^{18}F-FDG PET/CT在肝癌患者接受肝脏器官移植术前、后的临床应用价值

Prevention of postoperative tumor recurrence to promote the patients' long-term survival has remained the primary concern as well as the major difficulty in liver transplantation for hepatocellular carcinoma (HCC)[1]. Adequate assessment of the indications and thorough evaluation of the patients' eligibility for liver transplantation directly impacts on postoperative recurrence of HHC[2]. The long-term use of immuno-suppressants for potential graft rejection episodes following the transplantation also increases the risk of HHC recurrence. Currently thorough laboratory and imaging examinations including hepatic function examination, glucose tolerance test, detection of hepatitis markers, liver B-type ultrasound, CT and/or magnetic resonance imaging (MRI) as well as bone scanning have become routine procedures that the patients must go through before transplantation[3]. With increased clinical application of positron-emission tomography/computed tomography (PET-CT), ^{18}F-FDG PET-CT scanning gives full play to its capabilities of whole-body scanning and highly specific tumor detection[4]. In this article, the authors review the clinical and imaging data of 19 patients with HHC undergoing ^{18}F-FDG PET-CT scanning (for a total of 34 sessions of scanning) before and after liver transplantation, and explore the value of ^{18}F-FDG PET-CT in recipient evaluation for liver transplantation and in postoperative identification of recurrent tumor foci.

PATIENTS AND METHODS

Clinical data

This retrospective study included 19 male HCC patients with an average age of 47.24 years. Prior to PET examination, upper-middle retroperitoneal lymph node metastasis was identified in one patient and portal vein tumor embolus in another, and the examination was performed in these two cases for preoperative evaluation to identify other possible tumor metastatic foci.

Ten ^{18}F-FDG PET-CT examinations were performed in 8 patients before liver transplantation for preoperative evaluation. In these 8 patients, 5 were found with HHC for the first time who received no conservative or surgical treatment before PET, 2 had undergone previous interventional therapy in addition to surgical tumor resection, and 1 had previous transcatheter arterial chemoembolization.

Twenty-two ^{18}F-FDG PET-CT examinations (in 11 patients) were performed after liver transplantation to identify postoperative tumor recurrence or metastasis. Prior to PET examinations , alpha-fetoprotein (AFP) elevation was found in 9 patients and normal AFP in 2 patients. The time span between postoperative PET and the day of liver transplantation averaged 8.86 months.

Protocols of ^{18}F-FDG PET/PET-CT

Scanner A PET/CT scanner (Discovery LS GE Medical Systems) was used, which consisted of an Advance PET scanner with a Lightspeed 4-slice spiral CT scanner.

Imaging agent The imaging agent ^{18}F-FDG with radiochemical purity above 95% was produced by using circular accelerator and synthesized automatically by automated synthesis modules of GE Company.

Imaging protocol After fasting for at least 4 h, the patients were asked to rest for 10-15 min before injection of the imaging agent. After intravenous administration of ^{18}F-FDG with radioactivity of 259 to444 MBq (8-10 mCi) delivered via a T tube, the patient was allowed to rest in the dark in a supine position for 50-60 min, and data acquisition was carried out after urination. Whole-body PET scanning for 20 to 30 min covered the range from the head to the middle segment of the thigh. CT scanning was performed with the following parameters: voltage of 140 kV, current intensity of 160-200 mA, pitch of 0.75 and rotation time of 0.8 s.

Image reconstruction and fusion The images were reconstructed using an iterative algorithm for ordered-subset expectation maximization. The PET and CT images were uploaded to eNTEGRA workstation and registered for image fusion.

Image analysis All the PET images, CT images, and PET-CT fusion images were compared and analyzed by 3 radiologists.

RESULTS

Eight patients received totally 10 ^{18}F-FDG PET-CT examinations before liver transplantation, including 2 with giant HHC in the right hepatic lobe and 6 with giant HHC complicated by diffuse intrahepatic tumor foci. In the 8 patients receiving ^{18}F-FDG PET-CT scanning for preoperative evaluation, 2 were free of metastatic tumor foci and subsequently had liver transplantation as scheduled; 2 were found to have metastasis only in the retroperitoneal lymph nodes and large tumor emboli in the main portal vein without other metastasis, and they underwent the transplantation with careful retroperitoneal lymph node clearance; the other 4 patients, due to the presence of distal metastasis of varied degrees, received interventional therapy or other conservative treatments instead of the surgical approach. In patients with distal metastasis, 2 had retroperitoneal metastasis in the upper abdominal cavity, 4 had right infradiaphragmatic, portal fissure and retroperitoneal lymph node metastasis, 2 were found with tumor emboli in the portal vein, 1 with portal fissure invasion, 1 with anterior-lateral peritoneal metastasis of the ascending colon in the right upper quadrant, 1 with metastasis in the middle segment of the right lung, and 1 with tumor remnants around the necrotic foci in the right hepatic lobe after TACE. One patient was found to have bilateral renal function impairment in imaging examination.

Totally 22 ^{18}F-FDG PET-CT examinations (in 11 patients) were performed after liver transplantation, and the time span between the operation and the scanning ranged from 1 to 24 months for an average of 8.68 months. In 2 cases, PET did not find any recurrent or metastatic tumors, and one of them had higher-than- normal AFP level before PET and the other had normal AFP. In another case, a brain abscess focus (Fig.1) was found 5 months after the operation with also foci in the anterior border of the left psoas major muscle and the left medial femus, which were identified as Cryptococcus neoformans infection by subsequent abscess drainage via craniotomy and biopsy pathological examination. The other 19 ^{18}F-FDG PET-CT examinations (in 8 patients) identified recurrent tumors in the liver graft in 4 cases including 3 multiple foci (over 3) and 1 single focus (Fig.2), tumor emboli in the left and right hepatic veins and the inferior vena cava in 2 cases (Fig.3), lung metastasis in 5 cases (including 2 with single lung involvement and 3 with bilateral involvement), lymph node metastasis below the diaphragmatic muscle in 3 cases (2 right and 1 left infradiaphragmatic foci) (Fig.2), multiple metastasis in the retroperitoneal lymph nodes of the upper, middle, and lower abdomen in 4 cases, enlargement of the retroperitoneal lymph nodes of the middle abdomen (subsequently identified as inflammatory condition by pathological examination) in 1 case, bone metastasis in 3 cases (involving the vertebra in 3 cases and the limb bone in 1 case, including one with intramedullary metastasis(Fig.4), splenic metastasis in 1 case, lymph node metastasis posterior to the inferior vena cava in 1 case, parietal pleura metastasis in 1 case, and metastasis invading the intervertebral foramen of the thoracic vertebra in 1 case.

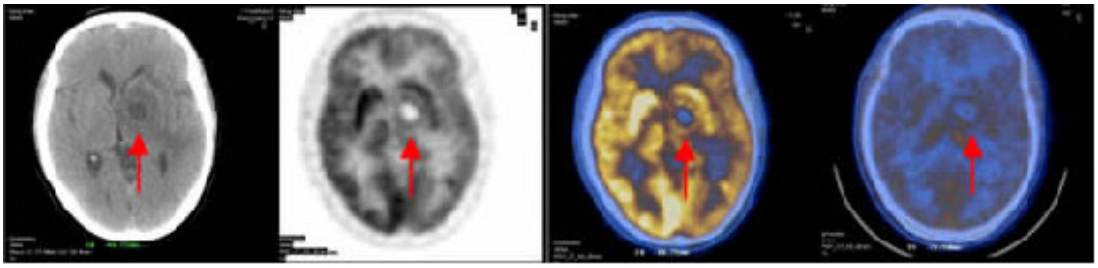

Fig.1 Brain abscess due to Cryptococcus neoformans infection in one case 5 months after liver transplantation

^{18}F-FDG PET scanning reveals circular hypermetabolic region surrounding a radioactivity defect in the left internal capsule. CT scanning presents circular low density region encompassing a region of even lower density in the corresponding area. 11C-methionine PET/CT scanning reveals no obvious metabolic normality in the left internal capsule.

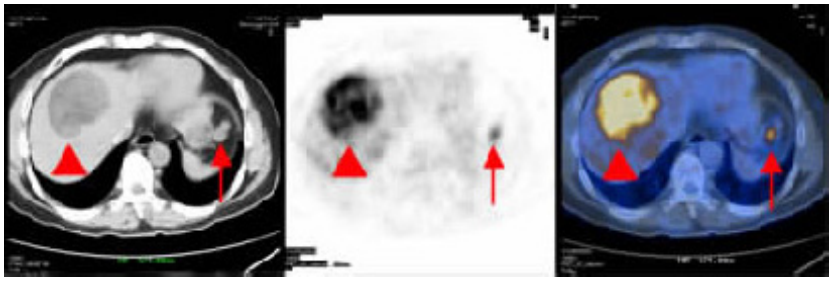

Fig.2 Two lymph node metastatic foci below the left diaphragm(↑) and the recurrent lesion in the transplanted liver graft (▲) 10 months after liver transplantation

^{18}F-FDG PET displays a roughly circular and mild hypermetabolic focus blow the left diaphragm and a large hypermetabolic mass in the liver graft. CT reveals two adjacent

small lymph nodes of soft tissue density below the left diaphragm and a heterogeneous low density focus with clear boundary in the liver graft.

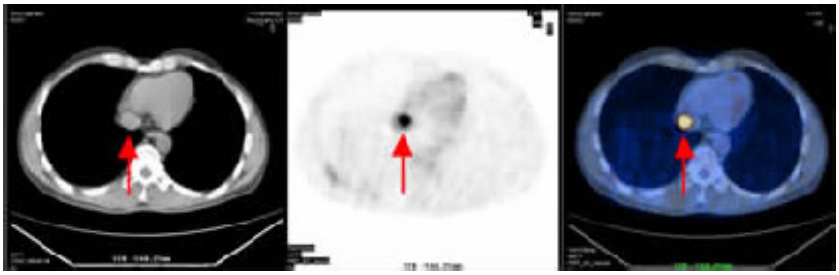

Fig.3 Metastatic tumor embolism in the inferior vena cava 24 months after liver transplantation

^{18}F-FDG PET shows a focal intense FDG uptake lesion in the inferior vena cava, which does not present abnormal density changes on CT image, and the inferior vena cava shows no obvious change of its diameter. CT alone is very likely to result in missed diagnosis. Accurate PET/CT fusion image displays precisely the hypermetabolic focus in the lumen of the inferior vena cava

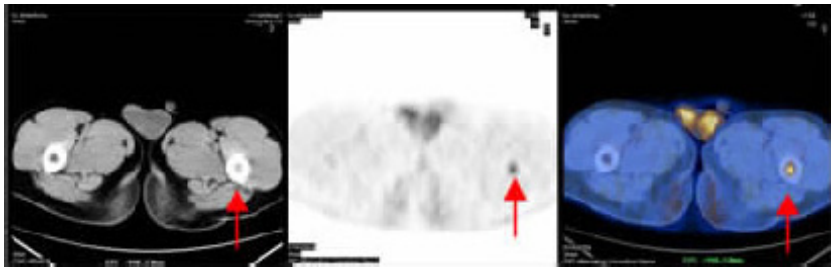

Fig.4 A intramedullary metastatic focus in the left upper femoral segment 3 months after liver transplantation

^{18}F-FDG PET presents a intramedullary nodular hypermetabolic focus in the left upper femoral segment, and CT in the same area shows increased density of the medulla without obvious change of the cortical bone density. Missed diagnosis of this focus is very likely with CT scanning alone

DISCUSSION

HCC is one of the most common malignancies and roughly 350 000 new cases are diagnosed annually worldwide, one third of which occur in China. The worldwide annual deaths due to HCC have exceeded 400 000. Liver transplantation first attempted in the 1960s has saved numerous lives threatened by end-stage benign liver diseases, and provides new options for liver cancer management. With increasing understanding of tumor relapse following liver transplantation and accumulation of clinical experience with the operation, liver transplantation has been considered an eligible therapeutic modality in cases of small HCC lesions with serious liver cirrhosis but free of major blood vessel involvement or extrahepatic metastasis[1],[2]. For surgeons, therefore, various imaging modalities can be of significant clinical value for accurate preoperative evaluation of the general condition of the candidate liver transplantation recipients and postoperative detection of tumor metastasis. The commonly used imaging modalities including chest X-ray, B-type

ultrasound[4], thoracic and abdominal CT scanning, and abdominal MRI all play significant roles in assisting clinical decision and provide a crucial portion of the clinical information of the patients before liver transplantation, but their scanning range can be much limited and very often, multiple sessions of scanning are required to obtain the whole-body scanning information. As for bone scanning, it fails to identify lesions in the tissues other than the bone. With the application of ^{18}F-FDG PET-CT, the dilemma in evaluation before liver transplantation seems to have a new solution[5].

The most prominent advantage of ^{18}F-FDG PET-CT lies in its capability of whole-body scanning in a single session, which enables thorough scrutiny for lesions in various organs and tissues and helps identify possible metastatic foci besides the primary lesion, and therefore can be instrumental in clinical diagnosis, staging and treatment planning for cancer[6]. In the cases reported herein, only 2 of the 8 cases receiving ^{18}F-FDG PET-CT for preoperative evaluation did not show extrahepatic metastasis in PET examination, while the other 6 cases all presented signs of lymph node metastasis at multiple sites, intravascular tumor embolism, portal fissure invasion, middle and lower abdominal peritoneal metastasis, lung metastasis and bilateral renal failure, and 4 cases lost the opportunity of operation due to extrahepatic metastasis found accidentally. In 6 cases, the evidence from the PET-CT images prompted the surgeons to increase the cancer stage and consequently revise their treatment plans. Among the total of 34 ^{18}F-FDG PET-CT examinations (in 22 patients), 20 examinations (in 17 patients) resulted in the revision of the clinical staging because of the newly identified adjacent or distal tumor metastasis.Besides good visualization of the lesions in the vital organs (such as the lungs, diaphragm, liver, pancreas, spleen, colon/rectum, adrenal glands and uterus), ^{18}F-FDG PET-CT scanning is also capable of clear display of occult lesions[7]. This capability is attributed to the second advantage of ^{18}F-FDG PET-CT, namely the high tumor-to-nontumor contrast, which allows the surgeons to capture the small lesions that may otherwise escape detection or those in the spaces between organs or tissues. These small or occult lesions often cause no clinical manifestations in early stage and can easily escape detection without the help of proper imaging examination, so as to delay timely treatment. In this series of cases, ^{18}F-FDG PET-CT also provided diagnostic information for the condition of the HCC lesions in 6 cases after interventional therapy.

The third valuable advantage of ^{18}F-FDG PET-CT is the merging of the PET and CT images based on computer programs, which enables the integration of information at functional and anatomical levels provided by the two PET and CT, respectively, to embrace the advantages of the two independent imaging modalities[8]. In the cases reported herein, CT detected 7 metastatic lesions in the lungs while ^{18}F-FDG PET only identified two relatively large ones. PET often fails to detect small (less than 5 mm in diameter) or well-differentiated metastatic foci in the lungs, but with the complementation by CT, these foci can be readily visualized due to the high spatial resolution of CT[9]. We also found that for the small lymph node metastatic lesions at the edge of the solid organs or in the interspace of the tissues, PET was insufficient for their accurate localization, which, however, was possible with the integration of CT (Figs.2-4). Obviously, ^{18}F-FDG PET-CT provides additional anatomical information of the lesions in comparison with ^{18}F-FDG PET. The fusion image resulted from ^{18}F-FDG PET-CT allows both accurate anatomical localization and clear description of the metabolism in the living tissues and cells within the foci,

therefore offers strong and crucial assistance for an accurate clinical diagnosis[10]. In one of our patients undergoing liver transplantation for small HCC, a 1.2-cm nodule with mild lobular appearance in the peripheral was found in the right upper lung 10 months after the operation. ^{18}F-FDG PET-CT findings indicated uneven mild increase of metabolic activity in the posterior edge of the lesion, and a second follow-up ^{18}F-FDG PET-CT 3 months after tuberculostatic treatment revealed no significant changes of the lesion, which was subsequently surgically removed and proved pathologically to be a recurrent tumor focus. This patient had obviously higher than normal AFP level before the operation and normal AFP after that, suggesting the importance of careful CT image-based observation of the lesions even when PET reveals no increased metabolic activity in the lesions (i.g. no signs of recurrent tumor).

In 6 of the cases, progressive AFP elevation was the major laboratory finding after liver transplantation but the patients complained no discomforts. Reexamination, however, identified small metastatic lesions in the lymph nodes, the thoracic, lumbar, and sacral vertebra, and the spleen in 5 cases, with only one free of recurrent tumors (but regular revisit was advised). Detailed review and recording of the AFP report before and after the operation in the 6 cases revealed a pattern that they all had elevated AFP before the operation, which was lowered to normal or roughly normal level in early stage following the operation but increased again progressively after a few months. In such cases, therefore, relapse should be highly suspected and serum AFP changes be closely monitored especially in patients whose serum AFP increases obviously with the tumor enlargement.

According to these clinical practices as well as available reports, ^{18}F-FDG PET-CT does not seem to be sensitive for well differentiated or some moderately differentiated HCC, but with the clinical application of other radioactive tracers for PET-CT such as 18F-FLT, 11C-choline, and 11C-methionine etc in addition to ^{18}F-FDG, early and more specific diagnosis of smaller or FDG metabolism-insensitive tumors can be achieved. The future clinical application of more imaging agents may bring about earlier and more accurate diagnosis of HCC, to win precious time for its treatment.

To conclude, ^{18}F-FDG PET-CT possess obvious advantages over other conventional imaging modalities in preoperative evaluation of liver transplantation and can be of much clinical value in early detection of recurrent tumors after the operation. The current high cost of ^{18}F-FDG PET-CT examination somehow restricts its wider clinical application, but this problem, we believe, can be solved with future technical improvement and wider application of the equipment.

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