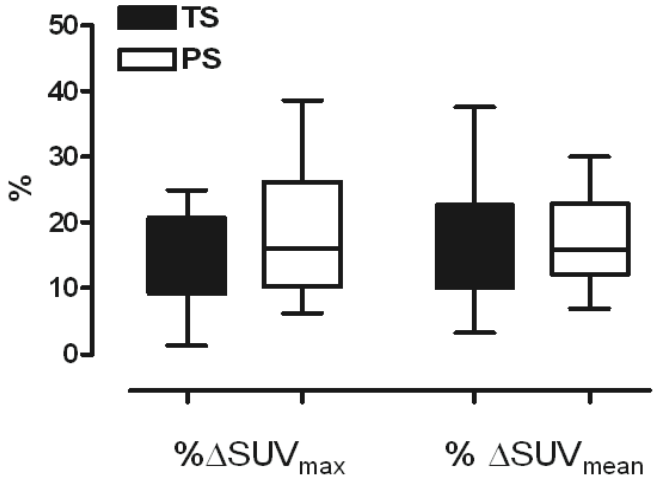

Fig. (2). The differences of $\%\Delta SUV_{max}$ and $\%\Delta SUV_{mean}$ between tuberculous and pyogenic spondylitis.

ROC Comparison of Quantitative Indices of Double Phase F-18 FDG PET for Discrimination of TS and PS

ROC comparison was performed whether the quantitative indices could differentiate the TS and PS. Table **2** reveals the results of ROC comparison between quantitative indices of double phase F-18 FDG PET for discrimination of TS and PS. None of these quantitative indices could differentiate the TS from PS.

Predictive Value of Quantitative Indices for TS and PS

Table **3** shows the potent predictors of quantitative indices of double phase F-18 FDG PET for differentiation of TS and PS.

Correlations of SUVmax and SUVmean Between Laboratory Tests

The quantitative indices reveal no statistically significant correlations with CRP and ESR in the current study (Table **4**).

DISCUSSION

In the current study, all of TS and PS showed increased F-18 FDG uptake with a high sensitivity. The lack of any other causes of F-18 FDG uptake in spine such as degenerative change or tumors restricts calculation of specificity. The quantitative indices of the double phase F-18 FDG PET did not show any statistical differences between TS and PS. Also, using these indices, the TS and PS could not be discriminated.

Skeletal manifestations of tuberculosis remain a major health problem in the world. No pathognomic radiographic appearance has been described in TS, and conclusive diagnosis cannot be made from imaging finding alone. Differential diagnosis between TS and PS is of clinical importance but may be of difficult on the basis of radiological findings alone.

Magnetic resonance imaging (MRI) has been reported to be useful in the early detection of spondylitis [21-23]. Previously, some authors have been attempted the possible role of MRI for discrimination of TS from PS and reported that TS has distinctive features on MRI and could be differentiated from PS [4, 7, 8]. Although rim enhancement of abscess on MRI is suggestive of TS [1, 4, 20], Jung *et al.* [7] reported that the most two reliable MRI findings suggesting TS were thin and smooth enhancement of the abscess wall and well-defined paraspinal abnormal signal. With these findings, they could differentiate TS from PS. However, they included small number of patients and more they could not obtained interobserver variablility and accuracy for discrimination of TS from PS. Although MRI is the modality of choice for diagnosing spinal infection, whether it could be used for differentiation of PS from TS is still controversial [5, 6].

The double phase acquisition of F-18 FDG PET was used in oncologic areas for differentiation of malignant from benign lesions in recent years [14-16]. Previously, Sahlmann *et al.* [24] described that dynamic dual time point F-18 FDG PET provides a characteristic pattern in chronic osteomyelitis similar to inflammatory processes. In their study, SUVs in patients with chronic osteomyelitis remained either stable or decreased over time in the majority of patients. They concluded that this pattern of dual time point F-18 FDG PET may be of value in the differentiation between chronic osteomyelitis and malignant bone disease. The current study adopted double phase method of F-18 FDG PET for discrimination of TS from PS. Although the double phase F-18 FDG PET had a high sensitivity for the detection of spondy-

Table 2. Pairwise Comparison of ROC Analyses of Quantitative Indices of Double Phase F-18 FDG PET for Discrimination of TS and PS

		SUV_{max1}	SUV_{max2}	$\%\Delta SUV_{max}$	SUV_{mean1}	SUV_{mean2}	$\%\Delta SUV_{mean}$
SUV_{mean1}	DBA	0.00652	0.0196	0.0707		0.00435	0.0522
	SE	0.056	0.0645	0.0893		0.0217	0.0639
	95% CI	-0.103~0.116	-0.107~0.146	-0.104~0.246		-0.0382~0.0469	-0.073~0.177
	p value	0.907	0.762	0.429		0.841	0.414
SUV_{mean2}	DBA	0.00217	0.0152	0.0663	0.00435		0.0478
	SE	0.0537	0.057	0.0989	0.0217		0.0805
	95% CI	-0.103~0.107	-0.096~0.127	-0.127~0.260	-0.038~0.046		-0.110~0.206
	p value	0.968	0.790	0.502	0.841		0.553
$\%\Delta SUV_{mean}$	DBA	0.0457	0.0326	0.0185			
	SE	0.0867	0.0967	0.0859			
	95% CI	-0.124~0.216	-0.157~0.222	-0.150~0.187			
	p value	0.598	0.736	0.830			

DBA; difference between areas, SE; standard error, CI; donfidence interval.

litis, unfortunately, the quantitative indices could not differentiate TS from PS in the current study.

Table 3. Logistic Regression Analysis of Quantitative Indices of Double Phase F-18 FDG PET for the Differentiation of TS from PS

Variable	Coefficient	Stanard Error	Odds Ratio	p Value
SUV_{max1}	0.1177	2.7078	1.1249	0.9653
SUV_{max2}	0.0565	2.2825	1.0582	0.9802
$\%\Delta SUV_{max}$	-0.0709	0.1199	0.9315	0.5542
SUV_{mean1}	6.9716	8.3709	0.0025	0.4049
SUV_{mean2}	-6.7900	7.1860	0.0011	0.3447
$\%\Delta SUV_{mean}$	0.1542	0.1748	1.1667	0.3778
Constant	0.00824			

The diagnosis of spinal infection usually relies on MRI findings, although bone scanning may help to determine the extent of the lesions. Gratz *et al*. reported that F-18 FDG PET performed better than MRI and bone scan in the detection of spinal infections [25]. Also, in 57 patients with suspected postoperative vertebral infections, including 30 who had metallic implants and 15 with a final diagnosis of vertebral infection, F-18 FDG PET had 100% sensitivity, 81% specificity, 65% positive predictive value, and 100% negative predictive value [26].

It is unclear why inflammatory and malignant lesions reveal a differential FDG uptake pattern over time. It has been reported that the rate of dephosphorylation of FDG-6-phosphate may be responsible for the different behavior of FDG uptake between malignant and benign lesions in dual-time FDG PET imaging [27]. Also, FDG uptake in benign lesions can be influenced by the cause and the state of acute or chronic inflammation [28]. Another assumption explains that the differences of FDG uptake could be influenced by the physiologic and immunologic state of cells and the type of inflammatory cells in the lesion [28]. Although this newly described dual time imaging of F-18 FDG PET seems to be effective method for distinguishing benign from malignant lesions, no other study has attempted to adopt the double phase F-18 FDG PET acquisition for differentiation of TS from PS.

CONCLUSION

Based on the presented data, the quantitative indices of double phase F-18 FDG PET could not differentiate TS from PS despite of high sensitivity for the detection of spondylitis of F-18 FDG PET.

Table 4. Correlations of Quantitative Indices of Double Phase F-18 FDG PET and Laboratory Results

		SUV_{max1}	SUV_{max2}	$\%\Delta SUV_{max}$	SUV_{mean1}	SUV_{mean2}	$\%\Delta SUV_{mean}$
CRP	Correlation coefficient	0.144	0.140	-0.0423	0.0315	0.0534	0.0313
	p value	0.3577	0.3702	0.7876	0.8413	0.7339	0.8419
ESR	Correlation coefficient	0.194	0.182	-0.116	0.221	0.216	-0.220
	p value	0.2124	0.2427	0.4599	0.1548	0.1638	0.1568

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