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Utility of FDG-PET for Investigating Unexplained Serum AFP Elevation in Patients with Suspected Hepatocellular Carcinoma Recurrence

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Abstract. *The aim of this study was to evaluate the potential role of positron emission tomography (PET) with ^{18}F-fluorodeoxyglucose (FDG) in patients with unexplained rising serum alpha-fetoprotein (AFP) levels after the treatment of hepatocellular carcinoma (HCC). Patients and Methods: Thirty-one FDG-PET studies were performed in 26 patients (age range, 45-83; 21 men and 5 women), who had undergone either surgical resection or interventional therapy for HCC, but were subsequently noted to have high AFP serum levels on routine follow-up examinations, although imaging studies and physical examinations were normal. The FDG-PET results were correlated with histological findings, as well as long-term radiological and clinical follow-up (shortest follow-up period after FDG-PET was 6 months). Results: FDG-PET was abnormal in 22 of the 31 studies (71.0%) among the 26 patients. Intrahepatic lesions were detected in 20 of a total 30 lesions (66.7%) in 18 studies of FDG-PET among 26 patients. Ten FDG-PET studies among 9 patients identified one intrahepatic lesion, while 3 studies among 3 patients identified more than one intrahepatic lesion. Extrahepatic metastases were found in 9/31 studies of FDG-PET (29.0%) among 8 patients. These metastatic foci, composed of increased FDG accumulation, were identified in several locations; lung (4 studies among 4 patients), bone (2 studies among 2 patients) and the peritoneum (4 studies among 3 patients). Overall, FDG-PET for detecting HCC recurrence demonstrated 22 true-positives, 8 false-negatives, 1 true-negative and 0 false-positive results. The sensitivity, specificity and accuracy of FDG-PET for detecting HCC recurrence was 73.3%, 100% and 74.2%, respectively. Conclusion: When conventional examinations are normal, FDG-PET is a valuable imaging tool in patients who have rising AFP levels after HCC treatment. FDG-PET whole-body scan also provides an important and valuable imaging study for detecting extrahepatic metastasis.*

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Hepatocellular carcinoma (HCC) is one of the most common causes of cancer death in the world (1). Technological advances in imaging modalities, such as ultrasound (US), computed tomography (CT), angiography, magnetic resonance imaging (MRI), CT-angiography and US-angiography have facilitated the early detection of HCC (2-5). HCC has a high recurrence rate (51% - 90%) even after 'curative' resection (6-9); therefore, the long-term outcome of patients with HCC remains unsatisfactory. Early detection of recurrent tumors is important. Re-resection correlated with better post-recurrent survival rates (9). Therefore, periodic examination of diagnostic modalities after curative treatment of HCC is essential for the early detection of recurrent HCC (10, 11). Measurements of serum alpha-fetoprotein (AFP) and periodic abdominal US and CT are very useful for detecting recurrent HCC in the early stages (10, 12).

However, rising AFP levels often occur even when conventional imaging studies and clinical examination are normal. Uncertainty regarding the presence of disease results in psychological distress to the patient. Accordingly, a more sensitive means for localizing tumor foci would aid in the management of such patients.

The ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) scan is an alternative way of examining the whole body metabolism of glucose. FDG is a glucose analog and its accumulation within cells is proportional to the rate of glucose transport and metabolism. FDG-PET is a diagnostic modality that can non-invasively and accurately survey the whole body. The preliminary data are promising for the use of FDG-PET as an indicator of tumor viability after therapy (13, 14). Therefore, the aim of this study was to evaluate the potential role of FDG-PET in patients with unexplained rising AFP levels after the treatment of HCC.

Patients and Methods

Patients. A retrospective study was conducted in our PET center from February 2001 to October 2004. Thirty-one FDG-PET studies were retrospectively performed in 26 patients (age range, 45-83; 21 men and 5 women) with a serum AFP concentration greater than 10 ng/mL, but normal imaging studies and physical examinations. PET scans were performed in 5 studies among 4 patients, while PET/CT scans were performed in 26 studies among 22 patients. All 26 patients had undergone surgical resections or interventional therapy for HCC, but subsequently had developed a serial rise in their AFP plasma levels on routine follow-up examinations. All patients gave informed consent to participate in the study, according to the guidelines established by the local ethics committee and the Helsinki Declaration.

FDG-PET imaging protocol. Our PET center was opened in February 2001 with a Siemens (ECAT EXACT HR+, model 962, Knoxville, TN, USA) whole-body scanner and a GE minitrace cyclotron. The second scanner, a PET-CT system (Discovery LS, GE Medical Systems, Waukesha, WI, USA), was added to the center in March 2002. Patients were required to fast for at least 8 hours before the PET scan; furthermore, patients had to be well hydrated and to avoid strenuous work or exercise for 24 hours prior to the scan. Patients were scanned in as many sequential images as necessary to include the entire head, thorax, abdomen and pelvis. Transmission images were obtained for 2 minutes per bed position to correct for photon attenuation using a germanium-68 line source. In the PET/CT scanner, the PET attenuation correction factors were calculated from the CT images. CT was performed using a multidetector helical CT scanner. Acquisitions occurred at 5-7 bed positions and had the following parameters: 140 kV, 40 mA, 0.8 s per CT rotation, a pitch of 6, a table speed of 22.5 mm/s, coverage of 722.5-1,011.5 mm and an acquisition time of 31.9-37 s. CT was performed before the emission acquisition. CT data were resized from a 512 x 512 matrix to a 128 x 128 matrix to match the PET data so that the images could be fused and CT transmission maps generated. The transaxial resolution (full width at half maximum) of PET and PET/CT were 4.58 mm and 4.8 mm, respectively. After *i.v.* administration of 370 MBq (10 mCi) of FDG, emission images were acquired for 5 minutes per bed position. The uptake period between the FDG injection and the beginning of the emission scan was 60±10 minutes (range, 50 to 70). Accurate positioning of the patient between transmission and emission scans was performed using laser marks. Image datasets were obtained by iterative reconstruction (ordered-subset expectation maximization method). Images were displayed in three orthogonal projections and as whole-body maximum-pixel-intensity reprojection images for visual interpretation. All FDG-PET images were evaluated qualitatively in a routine clinical fashion, including correlation with CT images; reported abnormalities represented the consensus of at least two nuclear medicine physicians.

Tumor marker test. Blood samples from all patients were obtained before the FDG injection, and the serum was stored at –20˚C. The determination of AFP was based on a solid phase two-site immunoradiometric assay for a direct quantitative measurement in serum. The reference range of AFP was less than 10 ng/ml.

Data analysis. The FDG-PET results were correlated with histological findings and long-term radiological and clinical follow-up periods (shortest follow-up period after PET was 6 months). On FDG-PET images, any FDG uptake that clearly exceeded the physiological liver uptake was defined as a "lesion". Lesions that were detected by FDG-PET, but which were not biopsied, were considered to be true-positive findings if the disease became obvious on a follow-up imaging study, such as MRI and angiogram. Abnormal foci seen on FDG-PET, that were not verified during follow-up, were considered false-positive findings. When no abnormality was seen on FDG-PET, and when there was no further intervention, the results was considered to be a true-negative, if by other imaging modalities or by clinical follow-up, no disease was identified within 6 months of the FDG-PET examination.

A study-based analysis of FDG-PET was performed. If more than one lesion was present in the same study of FDG-PET, at least one lesion with a true-positive FDG-PET finding was considered a true-positive. If any one of the lesions were detected by FDG-PET with a negative histological finding and long-term radiological and clinical follow-up result, the FDG-PET finding was classified as a false-positive. If none of the lesions were detected by FDG-PET, the FDG-PET finding was classified as a false-negative. Differences in AFP levels between FDG-PET groups were tested by the parametric two-sample Student's *t*-test and the nonparametric Willcoxon method. A *p*-value less than 0.05 indicated a statistically significant difference.

Results

The clinical and pathological features of the 26 patients with a total of 31 studies are outlined in Table I. Among the 26 HCC patients, 14 underwent surgical treatment (hepatectomy or lobectomy), 1 patient underwent radiofrequency ablation and 11 underwent transcatheter arterial embolization. At the time FDG-PET was performed, the mean±standard deviation AFP level in these patients was 7604.3±12466.3 ng/mL (range: 22-58423 ng/mL). The FDG-PET study results were correlated with histological findings, as well as long-term radiological and clinical follow-up (shortest follow-up period after FDG-PET was 6 months) (Table I).

Table I. *Summary of clinical, imaging and histopathological data of 31 FDG-PET studies (26 patients).*

Study No.	Pts No.	Age (yr)	Sex	Clinical history	AFP (ng/mL)	FDG-PET study	Follow-up (months)			
							Pathology	Radiology	Clinical	Therapy
1	1	45	M	HCC s/p hepatectomy 3 times	8739	R't lobe (VII) 3 cm L't lobe (II) 1.5 cm	NA	+	PD(6)	TAE
2	2	63	M	HCC s/p RFA 3 times	1210	R't lobe (VI) 3.7 cm	NA	+	PD(10)	RFA
3	3	65	M	HCC s/p hepatectomy	1346	-	NA	+	PD(10)	TAE
4	4	51	M	HCC s/p hepatectomy, TAE	23997	R't lobe (VII) 3 cm	NA	+	PD(9)	TAE
5	5	68	F	HCC s/p lobectomy	28	L't subdiaphragmatic	NA	-	PD(10)	C/T
6	5				64	L't subdiaphragmatic, L't lobe (IVa) 2 cm	NA	+	PD(7)	C/T
7	6	54	M	HCC s/p TAE	500	L't lobe (III) 1.5 cm	+	+	DF(5)	lobectomy
8	7	55	F	HCC s/p hepatectomy 2 times	5828	R't lobe (VII) 1.5 cm	+	+	DF(12)	hepatectomy
9	8	45	M	HCC s/p hepatectomy two times,	22	R't lobe (VIII) 2 cm	NA	+	PD(26)	PEI, R/T
10	8			TAE 6 times, PEI 5 times, R/T	442	R't lobe with metastasis to lung	NA	+	PD(10)	C/T
11	9	76	M	HCC s/p TAE	1154	R't lobe (VIII) 1.5 cm	NA	+	PD(10)	TAE
12	9				1007	R't lobe (VIII) 2.9 cm with lung metastasis	NA	+	Expired(6)	C/T
13	10	47	M	HCC s/p lobectomy	1313	-	NA	-	PD(30)	NONE
14	10			TAE, R/T	58423	R't lobe (VIII) 1.5 cm	NA	+	DF(12)	PEI
15	11	78	M	HCC s/p TAE	8266	T8, T11 metastasis	+	+	Expired(4)	C/T
16	12	75	M	HCC s/p hepatectomy, TAE, PEI, R/T	4672	-	NA	+	Expired(10)	NONE
17	13	64	F	HCC s/p TAE	11786	-	NA	+	PD(14)	TAE
18	14	64	M	HCC s/p TAE, PEI, hepatectomy 2 times	4259	ascites	NA	-	Expired(4)	NONE
19	15	71	M	HCC s/p TAE	434	-	NA	+	DF(16)	TAE
20	16	68	F	HCC s/p TAE, hepatectomy	4930	R't lobe (VI) 2 cm	NA	+	PD(17)	TAE, C/T
21	17	55	M	HCC s/p TAE 2 times	54	Lung metastasis	NA	+	Expired(13)	C/T, R/T
22	18	51	M	HCC s/p hepatectomy, TAE 10 times	19073	Ribs, T12, L1 metastasis	NA	+	Expired(10)	C/T
23	19	78	M	HCC s/p TAE, PEI	5000	PET (-) CT (+)	NA	+	DF(14)	TAE
24	20	55	M	HCC s/p TAE	120	-	NA	-	DF(7)	NONE
25	21	66	M	HCC s/p TAE	6798	PET (-) CT (+)	NA	+	DF(12)	TAE
26	22	35	M	HCC s/p hepatectomy, C/T, PEI	159	-	NA	+	PD(6)	TAE
27	23	52	M	HCC s/p TAE	34202	Hepatic tumor with lung, celiac LNs metastasis	NA	+	Expired(11)	C/T
28	24	71	M	HCC s/p TAE	19539	R't lobe (VI) 2 cm (VII) 1.5 cm	NA	+	DF(31)	TAE
29	25	50	M	HCC s/p hepatectomy, PEI	1998	R't lobe (VIII) 1.5 cm	NA	+	PD(12)	TAE
30	25				9159	R't lobe (VII) 2 cm	NA	+	Expired(10)	TAE
31	26	83	F	HCC s/p hepatectomy, TAE 6 times	1210	R't lobe VII, VIII three foci 1.5 cm L't lobe 2 lesion negative in PET, positive in CT	NA	+	PD(6)	TAE, C/T

M: male, F: female, HCC: hepatocellular carcinoma, AFP: alpha-fetoprotein, R't: right, L't left, NA: not available, -: no disease, +: presence of disease, C/T: chemotherapy, DF: disease-free, PD: progression of disease, PEI: percutaneous ethanol injection, Pts: patients, R/T: radiotherapy, RFA: radiofrequency ablation, TAE: transcatheter arterial embolization.

Abnormal foci of increased FDG accumulation were seen in 22 of the 31 studies (71.0%). Intrahepatic lesions were detected in 20 of the 30 lesions (66.7%) in 18 studies of FDG-PET (26 patients). Only one intrahepatic lesion was identified in 10 studies (9 patients) and more than one intrahepatic lesion was identified in 3 studies (3 patients) (Figure 1). The false-negative detection rate of intrahepatic lesions was 10/30 (33.3%) in 9 studies of FDG-PET (9 patients) (Figure 2). Extrahepatic

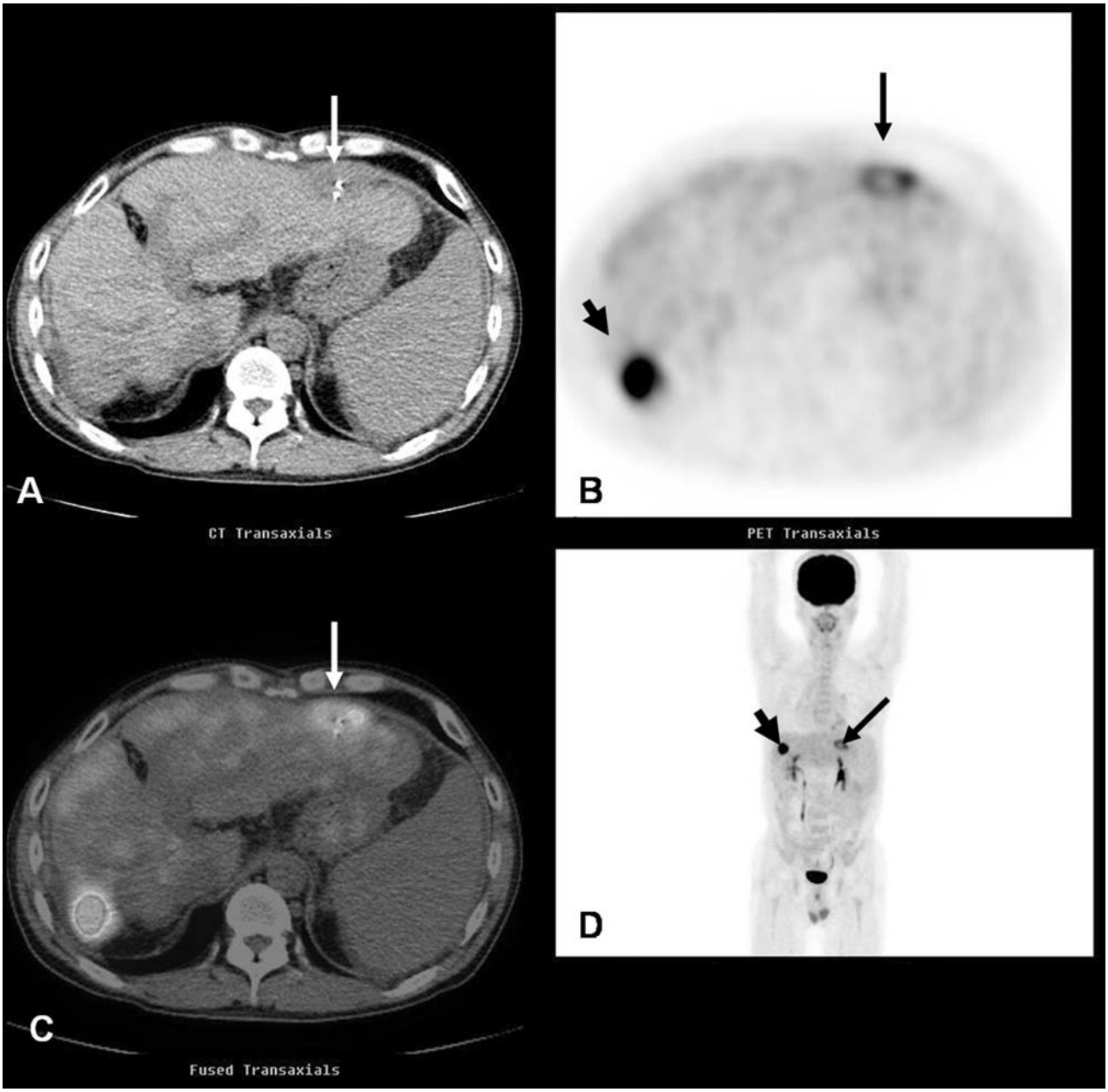

Figure 1. *A 45-year-old hepatitis B virus carrier was found to have liver cirrhosis and HCC 6 years previously. He had undergone hepatectomies and was followed with serum AFP, US and CT for 6 months. The serum AFP level progressively elevated and was higher than 5000 ng/mL, but US and CT imaging was normal. Therefore, the patient underwent FDG-PET/CT study using a GE discovery LS PET/CT hybrid imaging scanner. The short arrow points to an intense FDG uptake in the right lobe of the liver in the transaxial (B) and projection (D) image. The long arrow points to a halo of increased FDG uptake in the left lobe of the liver with the surgical clip (A, B, C). In addition, a combination of the anatomical (A) and physiological (B and D) images shows the right lobe of the liver is shrunken with splenomegaly due to cirrhosis of liver. The patient then underwent TAE therapy.*

metastases were found in 9/31 studies of FDG-PET (29.0%) among 8 patients. These metastatic foci of increased FDG accumulation were identified in several locations; lung (4 studies among 4 patients), bone (2 studies among 2 patients), and the peritoneum (4 studies among 3 patients).

Overall, the study-base analysis of FDG-PET for detecting HCC recurrence demonstrated 22 true-positives, 8 false-negatives, 1 true-negative and 0 false-positive. The sensitivity, specificity, accuracy, positive predictive value and negative predictive value of FDG-PET studies for detecting

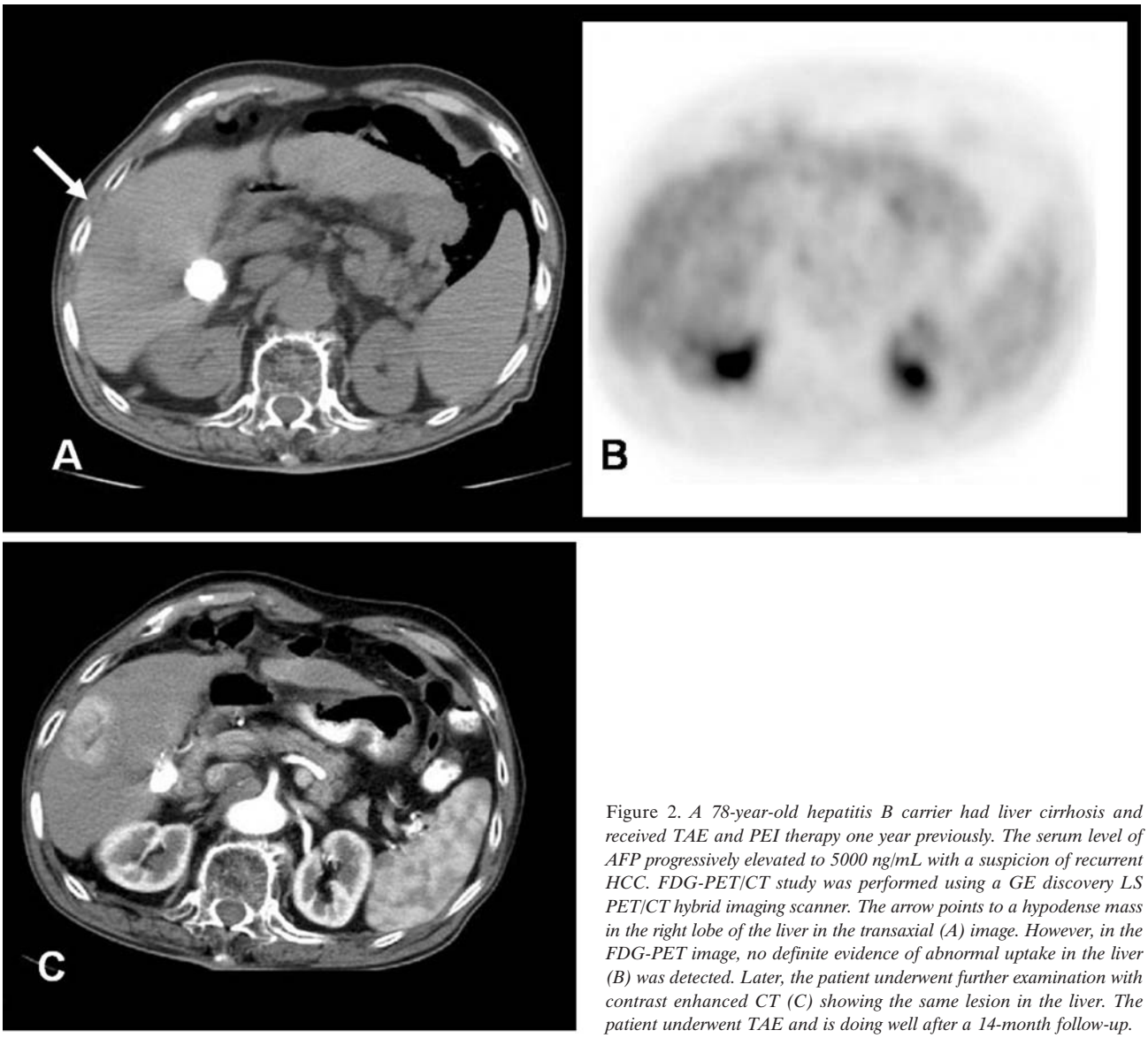

Figure 2. *A 78-year-old hepatitis B carrier had liver cirrhosis and received TAE and PEI therapy one year previously. The serum level of AFP progressively elevated to 5000 ng/mL with a suspicion of recurrent HCC. FDG-PET/CT study was performed using a GE discovery LS PET/CT hybrid imaging scanner. The arrow points to a hypodense mass in the right lobe of the liver in the transaxial (A) image. However, in the FDG-PET image, no definite evidence of abnormal uptake in the liver (B) was detected. Later, the patient underwent further examination with contrast enhanced CT (C) showing the same lesion in the liver. The patient underwent TAE and is doing well after a 14-month follow-up.*

HCC recurrence were 73.3%, 100%, 74.2%, 100% and 11.1%, respectively. One patient with 1 true-negative FDG-PET study is alive and disease-free after a follow-up of 7 months. In the remaining 8 patients with 8 false-negative FDG-PET studies, clinical follow-up and further radiological examinations revealed tumor recurrence.

Discussion

FDG-PET is a whole-body imaging technique that detects cancer by exploiting the increased rate of glycolysis in tumor cells. FDG is a glucose analog that is taken up by cellular glucose transport mechanisms and is phosphorylated by hexokinase. In most malignant cells, FDG-6-phosphate becomes metabolically "trapped" intracellularly because of the relative lack of glucose-6-phosphatase activity in tumor cells. Many studies have indicated a greater accuracy of metastatic staging and detecting recurrent cancers by FDG-PET than by CT and other standard diagnostic modalities.

Although surgical resection of HCC yields a better prognostic outcome than nonsurgical treatments, surgery is not an option for many patients because of their poor hepatic function reserve. Effective nonsurgical treatment of HCC usually invovles transcatheter arterial embolization (TAE) combined with percutaneous ablation therapy, such as percutaneous ethanol injection (PEI) or radiofrequency ablation. Early detection and treatment of recurrent HCC are keys to patient survival after hepatic

surgery and interventional treatment. US, CT and MRI are generally used to assess the reduction in size or changes in the internal structure. However, in some liver tumors, the diameter does not change and only the internal structure changes. In addition, lipiodol deposits can make the evaluation more difficult (15). In contrast to morphological image diagnosis, FDG-PET, which evaluates viability based on glucose metabolism, is not influenced by tumor size, morphology or lipiodol deposition (14). A completely successful embolization of the feeder artery causes tumor cell death, but incomplete embolization leads to hypoxia, favoring anaerobic metabolism (16). Therefore, FDG-PET findings reflect tumor viability more accurately than the extent of intratumor lipiodol retention on CT images (17).

In general, measurement of AFP, US and CT are carried out periodically after treatment. FDG-PET is not as sensitive, but is more specific than ultrasound and serum AFP levels in detecting HCC and differentiating them from other benign liver diseases in hepatitis B virus carriers (18). Serum AFP correlates significantly with both the standardized uptake value and tumor-to-nontumor ratio of FDG-PET images, indicating that AFP is involved in glucose metabolism and cell proliferation in HCC (19). The results of our study demonstrated that, in the majority of patients with inexplicably increased AFP levels, after having undergone conventional imaging modalities, whole body FDG-PET provided decisive diagnostic clues guiding further diagnostic and therapeutic interventions. In our group, which consisted of 31 studies in 26 patients, whole-body FDG-PET detected tumor relapse in 22/31 (73.3%) studies. These findings led to surgical, PEI or TAE intervention with a curative intent in 15.4% (4/26) of the patients. FDG-PET indicated the presence of unresectable disease (such as extrahepatic metastasis) in 29.0% (9/31) of the patients, leading to a treatment change combined with chemotherapy. These extrahepatic metastatic foci of increased FDG accumulation were identified in lung (4 patients), bone (2 patients) and peritoneum (3 patients). Therefore, the whole-body FDG-PET scan may be an important and valuable tool for detecting extrahepatic lesions.

False-negative FDG-PET findings in our study were found in 8/31 (26.7%) of the studies and 10/30 (33.3%) of the intrahepatic lesions. In some HCC, a higher glucose-6-phosphatase activity (k4) to phosphorylation kinase activity (k3) ratio causes low glucose metabolism and FDG uptake, especially in the well-differentiated and lower grade HCC (14). Therefore, the average reported false-negative rate using FDG-PET in primary HCC approaches 40%-50% (15, 20, 21). However, in our study, recurrent HCC often showed a high uptake of FDG. Tumor cells may alter their metabolism to produce more ATP under anaerobic conditions by up-regulating glucose metabolism. For example, hypoxia can increase FDG uptake by tumor cells, caused by the increased anaerobic glycolytic pathway (22, 23).

In this retrospective study, our preliminary data have shown that FDG-PET is a valuable imaging tool in patients who have a rising AFP level after HCC treatment. In addition, FDG-PET is a good tool for detecting extrahepatic spread.

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