Does dual-time-point ^{18}F-FDG PET/CT scan add in the diagnosis of hepatocellular carcinoma?

Bing Wu[1,2,3] **MD,**
Yanzhao Zhao[1,2,3] **MD,**
Yiqiu Zhang[1,2,3] **MD,**
Hui Tan[1,2,3] **MD,**
Hongcheng Shi[1,2,3] **MD, PhD,**

1. Department of Nuclear Medicine, Zhongshan Hospital, Fudan University, Shanghai, 200032, China
2. Nuclear Medicine Institute of Fudan University, Shanghai, 200032, China
3. Shanghai Institute of Medical Imaging, Shanghai, 200032, China

Keywords: ^{18}F-FDG PET/CT -Dual-time-point -Delayed scan -Hepatocellular carcinoma

Corresponding author:
Hongcheng Shi MD, PhD
No. 180, Fenglin Road,
Xuhui District, Shanghai
Tel.: 00862164041990-2064
shi.hongcheng@zs-hospital.sh.cn

Received:
4 January 2017
Accepted revised :
3 March 2017

Abstract

Objective: The aim of this study was to evaluate the usefulness of dual-time-point ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT) with semiquantitative analyses for patients with hepatocellular carcinoma (HCC). **Subjects and Methods:** The 150 patients with clinically suspected liver malignancies underwent dual-time-point ^{18}F-FDG PET/CT imaging. The maximum standardized uptake value (SUVmax) was calculated at both time points of PET imaging. The change in SUV max (retention index, RI) was defined as the ratio of increase in SUVmax between the early and delayed scans to the SUVmax in the early scan. The tumor-to-normal liver tissue (T/N) ratio of the early and delayed scan was also calculated. The final diagnoses were confirmed by histopathology. A hundred and twenty four patients had HCC, 4 with grade I, 64 with grade II, 55 with grade III and 1 with grade IV. Twenty six patients had benign liver diseases. **Results:** There were significant differences in the SUVmax and T/N between the early scan and the delayed scan in the HCC Group (t=4.23, P<0.01; t=6.02, P<0.01). There were no significant differences in the SUVmax or T/N of the early and delayed scans in the benign Group (t=1.20, P=0.24; t=1.63, P=0.12). There was no significant difference in the RI of the HCC Group and that of the benign Group (t=0.52, P=0.60). The SUVmax of the delayed scan was significantly higher than that of the early scan for both Groups (t=3.01, P<0.01 for grade III Group; t=2.93, P<0.01 for grade II Group). Significant differences were detected between the grade III Group and the grade II Group for the SUVmax on the early scan and the delayed scan (t=2.15, P<0.01 for early scan; t=2.11, P<0.01 for the delayed scan). There were no significant differences between the grade III and grade II Groups for the retention index of SUVmax (RI-SUVmax) (t=0.06, P=0.95). The T/N ratio on the delayed scan was significantly higher than that on the early scan for both Groups (t=4.21, P<0.01 for grade III Group; t=4.44, P<0.01 for grade II Group). Significant differences were also detected between the grade III and grade II Groups for the T/N ratio on the early and delayed scans (t=2.69, P<0.01 for the early scan; t=2.06, P<0.01 for the delayed scan).**Conclusion:** Dual-time- point ^{18}F-FDG PET/CT scan with semiquantitative analysis of SUVmax and T/N ratio may support the diagnosis of non-invasive HCC indicating its grade of malignancy.

Hell J Nucl Med 2017; 20(1): 79-82 *Epub ahead of print: 20 March 2017* *Published online: 20 April 2017*

Introduction

Hepatocellular carcinoma (HCC) is one of the five most common cancers worldwide. Positron emission tomography (PET) using ^{18}F-flurordeoxyglucose (^{18}F-FDG) has become the standard procedure for detecting a variety of malignant tumors. However, several reports suggest that the sensitivity of ^{18}F-FDG PET/computed tomography (CT) (50%-55%) for detecting HCC is insufficient [1]. Recently, many studies have used dual-time-point acquisition of ^{18}F-FDG PET/CT to improve differentiation between benign and malignant tumors [2, 3]. However, few studies have applied this technique for the detection of HCC. The objective of this study was to retrospectively investigate the value of dual-time-point ^{18}F-FDG PET/CT for the detection of HCC.

Subjects and Methods

Subjects

Patients with suspected liver malignancies underwent the dual-time-point ^{18}F-FDG PET/CT during June 2010 to December 2012. The inclusion criteria were: Patients who did not receive any treatment before ^{18}F-FDG PET/CT was performed and received surgery within

4 weeks of the PET scan; diagnosis of HCC was based on histological examination. There were no metastases. Patients' characteristics are shown in Table 1.

PET imaging

The PET studies were performed using a combined PET/CT machine (Discovery VCT, GE Medical Systems, Milwaukee, Wisconsin, USA). All patients were imaged after fasting for a minimum of 6h except for water and medications. All patients were required to have less than 7mmol/L blood sugar prior to injection. We injected intravenously ^{18}F-FDG in a dose of 5.1MBq/kg. Whole-body imaging commenced 60min after the injection of ^{18}F-FDG. Scanning was performed with the patient in a supine position with arms over the head. Scanning was initiated with a diagnostic CT scan (200mAs, 140kV, 3.75mm slice thickness) covering the thorax with attenuation correction. Scanning with PET was performed over the same region immediately following the CT scan and consisted of 6-7 bed positions with 2min per table position in 3-D mode. Delayed scanning (including CT and PET), began approximately 118.3±18.6min after ^{18}F-FDG injection and acquired images from only the upper abdominal cavity. Data sets from PET images were reconstructed iteratively using a row-action maximum likelihood algorithm, including segmented correction for attenuation using the CT data. The images were reconstructed and displayed in three dimensions (axial, sagittal, and coronal).

Imaging data analysis

Two experienced nuclear medicine physicians who were unaware of the histological results interpreted all of the PET/CT findings by consensus. For both scans, the following parameters were determined using the same image scale: the SUVmax of each lesion (SUV1, SUV2) and an average SUV for normal liver tissue. Furthermore, we calculated RI-SUVmax from SUVmax according to the following formula: RI-SUVmax (%)=[SUV2-SUV1]x100/SUV1. The tumor to normal liver tissue (T/N) ratio was calculated using the following equation: T/N ratio=SUV of tumor/average SUV of normal liver tissue. The circular region of interest (ROI) was placed on the transaxial images according to the corresponding CT images. The ROI was placed the same peripheral position of the liver in the first and delayed scans.

Statistical analysis

Data were analyzed with the SPSS statistical package (SPSS Windows, version 19.0). Metric data, such as age, maximum SUV of lesions, mean SUV of normal liver tissue, and T/N ratio, are expressed as mean±standard deviation (SD). Nominal data are presented as percentages. Furthermore, a 95% confidence interval for differences in paired proportions was calculated. To assess differences in T/N ratios of the two scans, paired t-tests were performed. A P-value<0.05 was considered to indicate a statistically significant result.

Results

Population

Patient characteristics, including age, sex and histological grade, are summarized in Table 1.

Table 1. *Characteristics of patients*

Characteristics	Number of patients
Age (means±SD)	51.3±11.3(16-80)
Sex (male/female)	129/21
Histological results	
HCC/ Benign	124/26
Granulomatous lesions	10
Cirrhosis regenerated nodular	8
Angiomyolipoma	5
Angiocavernoma	3
Histological grade of HCC	
Grade I/ II	4/64
Grade III/IV	55/1

SUVmax, RI-SUVmax and T/N ratio

Table 2 shows SUV1, SUV2, and RI-SUVmax values for the entire study group.

There was 38.5% (10/26) of cases' SUVmax increased in delayed scan in the benign lesion group, while 50.8% (69/124) of cases' SUVmax increased in delayed scan in the HCC group.

Table 2. *SUVmax values and RI-SUVmax of the study*

	HCC (n=124)	Benign lesions (n=26)	P value
SUV1	3.82±2.61	3.03±1.25	0.02
SUV2	4.22±3.18	3.25±1.58	0.02
P value	P<0.01	P=0.24	
RI-SUVmax (%)	9.52±24.98	6.29±29.47	0.60

HCC: hepatocellular carcinoma; SUV1: SUVmax of early scan; SUV2: SUVmax of delayed scan; RI: Retention Index

Table 3 shows the T/N ratio for the study group. There were 73.4% (91/124) HCC cases' RI>1 in the early scan, while 79.0% (98/124) HCC cases' RI>1 in the delayed scan.

Table 4 shows the SUVmax and RI-SUVmax according to the histological grade of HCC. The SUVmax and RI-SUVmax increased as the tumor grade increased.

Table 3. *T/N ratio of the study*

	T/N (early scan)	T/N (delayed scan)	P value
HCC (n=124)	1.74±0.98	2.02±1.28	<0.01
Benign lesion (n=26)	1.43±0.52	1.63±0.74	0.12
	P=0.02	P=0.04	0.60

HCC: hepatocellular carcinoma; T/N: SUVmax of tumor to normal liver tissue

Table 4. *SUVmax and RI-SUVmax of different histological grades of HCC*

	Grade I (n=4)	Grade II (n=64)	Grade III (n=55	Grad e IV (n=1)
SUV1	2.40± 0.42	3.37± 1.98	4.39± 3.14	5.4
SUV2	2.27± 0.36	3.67± 2.36	4.89± 3.88	11.1
RI-SUVmax (%)	-4.76± 4.78	9.13± 23.97	9.38± 25.53	105.6
Diameter（cm）	1.55± 0.59	3.69± 2.28	4.66± 3.38	6.67

SUV1: SUVmax of early scan; SUV2: SUVmax of dealyed scan; RI: Retention Index

Because of the small number of cases of grade I and grade IV tumors, we only compared the differences between the grade II and grade III Groups to reduce statistical bias. There were significant differences for SUV1 (t=2.15, P<0.01), SUV2 (t=2.11, P<0.01), T/N (early scan) (t=2.69, P=0.01), and T/N (delayed scan) (t=2.06, P=0.01) between the grade II and grade III Groups. However, no significant differences in RI were identified between the grade II and grade III Groups (P= 0.95). The majority of abnormal ^{18}F-FDG uptake showed higher SUVmax values on the delayed scans compared to the early scans. There were 68.8% (44/64) of cases with abnormal ^{18}F-FDG uptake in the grade II Group and 74.5% (41/55) of cases with abnormal FDG uptake in the grade III Group.

Discussion

Several investigators have reported the initial results of dual-time- point imaging in patients with malignant tumors [4-6]. Earlier reports have noted the advantages of dual-time-point ^{18}F-FDG PET/CT for the detection of hepatic metastases [7, 8]. Dirisamer et al. (2008) reported increased ^{18}F-FDG uptake in hepatic metastases with an SUVmax of 6.59 on the one-hour image to 8.09 on the two-hours image [8]. Lee et al. (2011) reported that the SUVmax of hepatic metastases increased from 6.0 on the one-hour scan to 7.0 on the two-hours scan [9]. However, few reports have described the value of dual-time-point ^{18}F-FDG PET/CT scanning in patients with HCC. In our study, the SUVmax increased in both groups, but showed a significant difference only in the HCC group.

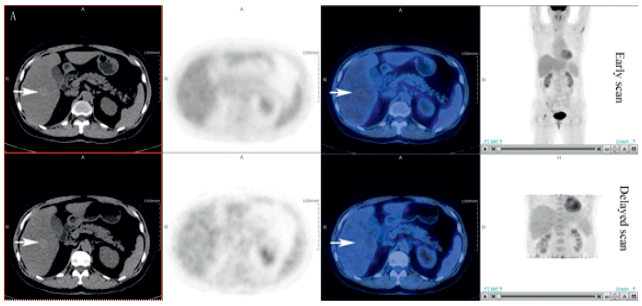

Figure 1A. Female, 49 years old. There was a high-density nodule in the right lobe. Early scan SUVmax: 2.3, delayed scan SUVmax: 2.2, RI-SUVmax:-4.3%. Histopathological diagnosis: cavernous angioma.

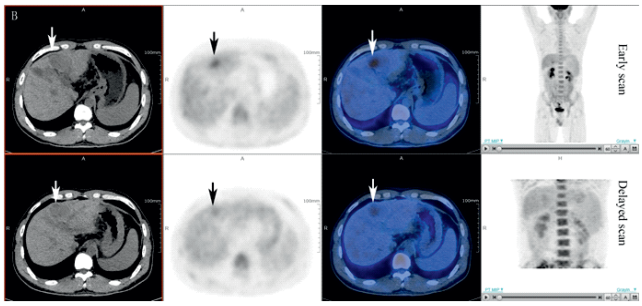

Figure 1B. Male, 36 years old. There was a low-density nodule in left lobe. Early scan SUVmax: 3.6, delayed scan SUVmax: 2.1, RI-SUVmax:-40.0%. Pathological diagnosis: HCC, grade II.

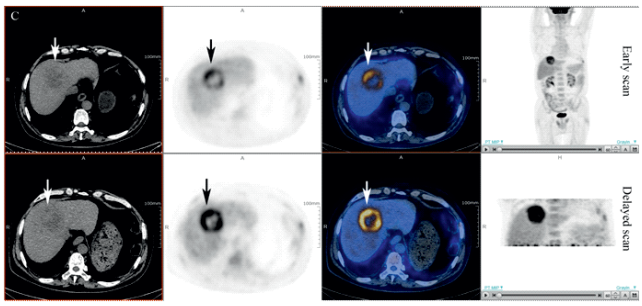

Figure 1C. Male, 66 years old. There was a low-density nodule between the right lobe and the left lobe. Early scan SUVmax: 5.4, delayed scan SUVmax: 11.1, RI-SUVmax: 105.6%. Histopathological diagnosis: HCC, grade IV.

Delayed imaging of ^{18}F-FDG has been reported to be useful for increasing the T/N ratio, as ^{18}F-FDG may gradually accumulate in tumor tissue with reduced accumulation in tu-

mor tissue with reduced accumulation in normal liver tissue. Therefore, tumors may be more clearly visualized by ^{18}F-FDG PET/CT on a delayed scan. Koyama et al. (2002) reported that visual improvements were observed in 6 of 18 HCC lesions based on imaging. In quantitative analysis, the T/N ratio increased from 1.9 at 1h to 2.2 at 2h, but the difference was not significant [10]. Lin et al. (2005) also reported that the T/N ratio increased from 1.56 at 1h to 1.68 at 2h [11]. In our study, we found that the T/N ratio increased over time in both Groups, but there was a significant difference only in the HCC Group. A potential reason that delayed imaging the ability to diagnose HCC may be that the liver is the site of glycogen storage; thus, the liver may accumulate in time more ^{18}F-FDG than other organs. Metabolic trapping through phosphorylation by hexokinase is the rate-limiting step for intracellular ^{18}F-FDG retention. This process can be reversed by glucose-6-phosphatase. Interestingly, normal tissue cells contain high levels of glucose-6-phosphatase, whereas malignant tumor cells have low levels of this enzyme but high levels of hexokinase [12].

We found that the SUV1 and SUV2 were significantly higher in the grade III Group than in the grade II Group, although there was no statistically significant difference in RI-SUV max. In our study, SUVmax correlated the pathological degree of differentiation; a higher SUVmax corresponded to a lower degree of differentiation. However, RI-SUVmax was not indicative of differentiation in this study and in-depth analysis may require a larger sample set. In China, HCC usually develops secondary to liver cirrhosis and HCC generally evolves in a step-wise process from regenerative nodules, dysplasia-differentiated nodules, well-differentiated nodules, and finally to poorly differentiated nodules. During this process, angiogenesis and changes in tumor blood supply cause alterations in the uptake of ^{18}F-FDG in tumor lesions. Some studies report that well-differentiated HCC often shows false negative results from ^{18}F-FDG PET imaging [12]. For most malignancies, Glut-1 plays a major role in the metabolism of ^{18}F-FDG; however, HCC cells express very little or no Glut-1 on their cell membrane [13, 14].

In conclusion, our study demonstrated that dual-time-point ^{18}F-FDG PET/CT scan showed higher uptake and T/N ratio thus supporting the diagnosis of HCC. There was higher ^{18}F-FDG uptake in indicating poorly differentiated HCC (grade III) than that of well-differentiated HCC (grade II). However, increase in SUVmax was not an independent determinant of HCC diagnosis. Therefore, ^{18}F-FDG PET/CT may be an effective diagnostic tool for the non-invasive diagnosis of HCC indicating its grade of malignancy. Further studies with a larger number of subjects are warranted.

Bibliography

1. Ho CL, Cheung MK, Chen S, et al, (^{18}F) fluoroacetate positron emission tomography for hepatocellular carcinoma and metastases: an alternative tracer for (^{11}C) acetate? *Mol Imaging* 2012; 11: 229-39.
2. Houshmand S, Salavati A, Segtnan EA et al, Dual-time-point Imaging and Delayed-time-point Fluorodeoxyglucose-PET/Computed Tomography Imaging in Various Clinical Settings. *PET Clin* 2016; 11: 65-84.
3. Saleh FH, Mohamed SM, Nasr HA, M.A. Abdelaziz, Dual time point fluorodeoxyglucose positron emission tomography/computed tomography in differentiation between malignant and benign lesions in cancer patients. Does it always work? *Indian J Nucl Med* 2015; 30: 314-9.
4. Subramanyam P, Palaniswamy SS, Dual Time Point ^{18}F-FDG PET/CT Imaging Identifies Bilateral Renal Tuberculosis in an Immunocompromised Patient with an Unknown Primary Malignancy. *Infect Chemother* 2015; 47: 117-9.
5. Pasha AK, Walsh TK, Ampel NM, Dual-Time-Point FDG PET/CT to Distinguish Coccidioidal Pulmonary Nodules from Those Due to Malignancy. *Lung* 2015; 193: 863-4.
6. Lohmann P, Herzog H, Rota KE, et al, Dual-time-point O-(2-[^{18}F]fluoroethyl)-L-tyrosine PET for grading of cerebral gliomas. *Eur Radiol* 2015; 25: 3017-24.
7. Miyake KK, Nakamoto Y, ogashi K, Dual-time-point ^{18}F-FDG PET/CT in patients with colorectal cancer: clinical value of early delayed scanning. *Ann Nucl Med* 2012; 26: 492-500.
8. Dirisamer A, Halpern BS, Schima W, et al, Dual-time-point FDG-PET/CT for the detection of hepatic metastases. *Mol Imaging Biol* 2008; 10: 33-5-40.
9. Lee JW, Kim SK, Lee SM, et al, Detection of hepatic metastases using dual-time-point FDG PET/CT scans in patients with colorectal cancer. *Mol Iaging Biol* 2011; 13: 565-72.
10. Koyama K, Okamura T, Kawabe J, et al, The usefulness of ^{18}F-FDG PET images obtained 2 hours after intravenous injection in liver tumor. *Ann Nucl Med* 2002; 16: 169-76.
11. Lin WY, Tsai SC, Hung GU, Value of delayed ^{18}F-FDG-PET imaging in the detection of hepatocellular carcinoma. *Nucl Med Commun* 2005; 26: 315-21.
12. Sacks A, Pelle PJ, Surasi DS, et al, Value of PET/CT in the management of primary hepatobiliary tumors, part 2. *Am J Roentgenol* 2011; 197: W260 -W265.
13. Tagliabue L, Del SA, Appropriate use of positron emission tomography with [^{18}F]fluorodeoxyglucose for staging of oncology patients. *Eur J Intern Med* 2014; 25: 6-11.
14. Amann T, Maegdefrau U, Hartmann A, et al GLUT1 expression is increased in hepatocellular carcinoma and promotes tumorigenesis. *Am J Pathol* 2009; 174: 1544-52.