Original Article

Use of ^{18}F-FDG PET/CT to locate primary malignancies in patients with hepatic cirrhosis and malignant ascites

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Objective: Ascites in patients with hepatic cirrhosis is caused by cirrhosis in most cases. For most malignant ascites, the primary malignancy could be readily identified using conventional imaging methods, e.g., computed tomography (CT) and magnetic resonance imaging (MRI). However, in a small fraction of the patients, the primary malignancy remains occult even with these examinations. In this retrospective study, we assessed the usefulness of ^{18}F-FDG PET/CT in patients with hepatic cirrhosis and malignant ascites of otherwise unknown origin.

Methods: Twenty-eight patients with malignant ascites of unknown primary sites after CT, MRI and ultrasound during the period of five years between January 2008 and December 2012 had received ^{18}F-FDG PET/CT. Medical records of these patients were reviewed and analyzed.

Results: Elevated ^{18}F-FDG absorption was found in 23 of 28 cases in the following sites: gastrointestinal tract (n=10, 43.5%), prostate (n=5, 21.7%), peritoneum (n=4, 13.3%), and ovary (n=4, 13.3%). Cancer was confirmed by pathology in 20 cases after open or laparoscopic surgeries. Five patients were found to have benign ascites, among which, 3 were found to be false positive due to tuberculosis. SUV values were significantly higher for tumors than for benign lesions (mean values, 6.95 *vs.* 2.94; P=0.005).

Conclusions: The ^{18}F-FDG PET/CT can be as a powerful imaging tool in identifying tissue origin in liver cirrhosis patients suspected of cancers or with cancers of unknown primary sites.

Keywords: PET/CT; liver cirrhosis; cancer, ascites

Submitted Aug 12, 2013. Accepted for publication Sep 10, 2013.
doi: 10.3978/j.issn.1000-9604.2013.09.01
Scan to your mobile device or view this article at: http://www.thecjcr.org/article/view/2823/3697

Introduction

The most common cause of ascites is liver cirrhosis which accounts for more than three-quarters of all cases (1). Malignant ascites is seen in about 10% of the patients with ascites. However, it could be a diagnostic challenge for clinicians to determine whether ascites is due to benign liver cirrhosis or due to malignancies. It is especially difficult to discover malignant ascites in cirrhotic patients. The cause of ascites can be diagnosed in most cases based on history, clinical examination, serum biochemical tests, fluid biochemistry and cytology, abdominal ultrasound, and paracentesis (2,3). However, in some cases the etiology still cannot be confirmed with laboratory tests (including cell count, albumin level, total protein level, Gram staining, and culture) and imaging including ultrasound and computer tomography (CT) scan, and further investigation is necessary (4).

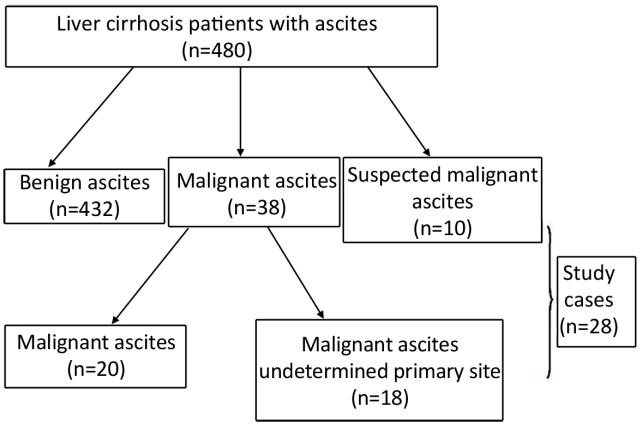

Figure 1 Flow chart of the patient selection process.

^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) is emerging as a useful noninvasive imaging technique to assess biochemical and metabolic differences between benign and malignant lesions. Recently, integrated PET/CT with functional and anatomical imaging has been shown to increase the diagnostic accuracy of malignant ascites (5,6). To date, few studies have focused on the role of ^{18}F-FDG PET/CT in the evaluation of ascites in liver cirrhosis patients. In this study, we assessed the value of ^{18}F-FDG PET/CT in determining the cause of ascites in liver cirrhosis patients who were clinically suspected of cancer or the primary sites of the malignancy were unknown.

Materials and methods

Patients

A retrospective study of liver cirrhosis patients with ascites who were referred for ^{18}F-FDG PET/CT because of clinical suspicion of cancer or unknown primary site was performed to determine the underlying causes of ascites and discriminate malignant ascites from benign causes.

A total of 480 liver cirrhosis patients with ascites from 2008 to 2012 were screened, and those in one of the following two categories were further investigated using ^{18}F-FDG PET/CT: (I) patients who were highly suspected of having malignancies clinically, but cytology and other noninvasive diagnostic imaging such as CT and ultrasound were negative; and (II) patients who had malignant cytological findings, but the primary sites of the cancers were not detected by CT or ultrasound. Written informed consent was obtained from all subjects.

^{18}F-FDG PET/CT protocol

Before surgery, gastroenterological endoscope, and pleural needle biopsy, all patients underwent whole-body ^{18}F-FDG PET imaging after 6 h fast. They had plasma glucose levels less than 140 mg/dL. ^{18}F-FDG (370 MBq each) was injected intravenously, and emission scanning using a whole-body technique (5-12 bed positions, acquisition time 5 min/bed position) was performed 60 min after the injection. The patients then underwent a transmission scan (3 min/bed) using a rotating 68 Ge sources. The raw data were then reconstructed using ordered subset expectation maximization (OSEM) algorithms method. The PET images were evaluated blindly by two experienced physicians.

Statistical analysis

Continuous data with normal distributions were expressed as $\bar{x}\pm s$, whereas continuous data with non-normal distributions were expressed as median (interquartile range). The Statistical Package for Social Science (SPSS), version 16.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. $P<0.05$ was considered statistically significant.

Results

Patient's characteristics

Of the 480 liver cirrhosis patients with ascites enrolled in the study, 20 (4.17%) patients had a known primary malignancy diagnosed. Eighteen patients were diagnosed with cancer but of undetermined primary sites, ten were suspected of cancer, and these 28 patients were further studied using ^{18}F-FDG PET/CT (*Figure 1*).

The baseline characteristics of the 28 patients including sex, age and causes of cirrhosis are summarized in *Table 1*. Median age was 64.5 years. Among the 28 patients, the causes of liver cirrhosis included hepatitis C virus infection (7, 25.0%), hepatitis B virus infection (9, 32.1%), autoimmune liver disease (1, 3.6%), alcoholic liver disease (6, 21.4%), schistosomiasis (4, 14.3%), and unknown (1, 3.6%).

Diagnostic accuracy of ^{18}F-FDG PET/CT in detection of clinically suspected cancer or cancer of unknown primary site of malignant ascites

Twenty-three cases were found to have sites with increased

^{18}F-FDG uptake including prostate 5 (21.7%), peritoneal 4 (13.3%), ovary 4 (13.3%), and gastrointestinal tract 10 (43.5%) (*Figure 2*). Cancers were confirmed by surgery and laparoscopic examination in 20 of the 23 patients. Three false positive patients were found to have peritoneal tuberculosis (*Figures 3,4*). The standardized uptake values (SUV) were significantly higher in cancers than in benign lesions (mean value, 6.95 *vs*. 2.94; P=0.005).

Table 1 Baseline characteristics of 28 liver cirrhosis patients with suspected cancer or cancer of unknown origin of malignant ascites

Baseline characteristics	n (%)
Age (year)	64.5 (34-87)
Sex, males	20 (71.4%)
Cause of cirrhosis	
HBV	9 (30%)
HCV	7 (23.3%)
Alcohol	6 (20%)
Schistosome	4 (13.3%)
Autoimmune liver disease	1 (3.3%)
Unknown	1 (3.3%)

HBV, hepatitis B virus; HCV, hepatitis C virus.

Discussion

Cancer of uncertain primary site is not an uncommon problem in clinical practice and the prognosis is usually poor (7,8). The survival depends on identifying the primary site and specific targeted therapy (9). The use of ^{18}F-FDG PET/CT is helpful to locate the primary site of malignancy in certain groups of patients. In patients with liver cirrhosis, the appearance of ascites is usually considered to be the complication of decompensated cirrhosis. However, malignant ascites is not uncommon in these patients (1). If the diagnosis and treatment are not timely, the prognosis is extremely dismal. Therefore, liver cirrhosis patients with ascites need to be screened for malignant ascites

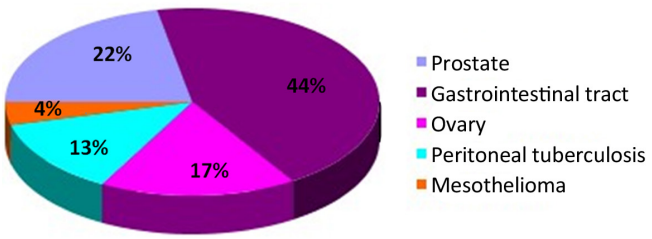

Figure 2 Origins of malignant ascites in liver cirrhosis patients.

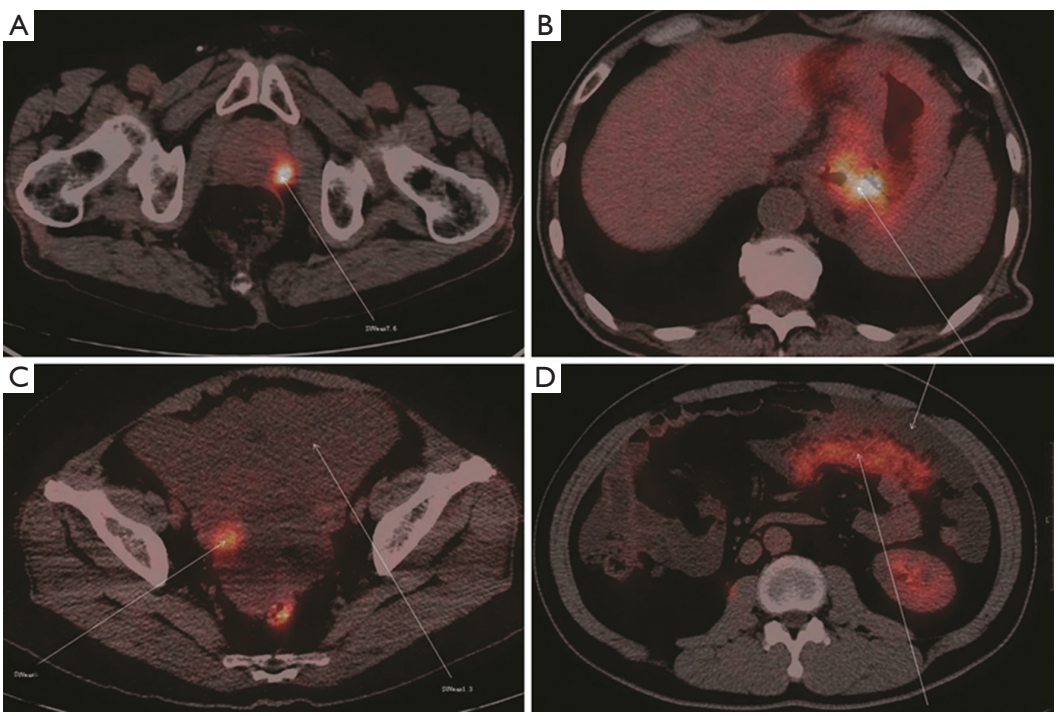

Figure 3 SUV_{max} of cancers with different sites. (A) Prostate SUV_{max} 7.6; (B) Gastrointestinal tract SUV_{max} 7.4; (C) Ovary SUV_{max} 5.2; (D) Peritoneal SUV_{max} 6.2.

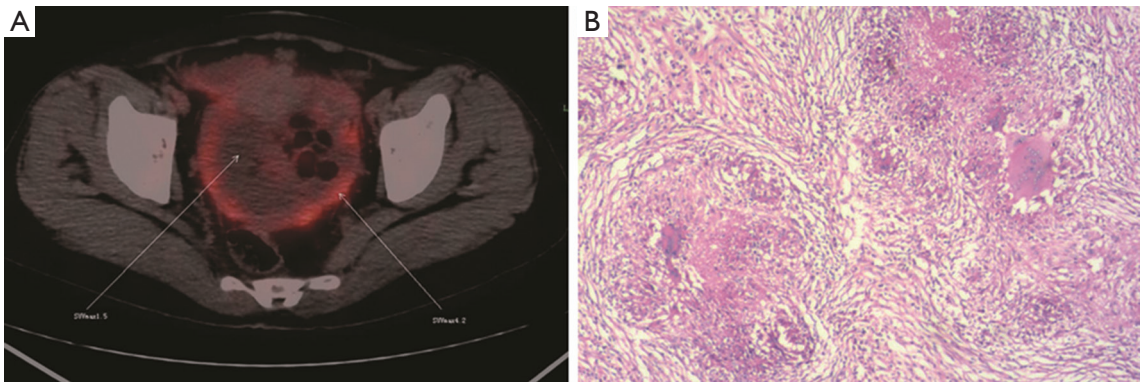

Figure 4 False positive patient with peritoneal tuberculosis.

by cytology, ascites albumin gradient, tumor markers, culture and non-invasive imaging, such as ultrasound and CT. Previous studies have shown that PET/CT has high diagnostic accuracy in mesothelioma, digestive tract cancer, prostate cancer and ovarian cancer, especially when the primary site of the tumor is uncertain (10-16). A more individualized treatment strategy is dependent on accurate pathological diagnosis. PET/CT guided fine needle biopsy can obtain tissue from high ^{18}F-FDG uptake area avoiding false positive results. In this study, we found that in patients with liver cirrhosis who are clinically suspected of cancer or have cancer of unknown primary sites, ^{18}F-FDG PET/CT can significantly reduce diagnostic uncertainty.

The potential ability of ^{18}F-FDG PET/CT to determine the tissue origin of cancer could be a very useful tool for more specific, less toxic treatment of cancer. Localization of the tumor by ^{18}F-FDG PET/CT plays an important role in radiation therapy to avoid damage to the normal tissues (17). Liver cirrhosis patients with malignant ascites sometimes cannot tolerate surgical treatment due to poor general condition. The appearance of malignant ascites in liver cirrhosis patients often indicates metastasis of tumor. Radiotherapy becomes the only choice and PET/CT also has its unique advantage in guiding radiotherapy (18) in terms of the radiation site, and dose distribution. For radiotherapy, CT is the standard method for tumor volume delineation. The major shortcoming is its inability to detect residual tumor and recurrence. PET-based treatment planning in radiotherapy can adjust the radiation field according to the edge of the tumor, increase the radiation dose to the target area, and at the same time, avoid the normal tissue. Adjustment of radiotherapy can also be made according to the patient's response (19). Ten patients in this study received radiotherapy without adverse reactions, but the long-term prognosis still needs further follow-up.

This study has several limitations. The retrospective study has case selection bias affecting the representativeness and credibility. In addition, the case number of this study is relatively small. There were also three false positive results (tuberculosis). It's been documented that FDG uptake in tuberculosis lesions is sparse (20). However, our study suggests that the patterns of FDG accumulation in tuberculosis need to be further evaluated (21).

In conclusion, ^{18}F-FDG PET/CT can be as a powerful imaging tool in identifying malignant origin in liver cirrhosis patients who are clinically suspected of cancers or have cancers of unknown primary sites. We believe that ^{18}F-FDG PET/CT is a valuable alternative to current diagnostic methods for identifying uncertain primary cancers. Further studies for evaluating the value of ^{18}F-FDG PET/CT on treatment choice and outcome for those patients are warranted.

Acknowledgements

Disclosure: The authors declare no conflict of interest.

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Cite this article as: Fan HB, Wang AJ, Yang DL, Xiao J, Ai Y, Huang L, Guo Y, Zhou MX, Wu JJ, Li Z, Yan FM, Wang YM. Use of ^{18}F-FDG PET/CT to locate primary malignancies in patients with hepatic cirrhosis and malignant ascites. Chin J Cancer Res 2013;25(5):500-504. doi: 10.3978/j.issn.1000-9604.2013.09.01

