Nuclear Science and Techniques **23** (2012) 169–175

Clinical value of ^{18}F-FDG PET/CT in evaluation of hepatic vein, inferior vena cava and right atrium tumor thrombi in hepatocellular carcinoma：Initial results

SUN Long ZHAO Long LUO Zuoming JIANG Maoqing WU Hua*

Minnan PET Center and Department of Nulear Medicine, No.1 Hospital Affiliated to Xiamen University, Xiamen 361003, China

Abstract In this paper, eleven consecutive hepatocellular carcinoma (HCC) patients with an embolus in the hepatic vein (HV), inferior vena cava (IVC)and right atrium (RA) were studied with ^{18}F-FDG PET/CT and contrast enhanced CT. When correlated with final diagnosis, ^{18}F-FDG PET/CT and contrast enhanced CT was positive in 11 patients (100%), 7 patients (63.6%), respectively. The accuracy of PET/CT and contrast-enhanced CT were 100%, 63.6%. Three cases with secondary blood thrombi in the distant IVC, which were confirmed by PET/CT, cannot be identified by contrast enhanced CT. The average survival was 3 months (range, 1-12mo). The 12 months survival rate was 9.1%. Our results suggest that highly metabolic tumor thrombus in the HV, IVC and RA may be depicted on ^{18}F-FDG PET/CT in HCC patients. It may discriminate between malignant and secondary benign blood thrombi.

Key words Hepatocellular carcinoma, Contrast-enhanced CT, Positron emission tomography/computed tomography, Hepatic vein tumor thrombus, Right atrium, Tumor thrombus

1 Introduction

Hepatocellular carcinoma (HCC), a common solid malignancies, tends to invade the intrahepatic vasculature, but encroachs rarely into the inferior vena cava (IVC) and right atrium (RA)[1]. Presence of neoplastic thrombus serves as a major determinant of tumor staging and prognosis, and thus affects the treatment choice[2]. The patients generally have a poor prognosis, as tumor proliferation is often rapid and accompanied by lung metastases, Budd-Chiari syndrome, intrahepatic metastases, acute upper gastrointestinal hemorrhage, refractory ascites, and finally, acute liver function failure. Such patients usually have palliation or experimental treatment[3,4].

Although the reference standard is pathologic examination, in clinical practice, diagnostic imaging plays a pivotal role[5]. In previous works[6,7], we demonstrated the potential value of ^{18}F-fluorodeoxyglucose PET/CT (^{18}F-FDG PET/CT) in HCC diagnosis, discriminating benign and malignant portal vein thrombi. To the authors' knowledge, studies on the role of ^{18}F-FDG PET/CT in HCC patients with hepatic vein (HV), IVC and RA tumor thrombi have not been reported so far. In this paper, we focus on evaluating the value of ^{18}F-FDG PET/CT combining with contrast-enhanced CT in diagnosis tumor thrombi and discriminating blood thrombi, by recognizing metabolic neoplastic activities and macromorphological characteristics.

2 Materials and methods

2.1 Patients

The 11 patients were aged 36–76 in a mean age of 52.2, and nine of them were male. The standard for ultimate diagnosis of HCC consisted of histopathological confirmation or clinical and imaging results. Three (27.3%) of the patients had received surgical resection or interventional treatment before PET/CT scan, while eight (72.7%) of the patients had not received any treatment. Five patients (45.5%) underwent transcatheter arterial chemoembolization after PETC/CT examination, while the other six patients (54.5%) were given liver protective medication until discharged, without any anti-tumor drugs.

Supported by National Science Foundation for Young Scholars of China (Grant No. 81101067)

* Corresponding author. *E-mail address:* wuhua1025@163.com

Received date: 2011-10-21

2.2 PET/CT and contrast enhanced CT technique

The patients were asked to fast for at least 4 h before undergoing ^{18}F-FDG PET/CT. Their blood glucose level should be within the normal range (70–120 mg/dL) prior to intravenous injection of ^{18}F-FDG. The patients received an intravenous injection of 370–666 MBq (10–18 mCi) of ^{18}F-FDG. Data acquisition by an integrated PET/CT system (Discovery STE; GE Medical Systems, Milwaukee, WI, USA) was performed within 45 min after injection.

Liver contrast enhanced CT was performed using the same PET/CT system with high-quality scanning mode, thickness 5 mm, 120 kV, 250mA. The contrast medium was 80 mL Ultravist 300 and the velocity was 3 mL/s. The PET/CT procedure of data acquisition was as follows: CT scanning was performed first, at 110 kV 110 mA and tube rotation time of 0.5 s, with a 3.3-mm section thickness, which was matched to the PET section thickness. PET acquisition time was 3 min per table position. PET image data sets were reconstructed iteratively by applying the CT data for attenuation correction, and coregistered images were displayed on a workstation.

2.3 Diagnoses of hepatic vein tumor thrombus

On integrated PET/CT images, thrombi were considered malignant if the maximum standardized uptake value (SUV) was greater than those of normal liver structures with a discrete margin and/or the ^{18}F-FDG uptake was greater than that of the lumen of the descending aorta in the same axial slice. Thrombi were considered benign if the maximum SUV was lower than those of normal liver structures and/or the ^{18}F-FDG uptake was lower than that of the lumen of the descending aorta in the same slice. Patients were followed-up monthly by CT or MRI. Shrinkage of the thrombus, recanalization of the vessels, stabilized thrombus on CT or MRI during follow-up were of definitive evidence of benign nature of the thrombosis, whereas enlargement of the thrombus, disruption of the vessel wall, and parenchymal infiltration over follow-up were consistent with malignancy.

3 Results

3.1 Patients and hepatic diseases

The most common cause of HCC was complicated with hepatic B virus infection (91%, 10/11). Marked edema in the lower extremities and marked venous dilatation in the abdominal wall were observed in 2 cases (18.1%) and 1 cases (9.1%), respectively. Macroscopically, 5(45.5%) cases of HCC primary lesions were massive type, multinodular type in 4 (36.4%) cases, and diffuse type in 2 (18.1%) cases. In 9 cases, primary tumors were located in right lobe.

According to the Chlid-Pugh classification, 5 patients were Chlid-Pugh A (45.5%), 3 patients each were Chlid-Pugh B (27.3%) and Chlid-Pugh C (27.3%). Lung metastases were identified in 5 patients (45.5%). Patients' characteristics are given in Table 1.

Table 1 Patient characteristics

Parameters		Values
Mean age (yr)		52.2 (36–76)
Gender	Male	9/11(81.8%)
	Female	2/11(18.1%)
Mean follow up months after PET/CT		3(1–12)
Hepatic B virus infection		10/11(91%)
Marked edema in the lower extremities		2/11(18.1%)
Marked venous dilatation in abdominal wall		1/11(9.1%)
Liver function	Chlid-Pugh A	5/11 (45.5%)
	Chlid-Pugh B	3/11(27.3%)
	Chlid-Pugh C	3/11(27.3%)

Table 2 Characteristics of tumor thrombi

Tumor thrombi characteristics	*n* / %
Massive type	5/11(45.5%)
Multinodular type	4/11(36.4%)
Diffuse type	2/11(18.1%)
Right lobe	9/11(81.8%)
Lung metastasis	5/11(45.5%)
Contrast CT findings	
Filling defect,	7/11(63.6%)
Enhancing and filling defect, expansile	4/11(36.4%)
AVF	4/11(36.4%)
Characteristics of tumor thrombi	
Hepatic vein thrombi	4/11(36.4%)
HV to IVC	3(27.3%)
HV to RA	2/11(18.1%)
HV to RV	1/11(9.1%)
Massive type	5/11(45.5%)
Multinodular type	4/11(36.4%)
Diffuse type	2/11(18.1%)
Right lobe	9/11(81.8%)
Lung metastasis	5/11(45.5%)
IVC to RA	1/11(9.1%)
T/NT SUVmax ratio >2.0	11/11(100%)
Complicated with portal vein tumor thrombi	9/11(81.8%)
Complicated with blood thrombus	3/11(27.3%)
Complicated with bile duct thrombi	1/11(9.1%)
Overall survival / months	3(1–12)

SUV: Standardized uptake value; T: Tumor target; NT: Non tumor target

3.2 HV, IVC and RA tumor thrombi

PET/CT was positive in 11 patients (100%). When correlated with final diagnosis, which was confirmed by histopathology in 3 (27.3%) patients and by clinical follow-up in 8 (72.7%). Macroscopically, tumor thrombi of most cases demonstrated a nodular growth pattern. Characteristics of tumor thrombi are summarized in Table 2.

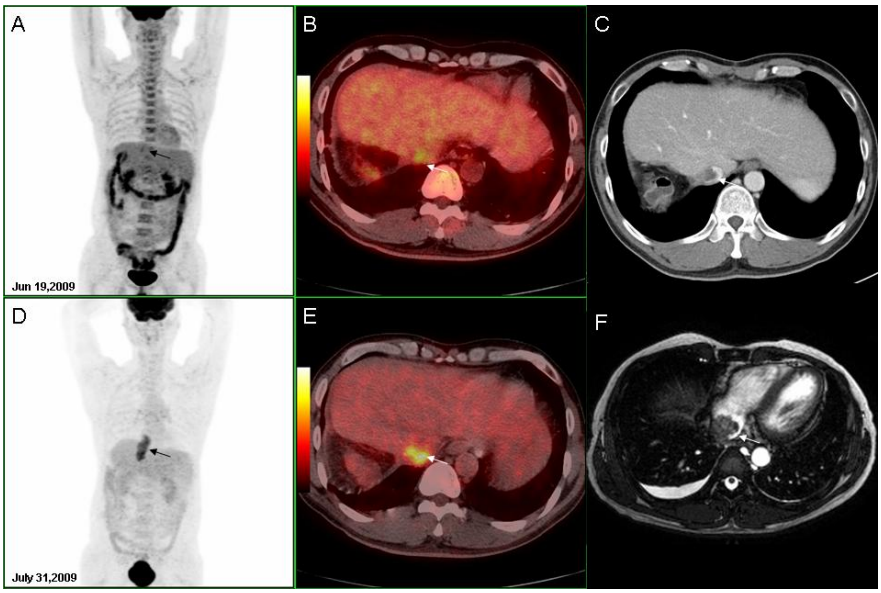

Fig.1 A 51-year-old man with a progress tumor thrombus in the IVC 5 mo after right lobe HCC resection. Contrast enhanced CT indicates a benign filling defect in the IVC without enhancing and expansile IVC lumen (arrows in C). PET and fused PET/CT imaging reveal a mild highly metabolic tumor thrombus in the IVC (arrows in A, B). The tumor thrombus progressed in 1 mo PET/CT and MRI follow-up (arrows in D, E and F).

Continuous tumor thrombi involving the HV, IVC and RA were seen in 2 (18.1%) cases. Continuous tumor thrombi involving from HV to IVC were seen in 4 (36.4%) cases. Tumor thrombus involving the HV alone was present in 4 (36.4%) cases. A tumor thrombi extended from IVC to RA was detected in 1 patient (Fig.1). In one cases, the tumor bolus originated from HV to RA crossed the tricuspid valve and entered the right ventricle (Fig.2).

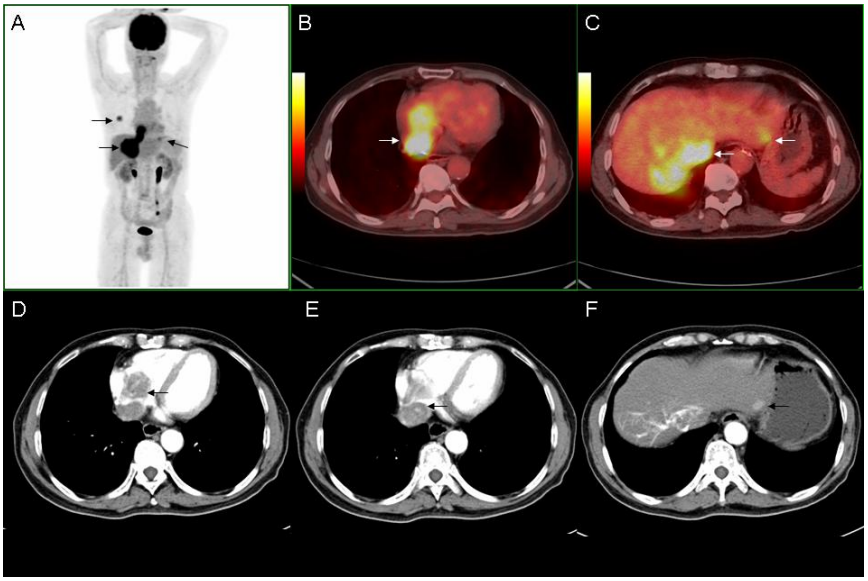

Fig.2 The same man in Fig.1, with continuous tumor thrombus involving the hepatic vein, IVC, right atrium and ventricle. PET reveals a highly metabolic thrombus in hepatic vein, inferior vena cava, right atrial and ventricle, lung and left lobe metastases (arrows in A, B and C,), which is verified by contrast enhanced CT (arrows in D, E and F).

3.3 HV, IVC and RA tumor thrombi complicated with blood thrombus

In 3 (36.4%) cases, tumor thrombi complicated with the blood thrombi in distant IVC (Figs.2 and 3). In one patient, tumor thrombi complicated with lung artery blood.

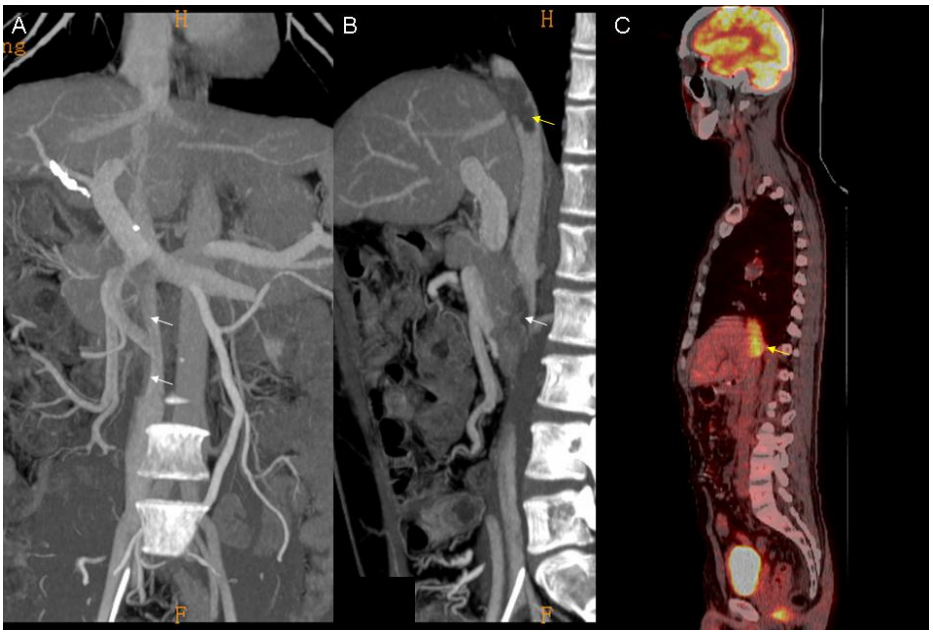

Fig.3 Complicated with distant IVC blood thrombus in the same case in Fig 1. Contrast enhanced CT shows tumor thrombus in the distant IVC (arrows in A, B). PET/CT displays low metabolic blood thrombus in the distant IVC, which is confirmed by imaging follow up (arrows in C).

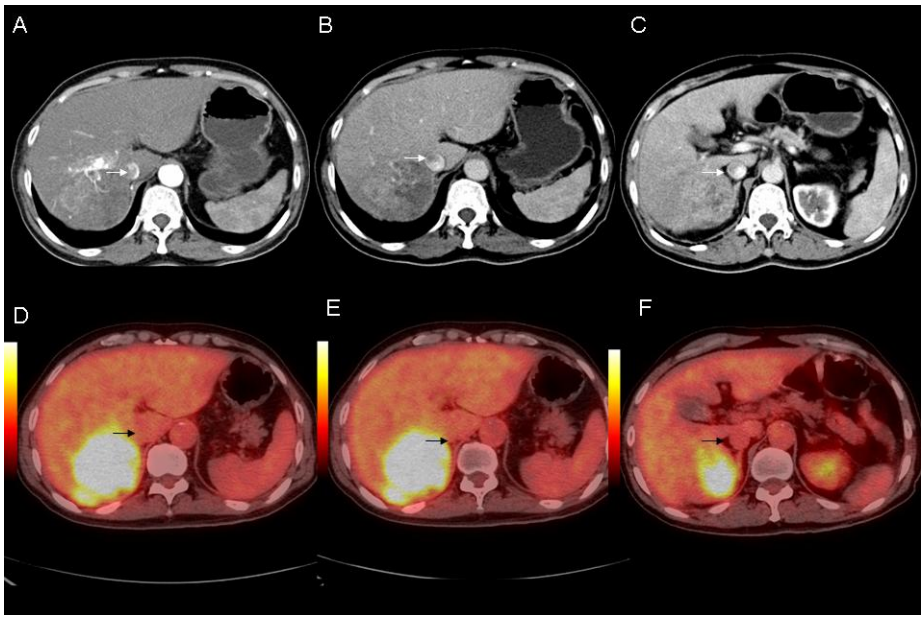

Fig.4 Complicated with IVC blood thrombus in the same case in Fig 2. Contrast CT scan displays right lobe mass and the IVC thrombus in the same patient. A filling defect was detected in the distant IVC (arrows in A, B and C). PET/CT fused images reveal no highly metabolic thrombus in the distant IVC, which is confirmed by imaging follow up (arrows in D, E and F).

3.4 HV, IVC and RA tumor thrombi complicated with portal vein tumor thrombi

In 9(81.8%) cases, hepatic vein, inferior vena cava or right atrial tumor thrombi complicated with portal vein thrombi (Fig.5). One patient with a continuous tumor thrombus involving from hepatic vein to the IVC complicated with tumor thrombi in common bile duct, which induced jaundice.

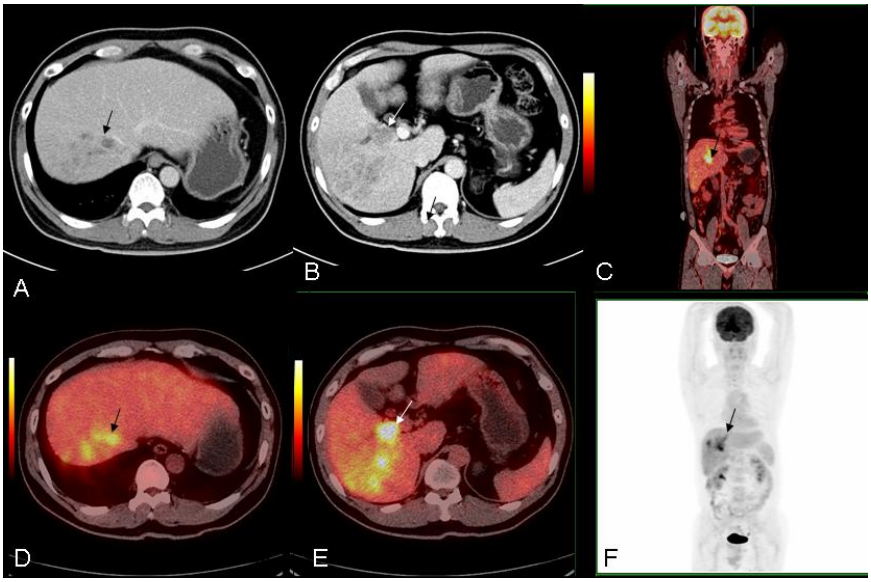

Fig.5 A 60-year-old man complicated with portal vein tumor thrombi. Contrast CT scans shows filling defect in right hepatic vein and right portal vein (arrows in A, B). PET/CT image reveals highly metabolic thrombi in right hepatic vein and right portal vein (arrows in C, D, E and F).

3.5 FDG PET/CT vs contrast-enhanced CT

In 7/11(63.6%) cases, contrast-enhanced CT image showed only filling defects in hepatic vein, inferior vena cava or right atria. In 4/11(36.4%) cases, contrast-enhanced CT image showed typical expansile filling defects in hepatic vein, IVC and/or RA with mild enhancing. contrast-enhanced CT demonstrated arteriovenous fistula (AVF) in 4/11(36.4%), but contrast CT could not different complicated blood thrombi in distant IVC in 3 (36.4%) patients.

^{18}F-FDG PET/CT and contrast enhanced CT were positive in 11 patients (100%), 7 patients (63.6%), respectively. When correlated with final diagnosis, which was confirmed by histopathology in 3 patients and by follow-up in 8. The accuracy of PET/CT and contrast-enhanced CT were 100%, 63.6%. Three cases with secondary blood thrombi in the distant IVC, which were confirmed by PET/CT, cannot be identified by contrast enhanced CT.

3.6 Survival time

The average survival was 3 months (1–12). The 12 months survival rate was 9.1% (1/11).

4 Discussion

The detection and etiologic characterization of vein thrombi are essential for treatment planning[8]. Invasion of venous systems indicates not only a poor prognosis but also a contraindication for further treatment[9,10]. Our findings in the present study demonstrated HV to RA tumor thrombi is a frequent complication of advanced HCC, especially those with diameters larger than 3.0 cm, multinodular tumors, which located in right lobe. The formation of the tumor embolus had a growth process. Firstly, the tumor perforated, involving the wall of the HV and/or IVC. Then the tumor extended into the lumen of the vein and grew there. The tumor within the lumen can grow upward, and if it grows upward, and thus it may get into the RA and continue slow growth there[11]. Cheng *et al.*[12] reported when the tumor thrombus extended IVC, which can grow upward and/or downward. But in our cases, there was no tumor thrombus growing downward along the IVC lumen.

Biopsy of portal vein thrombus relies on the skills of the radiologist and the size of the affected vein, which associated risks of metastases, insufficient samples for pathology evaluate and bleeding[13,14]. Contrast CT increase the detection rate of vein tumor thrombus by its contrast enhancement features in cross-sectional images[15]. However, all the noninvasive techniques currently used are imperfectly able to differentiate vein tumor thrombus from blood thrombus. Relying exclusively on contrast enhancement characteristics to make a conclusion runs the risk of misdiagnosis due mainly to the intrinsic

limitations of the imaging modalities themselves[16,17]. The reported increased sensitivity of ^{18}F-FDG PET/CT over CT has been attributed to the ability of the former to detect metabolic abnormalities that precede the morphologic changes seen by conventional image[18,19]. Our preliminary studies have already highlighted the potential value of ^{18}F-FDG PET/CT in discriminating benign and malignant portal vein thrombi[6,7].

HV thrombosis can be detected no invasively by CT. Typical appearances of venous thrombosis include an intraluminal filling defect, peripheral ring-like enhancement and collateral venous channels[20,21]. Only about 36.4% cases could be found typical CT features in this group of patients. In 7/11(63.6%) cases, contrast CT image showed only filling defects in hepatic vein, inferior vena cava or right atrial. In 4/11 (36.4%) cases, contrast CT image showed typical expansile filling defects in hepatic vein, inferior vena cava or right atrial with mild enhancing. Contrast CT demonstrated AVF in four cases, but contrast CT could not different complicated blood thrombi in the distant IVC in three patients.

^{18}F-FDG as a radiotracer has some advantages in evaluation of hepatic malignancies, such as diagnosing, staging and restaging tumors, evaluating biologic characters[22]. PET/CT is getting more and more widely applicable in clinical practice with combined functional and anatomical images. Tumor thrombus differentiates itself from blood thrombus by its intense uptake of ^{18}F-FDG as a result of its high metabolic neoplastic activity[23,24]. Continuous tumor thrombi involving the HV, IVC and RA were seen in 2 (18.1%) cases. Continuous tumor thrombi involving from HV to the IVC were seen in 4 (36.4%) cases; HV tumor thrombi alone was present in 4 (36.4%) cases; tumor thrombi extended from IVC to RA in 1 (9.1%) patient. In one (9.1%) cases, the tumor bolus originated from HV to RA crossed the tricuspid valve and entered the right ventricle.

About 70% patients with HCC have HV and portal vein (PV) invasion, with the frequency of PV invasion being much more than that of HV invasion, but encroachment into the RA is very rare[25,26]. HCC encroachment into the RA may not be an overt symptom. However, when the embolus obstructs the tricuspid orifice and coronary sinus opening, it may result in a severe hemodynamic disorder. This can include venous engorgement of upper extremities and the chest, hydroncus, pleural effusion, and flustered[27]. When the IVC is obstructed, engorgement of the veins of the lower extremities will appear, leading quickly to Budd-Chiari syndrome, and in this situation the prognosis of patients is very bad[28]. In this initial clinical experience, HV, IVC or RA tumor thrombi complicated with portal vein tumor thrombi in nine (81.8%) cases. Three (36.4%) patients were detected tumor thrombi in RA with obvious symptom.

Jaundice is present in 19-40% of patients with HCC at the time of diagnosis and usually occurs in advanced stages of diseases. The etiology of jaundice is mainly due to diffuse tumor infiltration of liver parenchyma, progressive liver failure and hepatic hilar invasion. Obstructive jaundice caused by bile duct tumor thrombi arising from HCC is rare[29,30]. One patient with a continuous tumor thrombus involving from hepatic vein to the IVC complicated with tumor thrombi in common bile duct, which induced jaundice. Many kinds of cancer including HCC can induce hypercoagulability. Tumor thrombi extended into the IVC, the blood speed became slower, which resulted blood thrombus in distant IVC[31,32]. In this initial clinical experience, ^{18}F-FDG PET/CT appears to be a reliable technique for evaluating the veins system thrombus. The main advantage of ^{18}F-FDG PET/CT over conventional imaging techniques is its ability to assess the ^{18}F-FDG metabolism activity of vein thrombi. In 3 (36.4%) cases, tumor thrombi complicated with the blood thrombi in distant IVC and lung artery blood thrombi in one (9.1%) patient, which confirmed by imaging follow-up after treatment.

In HCC patients, HV, IVC and RA tumor thrombi are not uncommon findings and are usually associated with extremely poor outcome[33]. Surgical interventions as well as nonsurgical approaches, such as transcatheter arterial chemoembolization and radiotherapy, have been used in the treatment of patients with symptomatic tumor thrombi. However, such therapeutic modalities are usually not feasible when a patient shows poor general performance, the presence of metastatic disease, and underlying hepatic dysfunction[34]. Such patients show limited survival. The average survival was 3 months (range, 1-12 mon). The 12 months survival rate was 9.1% in the study.

There are several limitations in this study. Firstly, we did not use pathologic findings as our reference standard for characterizing the thrombi. Next, the small sample size may have limited the robustness of our study in terms of statistics. Finally, because of the retrospective nature of our study, we were unable to obtain baseline clinical and laboratory data in some of the patients, except for one patient who accepted two PET/CT scans during his treatment.

5 Conclusion

In conclusion, the increased sensitivity of PET/CT over CT has been attributed to the ability of ^{18}F-FDG PET/CT to detect metabolic abnormalities that precede the morphologic changes seen by CT. ^{18}F-FDG PET/CT scan may provide valuable information for discriminating between highly metabolic malignant thrombus and lowly metabolic secondary blood thrombi in the HV, IVC and RA. Patients may benefit from ^{18}F-FDG PET/CT when vein thrombi cannot be diagnosed exactly by conventional image. However, further studies are needed to confirm the ability of ^{18}F-FDG PET/CT to evaluate the HV, IVC and RA tumor thrombi. The potential of this novel approach to characterize the veins of a portal system thrombus should be elucidated in large, ongoing clinical trials.

References

1 Agelopoulou P, Kapatais A, Varounis C, *et al*. Hepatogastroenterology, 2007, **54**: 2106−2108.

2 Lazaros G, Samara C, Nikolakopoulou Z, *et al*. Acta Cardiol, 2003, **58**: 563−565.

3 Sung A D, Cheng S, Moslehi J, *et al*. Am J Cardiol, 2008, **102**: 643−645.

4 Kitayama D, Yoshidome H, Mitsuhashi N, *et al*. Hepatogastroenterology, 2004, **51**: 1326−1329.

5 Lazaros G**,** Samara C, Nikolakopoulou Z, *et al*. Acta Cardiol , 2003, **58**: 563−565.

6 Sun L, Guan Y S, Pan W M, *et al*. World J Gastroenterol, 2008, **14**: 1212−1217.

7 Sun L, Wu H, Pan W M, *et al*. World J Gastroenterol, 2007, **1**3: 4529−4532.

8 Rossi S, Rosa L, Ravetta V, *et al*. Am J Roentgenol, 2006, **186**: 763−773.

9 Tarantino L, Francica G, Sordelli I, *et al*. Abdom Imaging, 2006, **31**: 537−544.

10 Hemming AW, Reed AI, Langham MR Jr, *et al*. Ann Surg, 2004, **239**: 712−719.

11 Ohwada S, Takahashi T, Tsutsumi H, *et al*. Hepatogastroenterology, 2008, **55**: 903−906.

12 Cheng H Y, Wang X Y, Zhao G L, *et al*. World J Gastroenterol, 2008, **14**: 3563−3568.

13 Sorrentino P, D'Angelo S, Tarantino L, *et al*. World J Gastroenterol, 2009, **15**: 2245−251.

14 Molinari G, Sardanelli F, Ottonello C, *et al*. Cardiologia, 1992, **37**: 431−434.

15 Chami L, Lassau N, Malka D, *et al*. AJR Am J Roentgenol, 2008, **190**: 683−690.

16 Ueno N, Kawamura H, Takahashi H, *et al*. J Ultrasound Med , 2006, **25**: 1147−1152.

17 Talbot J N, Gutman F, Fartoux L, *et al*. Eur J Nucl Med Mol Imaging, 2006, **33**: 1285−1289.

18 Park J W, Kim J H, Kim S K, *et al*. J Nucl Med, 2008, **49**: 1912−1921.

19 Song Z Z, Huang M, Jiang T A, *et al*. Eur J Radiol, 2010, **75**: 185−188.

20 Rossi S, Ghittoni G, Ravetta V, *et al*. Eur Radiol, 2008, **18**: 1749−1756.

21 Ho C L, Chen S, Yeung DW, *et al*. J Nucl Med, 2007, **48**: 902−909.

22 Kibel A S, Dehdashti F, Katz M D, *et al*. J Clin Oncol, 2009, **27**: 4314−4320.

23 Du Y, Cullum I, Illidge T M, *et al*. J Clin Oncol, 2007, **25**: 3440−3477.

24 Beadsmoore C J**,** Cheow H K, Sala E, *et al*. Br J Radiol, 2005, **78**: 841−844.

25 Hanajiri K, Mitsui H, Maruyama T, *et al*. J Gastroenterol, 2005, **40**: 1005−1006.

26 Catalano O A, Choy G, Zhu A, *et al*. Radiology, 2010, **254**: 154−162.

27 Miyazawa M, Torii T, Asano H, *et al*. Hepatogastroenterology, 2005, **52**: 212−216.

28 Vauthey J N, Lauwers G Y, Esnaola N F, *et al*. J Clin Oncol, 2002, **20**: 1527−1536.

29 Wallace M J. J Vasc Interv Radiol, 2003, **14**: 1339−1343.

30 Yogita S, Tashiro S, Harada M, *et al*. J Med Invest., 2000, **47**: 155−160.

31 Hemming A W, Reed A I, Langham M R, *et al*. Ann Surg, 2002, **235**: 850−858.

32 Azoulay D, Andreani P, Maggi U, *et al*. Ann Surg, 2006, **244**: 80−88.

33 Hemming A W, Langham M R, Reed AI, *et al*. Am Surg, 2001, **67**: 1081−1087.

34 Settmacher U, Thelen A, Jonas S, *et al*. Zentralbl Chir , 2005, **130**: 104−108.