Early diagnosis of recurrent hepatocellular carcinoma with ^{18}F-FDG PET after radiofrequency ablation therapy

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Abstract. The aim of this study was to evaluate the role of positron emission tomography (PET) with ^{18}F-fluoro-2-deoxy-D-glucose (^{18}F-FDG) in the restaging of hepatocellular carcinoma (HCC) treated with radiofrequency ablation (RFA). This study was performed on 33 lesions in 24 patients with HCC. ^{18}F-FDG PET and computed tomography (CT) studies were performed in all patients before treatment. PET acquisition was started 50-60 min after injection of ^{18}F-FDG (5-6 MBq/kg). Semi-quantitative analysis using Standardized Uptake Value (SUV) was measured for the evaluation of tumour ^{18}F-FDG uptake. All patients underwent RFA treatment and were followed up at least 2 years with ^{18}F-FDG PET, CT and clinical evaluation in the interval of every 3 months in the first year and every 6 months in the second year. ^{18}F-FDG PET detected recurrence earlier than CT between 4-6 months in 2 patients and between 7-9 months in 6 patients whereas CT was positive in 4 patients. Overall detection rate of recurrence with ^{18}F-FDG PET was 92% which was higher than that of CT (75%). Statistically significant difference in the SUV was observed between well and moderately differentiated HCC ($p=0.033$) and also between well and poorly differentiated HCC ($p=0.037$). The size of tumours showed a significant correlation with the time of recurrence ($p<0.00033$, $r=0.8601$, $n=12$). The results of this study indicate that ^{18}F-FDG PET could detect recurrence earlier in patients with HCC treated with RFA, as compared with CT and could diagnose extrahepatic lesions. SUV showed a significant correlation with time of recurrence after RFA. ^{18}F-FDG PET may be a dominant imaging modality as a follow-up procedure of HCC after RFA, in terms of early detection of recurrence.

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Introduction

Hepatocellular carcinoma (HCC) is one of the most common cancers of the world and causes about one million deaths annually (1,2). The optimum therapy for patient with HCC is surgical excision either by hepatic resection or orthotropic liver transplantation. Unfortunately many patients are not candidate for surgical resection and efforts have been made to provide various alternative therapies to treat the unresectable HCC. Radiofrequency ablation (RFA) is a technique that is recently developed for the ablation of liver tumours. It converts radio frequency waves into thermal energy, causing coagulation necrosis of the tumours. It has attracted great interest in recent years because of excellent response rate with little morbidity (3,4). Compared with other local ablative modalities, RFA has been shown to be safer and more effective (5,6).

Positron emission tomography (PET) with ^{18}F-fluoro-2-deoxy-D-glucose (^{18}F-FDG) is a functional imaging tool that provides metabolic information of the lesion. It is effective for diagnosis, monitoring therapy and detection of recurrent tumours of various cancers because of its high sensitivity and specificity (7-10). However, it is less successful in the detection of primary HCC because of variable uptake (11,12). Even though the value of ^{18}F-FDG PET for the detection of primary HCC remains controversial, ^{18}F-FDG PET would seem to be appropriate for the follow-up of liver tumours (13,14). In a recent study, Antoch *et al* mentioned that homogeneous tracer utilization was found in the area surrounding the lesion on ^{18}F-FDG PET and PET/CT (15). There was no area of focal or rim-like increase in the glucose metabolism where a rim-like increase in the contrast enhancement was found by the morphologic imaging immediately after RFA. Therefore ^{18}F-FDG PET seems to be accurate for the assessment of patients shortly after RFA, although there is no clear consensus on which imaging technique is most reliable to monitor RFA therapy. The purpose of this preliminary study was to evaluate the role of ^{18}F-FDG PET to assess the earlier recurrence of HCC treated with RFA as compared with CT.

Table I. Clinical characteristics and the results of ^{18}F-FDG PET in 24 patients with hepatocellular carcinoma (HCC).

Patient	Age	Sex	Tumours		SUV (^{18}F-FDG)	AFP (ng/ml)	Histology
			Location	Size (cm)			
1	69	M	S2/S5	1.6/1.5	1.56/0.5	26.6	Well diff
2	77	M	S4	2.0	1.27	19.2	Well diff
3	73	M	S5	2.6	2.18	17.0	Well diff
4	76	M	S3	3.0	1.34	20.0	Well diff
5	72	F	S8	2.5	1.90	15.0	Well diff
6	66	M	S4/S5	3.5/2.5	1.70/1.30	1.5	Well diff
7	74	M	S8	3.0	1.90	219.2	Well diff
8	63	M	S5	2.5	2.86	72.8	Mod diff
9	66	M	S4/S5	3.5/1.5	4.03/1.30	22.7	Mod diff
10	71	M	S3/S6	2.0/1.8	1.50/1.30	17.0	Mod diff
11	62	F	S8/S6	3.5/1.5	4.36/1.70	12.7	Mod diff
12	54	F	S4/S7	2.7/2.5	2.37/1.37	4.9	Mod diff
13	56	F	S8	1.5	1.50	81.5	Mod diff
14	54	F	S3	2.5	1.50	88.5	Mod diff
15	50	M	S6	3.8	4.93	4785.0	Mod diff
16	55	M	S3	3.0	1.60	11.1	Mod diff
17	66	M	S2	2.8	3.90	127.5	Mod diff
18	61	M	S6/ S8	2.0/0.8	1.34/1.23	47.2	Mod diff
19	72	F	S5/S8	4.0/2.5	5.64/1.36	59.9	Poorly diff
20	71	M	S3	2.0	3.14	10.1	Poorly diff
21	68	F	S6	2.0	3.86	31.6	Poorly diff
22	75	F	S5	3.0	3.97	59.9	Poorly diff
23	71	M	S3/S6	2.9/2.5	2.34/1.16	191.5	Poorly diff
24	58	M	S6	2.5	1.90	7.8	Poorly diff

M, male; F, female; AFP, serum concentration of alpha-fetoprotein; Well diff, well differentiated HCC; Mod diff, moderately differentiated HCC; Poorly diff, poorly differentiated HCC; SUV, standardized uptake value.

Materials and methods

Patients. This study was performed on 33 lesions in 24 patients with HCC (16 male and 8 female, age range from 50 to 77 years, median age 67 years) who underwent ^{18}F-FDG PET imaging and clinical follow-up between April 2000 and March 2005. ^{18}F-FDG PET and computed tomography (CT) studies were performed on all patients before treatment with RFA. The time interval between ^{18}F-FDG PET examination and RFA was 1-4 weeks (mean 2.1 weeks). Biopsy or surgical resection confirmed the histological diagnosis as shown in Table I. Three patients underwent subsegmentectomy and 3 patients had transhepatic arterial embolization (TAE) before the RFA. Nine patients had multiple HCCs. All patients underwent RFA and were followed up at least 2 years with ^{18}F-FDG PET and CT. Clinical evaluation was performed every 3 months in the first year and every 6 months in the second year. Detectability of recurrence was compared between ^{18}F-FDG PET and CT in these periods. The study protocols have been approved by the Institutional Review Board of our institute and informed consent was obtained from all patients participating in this study.

^{18}F-FDG PET study. PET study was performed using a SET2400W PET scanner (Shimadzu Corp., Kyoto, Japan) with a 59.5 cm transaxial field of view and 20 cm axial field of view. The scanner produced 63 image planes, spaced 3.125 mm apart. Transaxial spatial resolution was 4.2 mm full width half-maximum (FWHM) at the center of the field of view, and axial resolution was 5.0 mm FWHM. The blood glucose level in all patients was <110 mg/dl at the time of the ^{18}F-FDG injection. ^{18}F-FDG was synthesized by the method of Hamacher *et al* (16).

Patients fasted for at least 6 h before ^{18}F-FDG PET scanning. None of the patients had insulin-dependent diabetes. Data acquisition was initiated at 60 min after the injection of 5-6 MBq/kg ^{18}F-FDG by the simultaneous emission-transmission method with a rotating external source for absorption correction. Four to five bed positions from the head to the thigh were imaged for eight minutes per position. The attenuation-corrected transaxial images were reconstructed by the ordered subsets expectation maximization (OSEM) algorithm into a 128x128 matrix with pixel dimensions of 4.0 mm in a plane and 3.125 mm axially. Finally, every three consecutive slices were added to generate a transaxial image

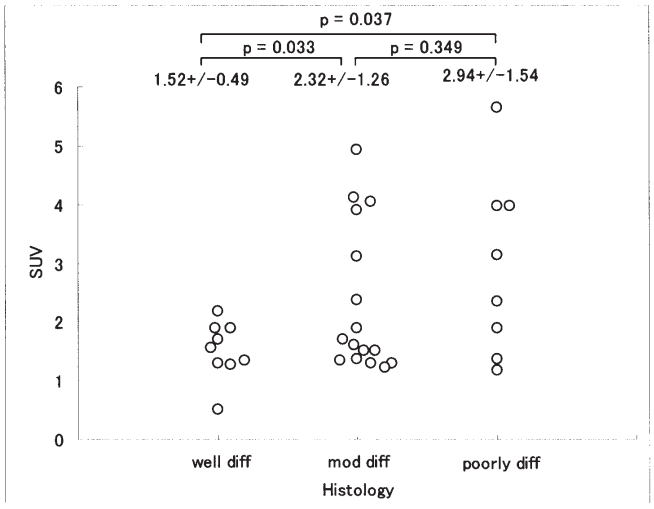

Figure 1. Comparison between standardized uptake value (SUV) and histological differentiation of HCC. Statistically significant difference is noted between well differentiated HCC and moderately differentiated HCC and also between well differentiated HCC and poorly differentiated HCC; however, no significant difference is noted between poorly differentiated HCC and moderately differentiated HCC.

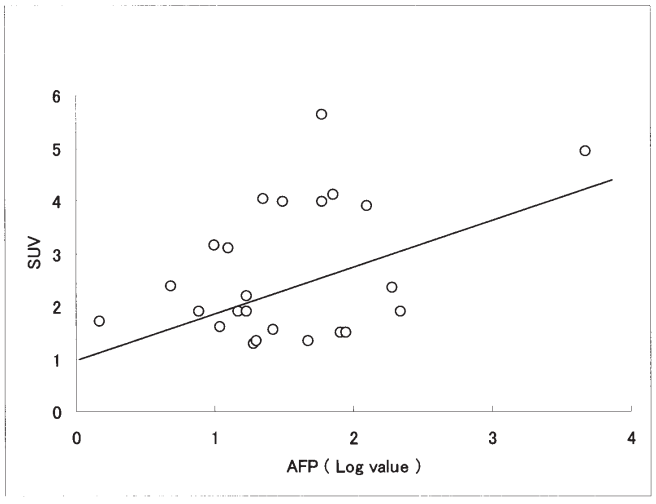

Figure 2. Correlation between pre-treatment serum concentration of AFP (log value) and SUV value of ^{18}F-FDG (p=0.0431, r=0.4162, n=24).

with 9.8-mm thick for the visual interpretation and quantitative analysis by using the standardized uptake value (SUV) which was calculated as follows:

$$SUV = \frac{\text{Radioactivity in the tissue or lesion (MBq/g)}}{\text{Injected dose (MBq)/patient's body weight (g)}}$$

Similarly coronal image of 9.8-mm thick were also reconstructed from attenuation-corrected transaxial images. All ^{18}F-FDG PET images were evaluated qualitatively by two experienced nuclear physicians in conjunction with CT and result was compared with clinical findings. In order to evaluate the ^{18}F-FDG uptake in the tumour, a 4x4 pixel square regions of interest (ROIs) were placed on the tumour, including the area of the highest activity but not covering the entire tumour. Positive lesions were identified if the uptake of ^{18}F-FDG in the tumour was higher than that in the background of the liver.

Statistical analysis. We analyzed data using Student's t-test to compare mean value of SUV between groups of patients. A linear regression analysis was performed to evaluate correlation of mean SUV with serum alpha-fetoprotein (AFP) concentration. Probability values of $p<0.05$ were considered significant.

Results

Relationship between ^{18}F-FDG uptake and histological findings. The results of ^{18}F-FDG PET and clinical finding of all patients before RFA are summarized in Table I. Among 24 patients, 12 (50%) were positive for ^{18}F-FDG PET prior to RFA. ^{18}F-FDG uptake and histological finding of all lesions were examined. Comparing ^{18}F-FDG uptake among different histological groups, poorly differentiated HCC and moderately differentiated HCC have high uptake of ^{18}F-FDG than well differentiated HCC (Fig. 1). A significant difference in the SUV was observed between well differentiated HCC and moderately differentiated HCC (1.52±0.49, n=9 vs. 2.32±1.26, n=16, p=0.033) and also between well differentiated HCC and poorly differentiated HCC (1.52±0.49, n=9 vs. 2.94±1.54, n=8, p=0.037), however, not between moderately differentiated HCC and poorly differentiated HCC (2.32±1.26, n=16 vs. 2.94±1.54, n=8, p=0.349).

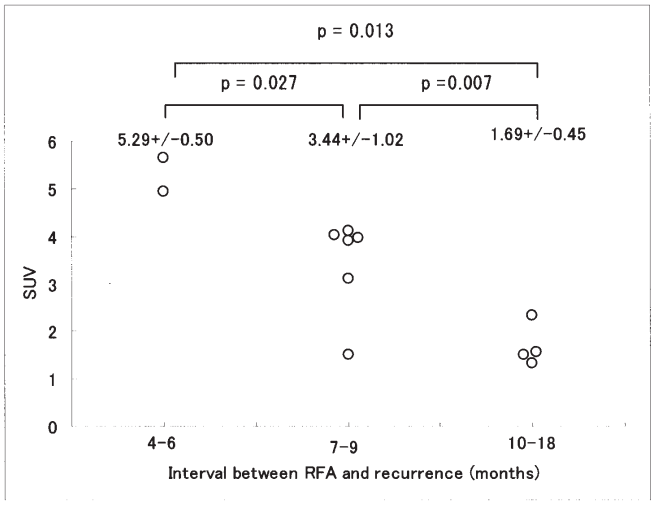

Figure 3. Relationship between ^{18}F-FDG uptake and interval between RFA and recurrence. SUV is significantly higher in cases with earlier recurrence of the tumour.

SUV of major tumours in 24 patients ranged from 1.27 to 5.64 (mean 2.61, n=24) and log value of AFP of these patients were compared with SUV (Fig. 2). Significant correlation was observed between AFP and SUV before RFA (p=0.0431, r=0.4162, n=24).

^{18}F-FDG PET detected recurrence of HCC in 12 patients, where SUV at the time of initial PET study ranged from 1.34 to 5.64 (mean 3.16, n=12). The time interval between RFA and recurrence was divided in 4-6 months, 7-9 months and 10-18 months. There was inverse correlation between SUV and the interval between RFA and detection of recurrence

Table II. Detection of recurrent hepatocellular carcinoma with ^{18}F-FDG PET and CT after radiofrequency ablation therapy in a two-year follow-up.

	0-3 M	4-6 M	7-9 M	10-12 M	13-18 M	19-24 M
^{18}F-FDG PET	0	2	6	3[a]	1[b,c]	0
CT	0	0	4	1	3	1

M, months after RFA; [a]One patient metastasized to the abdomen; [b]one patient developed a new lesion in a different segment of the liver; and [c]one patients metastasized to the lung.

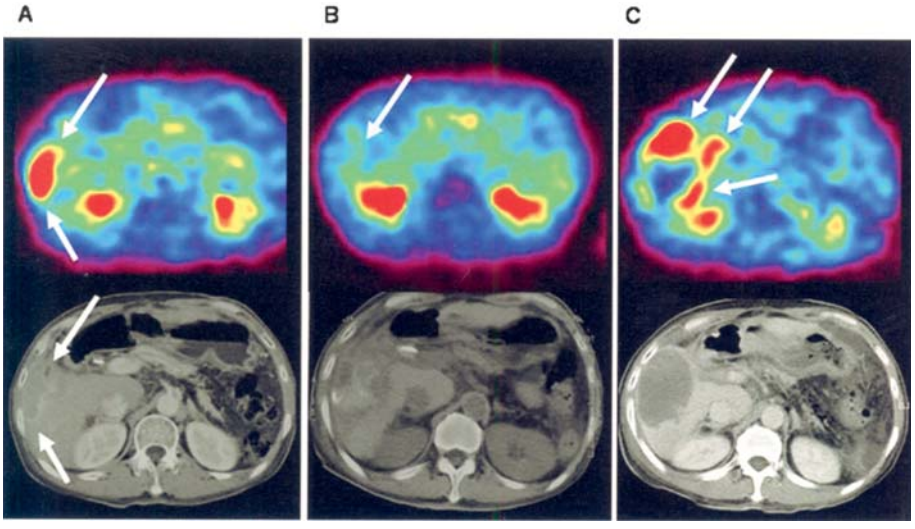

Figure 4. ^{18}F-FDG PET and corresponded CT before and after RFA in a patient with hepatocellular carcinoma (patient no. 8). (A) ^{18}F-FDG PET shows abnormal uptake in the lesion (arrow) and the corresponding CT shows marginal enhancement (arrow). (B) ^{18}F-FDG PET after RFA shows no uptake of ^{18}F-FDG (arrow). (C) ^{18}F-FDG PET shows high uptake of ^{18}F-FDG in the area after RFA (arrows), although CT is not conclusive for a recurrent tumour.

indicating that a higher SUV may predict earlier recurrence of HCC. A significant difference was noted in SUV between patients who showed recurrence during 4-6 and 7-9 months (5.29±0.50 vs. 3.44±1.02, p=0.027), 4-6 and 10-18 months (5.29±0.50 vs. 1.69±0.45, p=0.013), and 7-9 and 10-18 months (3.44±1.02 vs. 1.69±0.45, p=0.007 as shown in Fig. 3.

Detection of recurrence. Table II shows the numbers of patients with recurrence detected by ^{18}F-FDG PET and CT in a two-year follow-up period. No recurrence or new lesion was detected by ^{18}F-FDG PET and CT in the first 3 months after RFA. Between 4-6 months, 2 patients were positive by ^{18}F-FDG PET but they were negative by CT. Between 7-9 months, 6 patients were positive by ^{18}F-FDG PET while the CT showed only 4 positive. The patients with recurrence underwent second RFA within a month. Between 10-12 months, ^{18}F-FDG PET detected three recurrences with one having a metastasis to abdomen while CT showed recurrence in one patient. In first six months of the second year (13-18 months), ^{18}F-FDG PET detected one case with recurrence, one case with new lesion (in different segment of the liver) and one case with lung metastasis. In the same period CT detected three recurrences but was unable to detect the new lesion in the former patients. During last 6 months of the second year (19-24 months), ^{18}F-FDG PET did not detect any new lesion, while CT detected one lesion, which had been detected earlier by ^{18}F-FDG PET. A representative case of recurrent HCC is shown in (Fig. 4).

Discussion

The results of the present study indicated that ^{18}F-FDG PET detected recurrence of HCC after RFA earlier than CT. Overall detection rate of recurrence with ^{18}F-FDG PET was 92% (11/12) and it was higher than that of CT 75% (9/12), suggesting that ^{18}F-FDG PET is a potential diagnostic tool for detection of the recurrence of HCC after RFA. None of the patients without abnormal ^{18}F-FDG uptake developed a local recurrence during the follow-up period of two years. Another advantage of ^{18}F-FDG PET over CT is its whole body imaging method, due to this we diagnosed extra hepatic metastasis in two patients in this study. We correctly found extrahepatic metastasis in the abdomen and another in the lung by PET and made a proper decision for the treatment, although chest CT was not performed in the case with pulmonary metastasis.

Previously Donckier *et al* (17) reported that ^{18}F-FDG PET is a tool for early recognition of incomplete tumour destruction after RFA for liver metastasis and in another study Langenhoff *et al* (13) mentioned that ^{18}F-FDG PET accurately detected recurrence of colorectal liver metastasis earlier than CT, but to our knowledge there is no report yet on the value of ^{18}F-FDG PET as compared with conventional imaging modality to detect recurrence of HCC treated with RFA in a long follow-up period. The results of the preliminary study indicated that ^{18}F-FDG PET is a valuable tool to monitor the patients with HCC after RFA therapy to detect the recurrence earlier than CT in order to make a correct decision for the treatment.

In our study, poorly differentiated and moderately differentiated HCC have a higher ^{18}F-FDG uptake than well differentiated HCC and significant correlation was observed between SUV and histological differentiation as reported previously (11,18).

We found a significant correlation between the SUV in the HCC before RFA and the interval from the RFA to the time of recurrence which was detected by ^{18}F-FDG PET. Cases with high SUV showed recurrence significantly earlier than those with low SUV. Previous studies revealed that the tumour-to-normal ratio of SUV correlated with the survival of patients after surgery (19,20). The results of the present study indicate the possibility of the prognostic value of ^{18}F-FDG PET in patients with HCC undergoing RFA, and warrant further studies to evaluate it.

The limitations of our study were the retrospective nature, no exact protocol for the follow-up procedure, and a limited number of cases. In the present study we observed one false positive case with ^{18}F-FDG PET. This lesion turned out to be an infection. It is well known that ^{18}F-FDG is accumulated in inflammatory tissue therefore careful reading with reference to other modalities and clinical evaluation is needed.

In patients with HCC treated with RFA, ^{18}F-FDG PET detected recurrence earlier than CT and could diagnose extrahepatic lesions. ^{18}F-FDG uptake as evaluated with SUV showed a significant correlation with time of recurrence after RFA. ^{18}F-FDG PET may be a useful imaging modality as a follow-up procedure of HCC after RFA, in terms of early detection of recurrence and potential prognostic factor. An elaborated study with large number of patients with longer follow-up period will be needed to confirm the significance of these findings.

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