

## RESEARCH ARTICLE

# Clinical Value of Dual-phase $^{18}\text{F}$ -FDG SPECT with Serum Procalcitonin for Identification of Etiology in Tumor Patients with Fever of Unknown Origin

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### Abstract

**Objective:** The purpose of the study was to evaluate clinical value of dual-phase  $^{18}\text{F}$ -FDG SPECT with serum procalcitonin (PCT) in identifying cancers in patients with fever of unknown origin (FUO). **Methods:** PCT test and dual-phase  $^{18}\text{F}$ -FDG SPECT were sequentially performed on 50 consecutive patients with FUO. Two radiologists evaluated all  $^{18}\text{F}$ -FDG SPECT data independently. A consensus was reached if any difference of opinions existed. Final diagnosis was based on a comprehensive analysis of results for the PCT test, dual-phase  $^{18}\text{F}$ -FDG SPECT and bacterial cultivation, regarded as a gold standard. **Results:** Among 50 patients, 34 demonstrated PCT  $\geq 0.5 \mu\text{g/L}$ . Coincidence imaging showed in 37 patients with inflammatory lesions, and 13 with malignancy. Finally, 36 bacterial, 1 fungal and 1 viral infections, as well as 12 cancerous fevers were confirmed by dual-phase  $^{18}\text{F}$ -FDG SPECT with PCT, combined with bacterial cultivation and clinical follow-up. **Conclusion:** Our study demonstrated that dual-phase  $^{18}\text{F}$ -FDG SPECT in association with PCT could be a valuable tool for diagnosis in tumor patients with FUO.

**Keywords:** Tumor cases - fever of unknown origin - prediction - FDG SPECT - serum procalcitonin

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### Introduction

Fever is one of the most common symptoms in tumor patients, and identifying the etiology of FUO remains a continuous clinical challenge (Colpan et al., 2007; Sipahi et al., 2007). The significance of tests of white blood cells and neutrophils is decreased because of their low value due to long-term chemo radio therapy. Furthermore, the relatively long culture cycle and low positive rate make the new diagnostic methods urgent to identify the etiology in tumor patients with FUO. In the present study, the first step is to preliminary screen with PCT in tumor patients with FUO, positive patients should be highly suspected of bacterial infection; then all consecutive patients will be received dual-phase  $^{18}\text{F}$ -FDG SPECT examinations for the identification of the etiology. If possible, bacterial cultivation and drug sensitive test from the specimen are also taken to instruct application of the antibiotics reasonably. We reported here that dual-phase  $^{18}\text{F}$ -FDG SPECT in association with PCT is a useful test in the diagnosis of FUO of tumor patients.

### Materials and Methods

#### Patients

This study is a prospective analysis of 50 patients (29

men, 21 women) who underwent dual-phase  $^{18}\text{F}$ -FDG SPECT in association with PCT from May 2010 to May 2013. Criteria for inclusion were mono-symptomatic fever with a maximum above  $38.3^\circ\text{C}$  lasting for more than 3 weeks and lack of an established diagnosis after 1 week of diagnostic workup. All patients provided informed written consent for this study, which was approved by the local ethics committee. Age of the patients ranged from 14 to 89 years ( $55.7 \pm 17.1$ ).

#### Clinical evaluation of PCT levels

We measured the PCT levels in each patient. Serum PCT levels were quantitated by immunoassay (Elecsys BRAHMS PCT Procalcitonin). The lower and maximum limits of detection was  $0.5 \mu\text{g/L}$ .

#### $^{18}\text{F}$ -FDG SPECT scanning and diagnosis

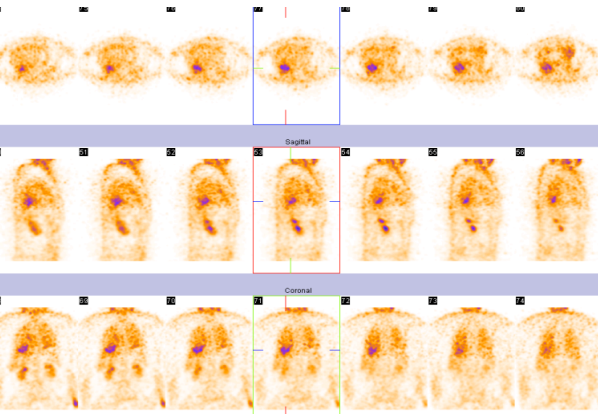
An integrated PET/CT scanner (Genesys SPECT, ADAC, USA) was used for data acquisition. Patients had to fast for at least 6 h before receiving intravenous injection of  $^{18}\text{F}$ -FDG. Blood glucose level was measured before injection and was less than  $7.8 \text{ mmol/L}$  for all patients. One hour after an intravenous injection of 240–259 MBq  $^{18}\text{F}$ -FDG, a low-dose CT scan, without contrast enhancement, between proximal femora and base of skull (two or three beds scanning included regions of neck,

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**Table 1. Case Number of <sup>18</sup>F-FDG SPECT and PCT**

Classification	Number	PCT (μg/L)	<sup>18</sup> F-FDG SPECT		
			Positive	Negative	
Bacterial infection (without tumor)	22	>0.5	19 cases	R<2.5 19	>2.5 3
Malignant tumor	12	<0.5	3 cases	R>2.5 11	<2.5 1
Viral infection	1	<0.5	12 cases		<2.5 1
Tumor with bacterial infection (tumor location)	15	<0.5	1 cases	R>2.5 13 (tumor)	
Total	50	>0.5	15 cases	R<2.5 11 (infection)	

Threshold value of PCT is 0.5μg/L. Non bacterial infection (PCT<0.5 μg/L), bacterial infection (PCT≥0.5 μg/L)



**Figure 1. Patient 1, Male, 50 Years Old, Had Sustained Fever More than 20 Days with a Posttumorectomy of Bladder.** With elevated WBCs counts and neutrophil differentials, he did not respond well to antimicrobial therapy. <sup>18</sup>F-FDG SPECT scan showed an abnormal circular radioactive concentrated area was shown in the back of right lobe of his liver, after 2 hours, the concentrated area was getting light up. Inflammatory foci were suggested in this case

chest, abdomen, inguinal region and head) was acquired for anatomic correlation. Subsequently, emission images of the same area were acquired.

#### <sup>18</sup>F-FDG SPECT data analysis

<sup>18</sup>F-FDG PET/CT images were evaluated by more than two independent physicians of nuclear medicine. The most concentrated area (T) in the target lesion was checked using computer and defined as region of interest (RoI). Then copy the same size of RoI in healthy tissue of contra lateral position or adjacent area (NT), and calculate the value of R ratio (T/NT=R value). The R value of <2 was considered as the inflammatory/infectious lesion, and the R value of >2.5 was malignant lesion. For visual analysis: the increased uptake of <sup>18</sup>F-FDG in the delayed imaging suggested a malignant lesion, otherwise, decreased or disappeared <sup>18</sup>F-FDG imaging at the delayed imaging stage suggested benign lesion (inflammation).

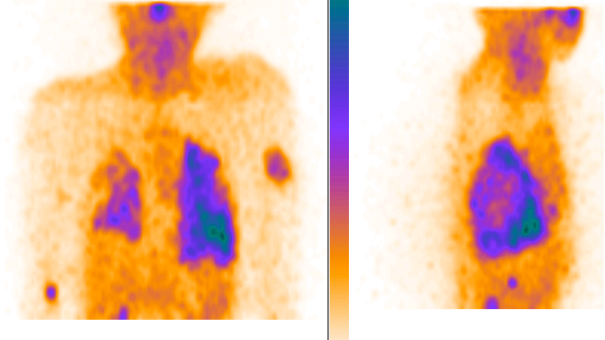
#### Statistical processing

The data between groups were compared by using McNemar test. Data were analysed by SPSS 16.0 for Windows and comparisons between groups were done using AVONA test. *P*<0.05 was considered significant.

### Results

#### Results of PCT testing

Among 50 patients, 34 patients were detected PCT



**Figure 2. Patient 1, Male, 47 Years Old, Had Sustained Fever More than 50 days with a History of Nasopharyngeal Carcinoma.** He had a bad respond to antimicrobial therapy. <sup>18</sup>F-FDG double phase imaging showed that abnormal radioactive concentration area appeared in his nose and right arm. Two hours left, the concentration has no obvious fades. It suggested the possibility of malignant disease. At the same time, abnormal accumulation of radioactivity was seen in both lungs, the left one is significant. After 2 hours, the concentration zone fades, suggesting the possibility of inflammation

≥ 0.5 μg/L, and 16 patients < 0.5 μg/L (as seen in Table 1). PCT positive patients were finally diagnosed as follows: 1 liver abscess with 20μg/L (postoperative bladder Figure 1); 1 metastatic kidney neoplasms with infection; 1 nasopharyngeal carcinoma with infection (Figure 2); 1 myeloma with infection; 1 mammary cancer with infection; 1 oophoroma with infection; 1 cancerous goiter with infection; 2 laryngocarcinoma with infection; 2 pancreatic cancer with infection; 2 prostatic cancer with infection; 4 liver cancer with infection; 4 colon cancer with infection; 5 lymphadenoma with infection; 8 lung cancer with infection. In 16 PCT negative patients, 2 patients were false negative with lung cancer, 1 prostatic cancer with mycotic infection, 1 viral infection, the rest 12 patients were all cancerous fever. PCT has a positive predictive value of 94.4% (34/36) for bacterial infection.

#### Results of <sup>18</sup>F-FDG SPECT

Dual-phase <sup>18</sup>F-FDG SPECT were sequentially performed on 50 consecutive patients, data was checked using computer and defined as RoI for visual analysis. 37 patients were tumor with infection; 13 patients were simple malignant lesions: 1 lymphadenoma with viral infection, the rest 12 cancerous fever.

#### Diagnostic relevance of the results between <sup>18</sup>F-FDG SPECT and PCT

By McNemar test (as seen in Table 2), diagnostic results between <sup>18</sup>F-FDG SPECT and PCT are in good

**Table 2. Correlation Analysis of  $^{18}\text{F}$ -FDG SPECT and PCT**

PCT	$^{18}\text{F}$ -FDG SPECT		Kappa	P
	Benign (infectious)	Malignant		
Benign (infectious)	19	4	0.616	0.001
Malignant	4	11		

agreement (Kappa = 0.616), in other words, the two methods of diagnostic results between benign and malignant are in good agreement.

## Discussion

Incidence of cancer keeps increasing with ageing of population, environmental pollution and food problems (Zhao et al., 2012; Chen et al., 2013). Fever in tumor patients, which will cause a steady deterioration due to increased depletion, is common because of long-term chemoradiotherapy and suppressed immunity (Canyilmaz et al., 2013; Engin et al., 2013; Unal et al., 2013; Wang et al., 2013). Thus, a fast and accurate test is specially needed for defining the etiology of FUO. Because of the specificity of tumor patients, it is difficult to differentiate the bacterial infection. On the other side, the bacterial cultivation has a relatively long culture cycle and low positive rate. The identification of etiology of tumor patients with FUO, the confirmation of infected areas and pathogen, the choice and course period of antibiotics, all of the above need a specialist in FUO, and a accurate, reliable, and practicable diagnostic method.

Procalcitonin is a peptide precursor of the hormone calcitonin. It is composed of 116 amino acids and has a half-life of 20 to 24 hours. The level of procalcitonin in the blood stream of healthy individuals is below the limit of detection of clinical assays (Hammer et al., 2000). The level of procalcitonin rises in a response to a proinflammatory stimulus, especially of bacterial origin. Measurement of procalcitonin can be used as a marker of severe sepsis caused by bacteria and generally grades well with the degree of sepsis. Procalcitonin levels may be useful to distinguish bacterial infections from nonbacterial infections (Assicot et al., 1993; Becker et al., 2008). They may help guide therapy and reduce antibiotic use, which can help save on cost of antibiotic prescriptions and drug resistance (Viallon et al., 2005; Celebi et al., 2006; Watkin et al., 2007).

$^{18}\text{F}$ -fluoro-2-deoxy-D-glucose ( $^{18}\text{F}$ -FDG) has been shown to accumulate in malignant tumours owing to their increased glucose metabolism and has been used extensively with PET for tumour imaging. It has been recognised for some time that FDG may accumulate not only in malignant tissues but also in inflammatory processes. This characteristic is a source of false-positive results in oncological diagnosis; however, it can also be positively used for the diagnosis of inflammatory diseases (Suqawara et al., 1998; Stumpe et al., 2007). Several clinical studies of FDG-PET for the diagnosis of inflammatory diseases, such as FUO, rheumatoid arthritis, spondylitis, large vessel vasculitis, and inflammatory bowel disease have been reported recently. The application

of  $^{18}\text{F}$ -FDG might be especially helpful for localizing the focus of inflammation through the whole-body scanning of FUO patients (Meller and Becker, 2001; Keidar et al., 2008). Some preliminary data show that PET and SPECT are increasingly used to diagnose, characterize, and monitor disease activity in the setting of inflammatory disorders of known and unknown etiology (Dumarey et al., 2006; Jaruskova and Belohlavek, 2006).

Among 50 tumor patients, 38 cases were benign fever (36 bacterial infectious), the rest 12 cases were malignant fever. PCT, which was detected positive in 34 patients, 2 false negative, had a positive predictive value of 94.4% for bacterial infection. Among 36 bacterial infectious patients, bacterial cultivation, which was detected positive in 23 patients, had a positive predictive value of 63.9%, which is obviously lower than the predictive value of dual-phase  $^{18}\text{F}$ -FDG SPECT in association with PCT. Unaffected by antibiotics, high determination speed, PCT has a obvious advantage over bacterial cultivation. Lower cost than PET/CT,  $^{18}\text{F}$ -FDG SPECT is more acceptable for the developing countries. Therefore, dual-phase  $^{18}\text{F}$ -FDG SPECT in association with PCT can play an effective role for early diagnosis and assessment to identify the etiology in tumor patients with FUO.

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## References

- Assicot M, Gendrel D, Carsin H, et al (1993). High serum procalcitonin concentration in patients with sepsis and infection. *Lancet*, **341**, 515-8.
- Becker KL, Snider R, Nylen ES (2008). Procalcitonin assay insystemic inflammation, infection, and sepsis: clinical utility and limitations. *Crit Care Med*, **36**, 941-52.
- Canyilmaz E, Serdar L, Uslu GH, et al (2013). Evaluation of prognostic factors and survival results in pancreatic carcinomas in Turkey. *Asian Pac J Cancer Prev*, **14**, 6573-8.
- Celebi S, Koner O, Menda F, et al (2006). Procalcitonin kinetics in pediatric patients with systemic inflammatory response after open heart surgery. *Intensive Care Med*, **32**, 881-7.
- Chen WQ, Liang D, Zhang SW, et al (2013). Pancreatic cancer incidence and mortality patterns in china, 2009. *Asian Pac J Cancer Prev*, **14**, 7321-4.
- Colpan A, Onquru P, Erbay A, et al (2007). Fever of unknown origin analysis of 71 consecutive cases. *Am J Med Sci*, **334**, 92-6.
- Dumarey N, Egrise D, Blocklet D, et al (2006). Imaging infection with  $^{18}\text{F}$ -FDG-labeled leukocyte PET/CT: initial experience in 21 patients. *J Nucl Med*, **47**, 625-32.
- Engin H, Bilir C, Tekin IO (2013). Prognostic significance of peripheral blood flow cytometry parameters in patients with non-metastatic breast cancer. *Asian Pac J Cancer Prev*, **14**, 7645-9.
- Hammer S, Meisner F, Dirschedl P, et al (2000). Procalcitonin for differential diagnosis of graft rejection and infection in patients with heart and/or lung grafts. *Intensive Care Med*, **26**, S182-6.
- Jaruskova M, Belohlavek O (2006). Role of FDG-PET and PET/CT in the diagnosis of prolonged febrile states. *Eur J Nucl*

- Med Mol Imaging*, **33**, 913-8.
- Keidar Z, Gurman-Balbir A, Gaitini D, et al (2008). Fever of unknown origin: the role of  $^{18}\text{F}$ -FDG PET/CT. *J Nucl Med*, **49**, 1980-5.
- Meller J, Becker W (2001). Nuclear medicine diagnosis of patients with fever of unknown origin (FUO). *Nuklearmedizin*, **40**, 59-70.
- Sipahi OR, Senol S, Arsu G, et al (2007). Pooled analysis of 857 published adult Fever of unknown origin cases in Turkey between 1990-2006. *Med Sci Monit*, **13**, 318-22.
- Stumpe KD, Dazzi H, Schaffner A, et al (2007). Infection imaging using whole body FDG-PET. *Eur J Nucl Med*, **27**, 822-32.
- Suqawara Y, Braun DK, Kison PV, et al (1998). Rapid detection of human infections with fluorine-18 fluoro-deoxyglucose and positron emission tomography: preliminary results. *Eur J Nucl Med*, **25**, 1238-43.
- Unal OU, Oztop I, Unek IT, et al (2013). Two-week combination chemotherapy with gemcitabine, high-dose folinic acid and 5 fluorouracil (GEMFUFOL) as first-line treatment of metastatic biliary tract cancers. *Asian Pac J Cancer Prev*, **14**, 5263-7.
- Viallon A, Guyomarch P, Guyomarch S, et al (2005). Decrease in serum procalcitonin levels over time during treatment of acute bacterial meningitis. *Crit- Care*, **9**, 334-50.
- Wang JY, Cai Y (2013). Clinical observation and prognostic analysis of pemetrexed plus platinum as first-line treatment in patients with advanced non-small cell lung cancer. *Asian Pac J Cancer Prev*, **14**, 6267-71.
- Watkin RW, Harper LV, Vernallis AB, et al (2007). Pro-inflammatory Cytokines IL-6, TNF-alpha, IL1beta, procalcitonin, lipopolysaccharide Binding protein and c-reactive protein in infective endocarditis. *Clin Rrs Cardiol*, **96**, 413.
- Zhao J, He YT, Zheng RS, et al (2012). Analysis of esophageal cancer time trends in China, 1989- 2008. *Asian Pac J Cancer Prev*, **13**, 4613-7.