Usefulness of $^{18}$F-FDG Positron Emission Tomography/Computed Tomography for Detecting Recurrence of Hepatocellular Carcinoma in Posttransplant Patients

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$^{18}$F-fluoro-2-deoxy-D-glucose ($^{18}$F-FDG) positron emission tomography (PET)/computed tomography (CT) has recently been shown to be able to predict a poor outcome after liver transplantation (LT) for patients with hepatocellular carcinoma (HCC). However, there are few reports on the usefulness of PET during follow-up after LT. In this study, we assessed the efficacy of $^{18}$F-FDG PET/CT for the detection of HCC recurrence after LT. From February 2005 to December 2008, out of 93 adult LT cases (91 living donors and 2 deceased donors), 10 patients who showed HCC recurrence and received $^{18}$F-FDG PET/CT during follow-up were included. The accuracy of $^{18}$F-FDG PET/CT was assessed with imaging and histological studies. The most common sites of recurrence were extrahepatic (60%). The most common extrahepatic sites were the lungs and bone (31.3% each). Among 4 patients with intrahepatic recurrence, 1 patient (25%) was positive according to $^{18}$F-FDG PET/CT. The detection rate of $^{18}$F-FDG PET/CT was 92.9% for extrahepatic metastases $\geq 1$ cm and 0% for lesions $< 1$ cm. The detection rate of $^{18}$F-FDG PET/CT was 100% in bone and the lymph nodes, 60% in the lungs, and 0% in the brain. $^{18}$F-FDG PET/CT identified 2 lesions in bone that were not found in a bone scan. In conclusion, because of its limitations for small lesions, intrahepatic lesions, and brain lesions, $^{18}$F-FDG PET/CT is not suitable as a screening tool after LT. However, $^{18}$F-FDG PET/CT could provide additional information beyond that provided by conventional modalities, and it could contribute to the clinical management of HCC recurrence after LT, especially in patients with extrahepatic recurrence. Liver Transpl 16:767-772, 2010. © 2010 AASLD.

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Hepatocellular carcinoma (HCC) has been important indication for liver transplantation (LT) since the 1990s. The clinical staging of HCC is required to determine a treatment plan. $^{18}$F-fluoro-2-deoxy-D-glucose ($^{18}$F-FDG) positron emission tomography (PET)/computed tomography (CT) has been used at some institutions for clinical staging of HCC.

The principle of $^{18}$F-FDG PET is that $^{18}$F-FDG uptake allows cellular glucose metabolism to be estimated by PET. The normal cell contains a relative abundance of glucose-6-phosphatase and lower levels of hexokinase, whereas tumor cells tend to have increased hexokinase levels but little if any, glucose-6-phosphatase activity. This difference in metabolism results in an increased accumulation of $^{18}$F-FDG in tumors, and it potentially allows normal tissue and tumor tissue to be differentiated on PET scans.

$^{18}$F-FDG PET/CT is a well-established, noninvasive diagnostic tool for the detection of a variety of malignant tumors such as neck, lung, pancreas, and colon.

Abbreviations: AFP, alpha-fetoprotein; CT, computed tomography; $^{18}$F-FDG, $^{18}$F-fluoro-2-deoxy-D-glucose; FN, false negative; HCC, hepatocellular carcinoma; LN, lymph node; LT, liver transplantation; MRI, magnetic resonance imaging; PET, positron emission tomography; SUV, standardized uptake value; TP, true positive; UCSF, University of California San Francisco.

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tumors. However, 18F-FDG PET/CT is less suitable for the detection of primary HCC because of the variable 18F-FDG uptake pattern in HCC. However, 18F-FDG PET/CT is known to be useful in the evaluation of extrahepatic metastases. Furthermore, pretransplant 18F-FDG PET/CT has recently been shown to be able to predict a poor outcome after LT for patients with HCC. Therefore, 18F-FDG PET/CT has been routinely applied to the assessment of patients with HCC before LT at some centers. However, there are few reports on the usefulness of PET during follow-up after LT. In this study, we assessed the efficacy of 18F-FDG PET/CT for the detection of HCC recurrence after LT.

PATIENTS AND METHODS

Patients

From February 2005 to December 2008, 93 patients underwent adult LT (91 living donors and 2 deceased donors) for HCC at the National Cancer Center of Korea. All 93 patients received routine follow-up care at the outpatient clinic. Twelve of the 93 patients developed HCC recurrence during the follow-up period. Two of the 12 patients who did not undergo 18F-FDG PET/CT testing were excluded. All 10 patients were tested with 18F-FDG PET/CT before LT and when HCC recurrence was suspected on the basis of conventional screening imaging modalities. Patient data were collected from medical records retrospectively. The serum level of alpha-fetoprotein (AFP) was checked monthly. Routine spiral liver CT, covering the area from the hila of the lungs through the symphysis pubis, was performed at 3-month intervals. Chest spiral CT, bone scan, and brain CT procedures were performed when HCC recurrence was suspected. Magnetic resonance imaging (MRI) was performed if needed.

18F-FDG PET/CT

PET studies were performed with a dedicated PET scanner (Biograph LSO, Siemens Medical Systems, Chicago, IL) or a PET/CT scanner (Discovery LS, GE Healthcare, Milwaukee, WI). For the Biograph LSO scanner, we used a scout view at 30 mA and 130 kVp, and this was followed by a spiral CT scan [50 mA (effective), 130 kVp, 5-mm section width, 4-mm collimation, 12-mm table feed per rotation, and 0.8 s per rotation] with the patient’s arms raised. For the Discovery LS scanner, we used a scout view with 30 mA and 120 kVp, and this was followed by a spiral CT scan (0.8-s rotation time, 80 mA, 140 kVp, 5-mm section thickness, and 4.25-mm interval in the high-speed mode) with the patient’s arms at the sides of his torso. PET images were acquired after CT scans with 3 minutes per bed position of 11.2 cm in the 3-dimensional acquisition mode (Biograph LSO) or with 4 minutes per bed position of 14.2 cm in the 2-dimensional acquisition mode (Discovery LS). CT images were reconstructed onto a 512 × 512 matrix and converted into 511-keV-equivalent attenuation factors for attenuation correction. PET images were reconstructed onto a 128 × 128 matrix with ordered-subset expectation maximization and attenuation correction. The standardized uptake value (SUV) was calculated as follows:

\[
\text{SUV} = \frac{\text{[Decay-corrected activity (kBq)/Tissue volume (mL)]} - \text{[Injected 18F – FDG activity (kBq)/Body mass (g)]}}{\text{Body mass (g)}}
\]

The SUVs of lesions were obtained by manual placement of regions of interest around the lesion. The maximum SUV within a region of interest was used to minimize partial-volume effects.

All patients were normoglycemic and had fasted, except for water and medications, for at least 8 hours before the PET studies. The patients were kept well hydrated because 18F-FDG is excreted through the kidneys and urinary bladder. Twenty milligrams of furosemide was administered intravenously within 10 minutes of the 18F-FDG injection, and then 500 mL of water was given. 18F-FDG (444-740 MBq, 12-20 mCi) was injected intravenously. Patients were encouraged to rest during the 18F-FDG uptake period. Sixty minutes after the 18F-FDG injection, whole-body static PET/CT was performed.

Interpretation of 18F-FDG PET/CT and Diagnosis of HCC Recurrence

Separate CT and PET scan data were accurately coregistered. PET, PET/CT, and CT images were reviewed with a dedicated workstation and software (eNtegra, GE Healthcare, and eSoft, Siemens Medical Solutions). With this system, 3-dimensional displays (transaxial, coronal, and sagittal) were available, as were maximum-intensity projections of the PET data. PET/CT scans were interpreted by a nuclear medicine physician who was unaware of the results of other imaging studies of these patients. Intrahepatic primary lesions were interpreted visually with a 3-point grading system (isometabolic, hypermetabolic, and hypometabolic) that compared data with tracer uptake by normal liver parenchyma for 18F-FDG PET. If a lesion was hypermetabolic on at least 1 image from 18F-FDG PET, it was assumed to be a malignant hepatic mass. Extrahepatic lesions were interpreted visually with a 5-point scale: 0, no visible accumulation; 1, less accumulation than that in the liver; 2, accumulation about the same as that in the liver but less than that in the brain cortex; and 4, accumulation comparable to that of the brain cortex. An extrahepatic lesion was considered to be malignant when its accumulation of 18F-FDG was more than 3 on this scale. The accuracy of 18F-FDG PET/CT was assessed by conventional imaging studies and histological confirmation. 18F-FDG PET/CT was compared with...
dynamic CT for intrahepatic and intra-abdominal lesions, with a bone scan or MRI for bone lesions, with chest CT for lung lesions, and with brain CT for brain lesions. When metastatic lesions were resectable, resection of metastatic lesions was performed; otherwise, sonograph-guided percutaneous core biopsy was performed. When resection or sonograph-guided biopsy was impossible, HCC recurrence was diagnosed by reference to the imaging studies and the serum level of AFP.

**RESULTS**

**Preoperative Characteristics of the Patients with HCC Recurrence (Table 1)**

The median age of the patients was 48.5 years. All 10 patients had hepatitis B virus-related liver cirrhosis. Fifty percent of the patients fit Child-Pugh classification A, and 50% of the patients had increased 18F-FDG tumor uptake in the liver on pretransplant PET scans. The numbers of patients beyond the Milan criteria and the University of California San Francisco criteria were 5 (50%) and 4 (40%), respectively. Two patients (20%) had a serum AFP level higher than 200 ng/mL before LT.

**Initial Detection Method for HCC Recurrence and Recurrence Sites**

HCC recurrence was asymptomatic and detected during the follow-up liver spiral CT scan in 40% (n = 4) of the cases. The elevation of serum AFP without any symptoms was reason for suspicion of HCC recurrence in 30% (n = 3) of the cases. An abnormal physical examination and/or symptoms were the reason for suspicion of HCC in 30% (n = 3) of the cases. The most common sites of HCC recurrence were extrahepatic (60%). The rate of intrahepatic recurrence was 30%, and the rate of combined recurrence was 10%. The most common extrahepatic sites of HCC recurrence were the lungs and bone (31.3% each). The

**Detection Rates of 18F-FDG PET/CT for Lesions of HCC Recurrence**

18F-FDG PET/CT showed a low detection rate of intrahepatic recurrence. Among 4 patients with intrahepatic recurrence, 1 patient (25%) was positive according to 18F-FDG PET/CT. A total of 27 intrahepatic lesions of HCC in 4 patients with intrahepatic recurrence were identified by dynamic CT. The detection rate of 18F-FDG PET/CT was 92.9% (13 of 14 lesions) for extrahepatic metastases larger than or equal to 1 cm in greatest diameter and 0% (0 of 2 lesions) for lesions smaller than 1 cm. According to the site, the detection rate of 18F-FDG PET/CT was 100% in bone, 60% in the lungs, and
According to pretransplant 18F-FDG PET/CT, 2 spine MRI (Table 4).

**DISCUSSION**

The most common pattern of HCC recurrence after partial hepatectomy is solitary intrahepatic recurrence.17,18 However, extrahepatic recurrence is more frequent than intrahepatic or combined recurrence in the setting of LT.19 Similarly, multiple extrahepatic recurrence was the most common pattern in this study. Therefore, transplant physicians should focus on the detection of extrahepatic HCC recurrence (in contrast to intrahepatic recurrence in patients who have undergone partial hepatectomy).

Pretransplant 18F-FDG PET/CT in HCC patients can help the transplant physician to detect extrahepatic metastases and select LT candidates before LT.14,15 Moreover, pretransplant 18F-FDG PET/CT has been used to predict prognosis after LT.14 However, the usefulness of 18F-FDG PET/CT during follow-up has not been established. To the best of our knowledge, there has been no report of 18F-FDG PET/CT as a screening tool for HCC recurrence after LT. In this study, 18F-FDG PET/CT had a high detection rate (92.9%) for HCC recurrence in patients with extrahepatic lesions larger than 1 cm in greatest diameter. However, it was limited in its ability to detect even large brain lesions. Because the brain uses glucose as a source of energy, the lesions in the brain cannot be differentiated from adjacent normal brain tissue. A brain contrast-enhanced MRI or CT scan should be recommended in such cases.

Furthermore, in this study, 18F-FDG PET/CT had a very low detection rate (0%) of HCC recurrence in extrahepatic lesions smaller than 1 cm in greatest diameter. The limitations of 18F-FDG PET/CT are poor spatial resolution in comparison with other modalities, low uptake in hypometabolic tumors, and false-positive accumulations in inflammatory lesions.20-22 Poor spatial resolution results in very low detection rates for small lesions. In this study, all lesions smaller than 1 cm in diameter occurred in the lungs. Therefore, 18F-FDG PET/CT would not be adequate as a screening tool for the detection of HCC recurrence in the lungs. A chest spiral CT scan is better than 18F-FDG PET/CT for detecting HCC in a patient with small lesions of HCC recurrence in the lungs.

In this study, all 5 lesions of HCC recurrence in bone were detected by 18F-FDG PET/CT. However, a bone scan could not detect 2 lesions of HCC recurrence in bone. This result is consistent with other reports in nontransplant settings. Sugiyama et al.9 reported that 18F-FDG PET/CT is more sensitive than a bone scan for the detection of osteolytic bone metastases in patients with HCC. Therefore, 18F-FDG PET/CT can be a more sensitive follow-up tool for detecting HCC lesions in bone after LT.

The detection rate of intrahepatic recurrence of HCC is very low in posttransplant patients and is similar to that in nontransplant patients. Therefore, 18F-FDG PET/CT cannot be used as a screening tool to detect intrahepatic recurrence of HCC. Furthermore, 1 patient who tested positive for HCC lesions according to pretransplant 18F-FDG PET/CT tested negative for lesion recurrence according to 18F-FDG PET/CT in this study. Because the biological characteristics of a recurring tumor might be different from those of the original tumor, 18F-FDG PET/CT cannot be used as a

**TABLE 3. Comparison of Conventional Modalities and 18F-FDG PET/CT in Terms of the Detection Rates of Extrahepatic Lesions of Recurrence According to Sizes and Sites**

| Lesions       | Conventional Modalities | 18F-FDG PET/CT |
|---------------|-------------------------|----------------|
| Tumor size    |                         |                |
| (n = 16)      |                         |                |
| >1 cm         | 14                      | 13 (92.7%)     |
| <1 cm         | 2                       | 0 (0%)         |
| Sites         |                         |                |
| Bone          | 5*                      | 5 (100%)       |
| Lung          | 5                       | 3 (60%)        |
| Lymph node    | 3                       | 3 (100%)       |
| Adrenal gland | 1                       | 1 (100%)       |
| Muscle        | 1                       | 1 (100%)       |
| Brain         | 1                       | 0 (0%)         |

*Two lesions were not identified by a bone scan but were identified with spine magnetic resonance imaging.

100% in the lymph nodes. The recurring lesions at the adrenal gland and in the muscle were also all positively detected by 18F-FDG PET/CT. However, the recurring lesions in the brain were not found by 18F-FDG PET/CT. 18F-FDG PET/CT was more sensitive than a bone scan. Among the 3 bone lesions in case 3, 2 lesions were not identified in the bone scan; however, they were identified by 18F-FDG PET/CT and spine MRI (Table 4).

Among 5 patients with positive intrahepatic lesions according to pretransplant 18F-FDG PET/CT, 2 patients showed intrahepatic recurrence. One patient (case 9) showed a positive intrahepatic lesion in follow-up 18F-FDG PET/CT. However, the other patient (case 8) showed a negative intrahepatic lesion in follow-up 18F-FDG PET/CT (Table 4).

**Treatment and Clinical Outcome After HCC Recurrence**

As an initial treatment modality for HCC recurrence, resection was performed for extrahepatic lesions in all cases except case 6. Transarterial chemoembolization was performed for intrahepatic lesions in all cases with intrahepatic recurrence. Two patients (cases 2 and 5) were still alive without evidence of disease 27 and 16 months after the initial treatment, respectively. Four patients (cases 1, 6, 9, and 10) died within 8 months after the initial treatment with rapid disease progression. The other 4 patients (cases 3, 4, 7, and 8) were still alive with recurrent HCC for more than 1 year.

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TABLE 4: Clinical Details and PET Results for Ten Patients with HCC Recurrence

| Patient No. | Pretransplant 18F-FDG Tumor Uptake in the Liver | Level of Serum AFP at the Time of PET Examination (ng/mL) | Vascular Tumor Invasion | Milan Criteria of HCC (Radiological) | Duration from LT to First Detection of HCC (months) | Extrahepatic Recurrence | Extrahepatic Recurrence Location (Number of Lesions) | Extrahepatic Recurrence Maximum Size of the Lesion (cm) | Intrahepatic Recurrence | Intrahepatic Recurrence Number of Lesions | Intrahepatic Recurrence Maximum Size of the Lesion (cm) | PET/CT Results |
|-------------|-----------------------------------------------|----------------------------------------------------------|-------------------------|--------------------------------------|--------------------------------------------------|--------------------------|------------------------------------------------------|----------------------------------------------------|---------------------|---------------------------------------|--------------------------------------------------------|------------------|
| 1           | Isometabolic                                  | 12,344                                                   | No                      | Within                               | 11.8                                             | Brain (1)                | 2.0                                                  | —                                                  | —                   | —                                | —                                      | FN              |
| 2           | Isometabolic                                  | 2.5                                                      | No                      | Within                               | 18.5                                             | Muscle (1)               | 1.4                                                  | —                                                  | —                   | —                                | —                                      | TP              |
| 3           | Hypermetabolic                                | 10.5                                                     | No                      | Within                               | 23.7                                             | Bone (3)*                | 2.2                                                  | —                                                  | —                   | —                                | —                                      | TP              |
| 4           | Isometabolic                                  | 7.2                                                      | No                      | Beyond                               | 25.5                                             | Left adrenal gland (1)  | 2.0                                                  | —                                                  | —                   | —                                | —                                      | TP              |
| 5           | Isometabolic                                  | 4.1                                                      | Micro                   | Beyond                               | 19.9                                             | Lung (2)                 | 1.2                                                  | —                                                  | —                   | —                                | —                                      | TP              |
| 6           | Hypermetabolic                                | 323.3                                                    | No                      | Beyond                               | 8.0                                              | Lung (2)                 | 1.9                                                  | 11                                                 | 1.5                 | TP                                | TP                                      | TP              |
| 7           | Isometabolic                                  | 3                                                        | Micro                   | Beyond                               | 8.7                                              | LN (3)                   | 2.7                                                  | —                                                  | —                   | 7                                | 1.6                                    | FN              |
| 8           | Hypermetabolic                                | 2.7                                                      | Micro                   | Within                               | 7.7                                              | —                        | —                                                    | 3                                                  | 1.4                 | —                                | FN                                      | —                |
| 9           | Hypermetabolic                                | 1.6                                                      | Micro                   | Within                               | 5.7                                              | —                        | —                                                    | 6                                                  | 3.8                 | —                                | TP                                      | —                |
| 10          | Hypermetabolic                                | 546.8                                                    | Micro and macro         | Beyond                               | 4.1                                              | Bone (2)                 | 1.3                                                  | —                                                  | —                   | 3                                | 1.3                                    | TP              |

*Two lesions were not identified by a bone scan but were identified with 18F-FDG PET/CT and spine magnetic resonance imaging.
screening tool even in cases testing positive for pretransplant HCC by 18F-FDG PET/CT.

As mentioned earlier, extrahepatic multiple recurrence was more frequent in an LT setting than in a partial hepatectomy setting. Therefore, 18F-FDG PET/CT, which is more sensitive for the detection of extrahepatic lesions, could be a more useful screening tool during follow-up after LT. Because of its limitations for small lesions, intrahepatic lesions, and brain lesions, it would be better used as a secondary method when an extrahepatic recurrence of HCC is detected by conventional modalities. Alternatively, if a recurrence is suspected on the basis of a physical examination, symptoms, and/or tumor markers, but no lesion has been identified by conventional screening imaging modalities, 18F-FDG PET/CT could be helpful for detecting such a lesion.

In conclusion, 18F-FDG PET/CT after LT could provide additional information beyond that provided by conventional modalities and contribute to the clinical management of HCC recurrence, especially in patients with extrahepatic recurrence. Further study with a large number of patients may be required to draw concrete conclusions on the use of 18F-FDG PET/CT after LT.

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