FDG positron emission tomography/computed tomography findings for the prediction of early recurrence of hepatocellular carcinoma after surgical resection

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Abstract. We investigated the predictive value of fluorine-18-fluorodenoxyglucose positron emission tomography/computed tomography for pathological malignant potential and early recurrence of hepatocellular carcinoma (HCC) after resection. From April 2006 to October 2009, 53 patients with naïve HCC were enrolled. Accumulations of 2-[18F]-fluoro-2-deoxy-D-glucose (FDG) standardized uptake value (SUVmax) in both HCC and non-HCC areas of the liver as well as the ratio of SUVmax (R-SUV; HCC/liver) were calculated. The results were evaluated to determine prognostic factors for early recurrence. One patient was graded as tumor node metastasis stage I, 35 as II, 14 as III and 3 as stage IV. Elevated protein induced by vitamin K absence or antagonist II (≥200 mAU/ml) as well as elevated fucosylated α-fetoprotein (≥15%), tumor size (≥5 cm) and high R-SUV (≥1.5) were risk factors for early recurrence in a univariate analysis (P<0.05). In a multivariate analysis, high R-SUV (≥1.5) was the only risk factor (P<0.05). The recurrence-free rate in patients with low R-SUV (<1.5, n=34) was higher than that in those with high R-SUV (≥1.5, n=19) (1- and 2-year rates: 100 and 67%, 67 and 17%; respectively, P<0.01). Patients with Edmondson III showed higher R-SUV values than those with Edmondson I and II (3.0±1.8, 1.4±0.3 and 1.9±0.9, respectively, P<0.01), while those with micro-vascular invasion (vp)(+), micro-intrahepatic metastasis (im)(+) or non-boundary type showed higher R-SUV values than vp(-), im(-) and boundary type (3.6±2.4 vs. 2.0±0.9, 3.5±2.3 vs. 1.9±0.8 and 2.9±1.8 vs. 1.6±0.5, respectively, P<0.01). R-SUV is proposed to be a useful marker for the prediction of early recurrence of HCC after resection.

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Introduction

Recently, 2-[18F]-fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET)/computed tomography (CT) has been used for diagnosing malignant tumors, and many reports have described its role for predicting the malignant potential of these tumors. However, the clinical efficacy of PET/CT for diagnosing hepatocellular carcinoma (HCC) remains controversial, and only a few reports have described the predictive value of its findings for pathological malignant potential and prognosis (1-3).

Hepatic resection is performed as a standard therapy for HCC in Japan (4,5). However, recurrence of HCC after resection is known to occur at a high rate, and early recurrence is considered to be a significant prognostic factor for death. Although macroinvasion of HCC to the portal vein is also a factor for poor prognosis (6), most patients with HCC without macro-tumor thrombosis suffer from recurrence after resection. Previous reports have investigated prognostic markers for early recurrence and survival, including the doubling time of pre-operative serum α-fetoprotein (AFP) and protein induced by vitamin K absence or antagonist II (PIVKA-II) (7), complication with diabetes mellitus (8), hepatic steatosis (9) and tumor node metastasis (TNM) stage (10), although these are not adequately sensitive. In the present study, we investigated the predictive value of PET/CT for the pathological malignant potential of HCC as a new indicator for early recurrence after hepatic resection.

Materials and methods

From April 2006 to October 2009, 53 patients with naïve HCC, examined by PET/CT and treated by hepatic resection, were enrolled. None had poorly controlled diabetes mellitus. All were examined using PET/CT (Discovery ST Elite 16; GE Healthcare Japan Co. Ltd., Tokyo, Japan) within the month

Table I. Univariate analysis of clinical parameters for early recurrence after resection.

Factors	No.	Hazard ratio	95% CI	P-value
Age in years (<70:≥70)	23:30	0.662	0.234-1.873	0.437
Anti-HCV (positive:negative)	28:25	0.612	0.221-1.674	0.345
Gender (male:female)	40:13	0.688	0.189-2.507	0.571
Aspartate transferase (IU/l) (<80:≥80)	44:9	2.501	0.841-7.437	0.099
Alanine transferase (IU/l) (<80:≥80)	48:5	3.710	0.956-14.402	0.058
Total bilirubin (mg/dl) (<2:≥2)	52:1	0.048	0.000-2.823	0.810
Albumin (g/dl) (<3.5:≥3.5)	11:42	1.456	0.307-6.904	0.636
Prothrombin time (%) (<80:≥80)	25:28	0.923	0.341-2.493	0.874
Platelets (x10^4 cells/μl) (<12:≥12)	18:35	1.453	0.515-4.098	0.480
Child-Pugh (A:B)	44:9	1.679	0.352-8.003	0.515
AFP (ng/ml) (<100:≥100)	41:12	1.996	0.619-6.441	0.248
AFP-L3 (%) (<15:≥15)	38:15	3.165	1.101-9.095	0.032
PIVKA-II (mAU/ml) (<200:≥200)	31:22	3.805	1.285-11.267	0.016
Diabetes mellitus (positive:negative)	16:37	0.371	0.102-1.354	0.133
No. of HCC (multiple:single)	15:38	1.578	0.540-4.607	0.404
Tumor size (<5 cm:≥5 cm)	31:22	3.050	1.036-8.983	0.043
R-SUV (<1.5:≥1.5)	19:34	10.581	1.394-80.343	0.023

CI, confidence interval; HCV, hepatitis C virus; AFP, α-fetoprotein; AFP-L3, fucosylated AFP; PIVKA-II, protein induced by vitamin K absence or antagonist II; TNM stage, tumor node metastasis stage; R-SUV, ratio of accumulations of FDG in HCC and non-HCC areas of the liver.

prior to resection. PET/CT was performed 60 min after a bolus injection of F-18 FDG (3 MBGq/kg). Accumulations of FDG [standardized uptake value (SUVmax)] in HCC and non-HCC areas of the liver as well as the ratio of SUVmax (R-SUV), which indicated the tumor to non-tumor ratio, were determined. In cases with multiple HCC, the SUVmax was calculated for the main nodule. From these findings, we evaluated prognostic factors for early recurrence, which was defined as recurrence within 2 years of resection. Moreover, R-SUV values were compared to the pathological findings, including microvascular invasion (vp), micro-intrahepatic metastasis (im) and gross type of HCC (11,12). The patients were divided into two groups, low R-SUV (n=19) and high R-SUV (n=34), and their clinical parameters were compared.

Statistical analysis. Data are expressed as the mean ± standard deviation (SD). Statistical analyses were performed using the Student's t-test for unpaired data, a χ^2 test, Fischer's exact test, a Mann-Whitney U test and a log-rank test, as appropriate. All statistical analyses were performed with SPSS 16.0J (SPSS Japan Inc., Tokyo, Japan). A P-value of <0.05 was considered to represent statistical significance.

Results

One patient was classified as TNM stage I, 35 as stage II, 14 as stage III and 3 as stage IV, based on the results of imaging examinations (abdominal ultrasonography and dynamic CT). There were no cases with extrahepatic metastasis. R-SUV values ranged from 1.0 to 6.9. In pathological analyses, all were diagnosed as typical HCC. PIVKA-II (≥200 mAU/ml), fucosylated AFP (AFP-L3) (≥15%), tumor size (≥5 cm) and high R-SUV (≥1.5) were found to be risk factors for early recurrence in a univariate analysis (P<0.05, respectively) (Table I). In a multivariate analysis, high R-SUV (≥1.5) was the only risk factor (P<0.05) (Table II). The recurrence-free rate in the low R-SUV group was higher than that in the high R-SUV group (1- and 2-year recurrence-free rates: 100 and 67%, 67 and 17%, respectively; P<0.01) (Fig. 1). While the frequencies of high levels of PIVKA-II (≥200 mAU/ml) and AFP-L3 (≥15%) were greater in the high R-SUV group (52.9 and 38.2% vs. 21.1 and 10.5%, respectively; P<0.01), there were no significant differences in regard to the frequencies of high levels of AFP (≥100 ng/ml), tumor diameter ≥5 cm, Child-Pugh class, number of tumors and TNM stage between the groups (Table III).

Table II. Multivariate analysis of clinical parameters for early recurrence after resection.

Factors	Hazard ratio	95% CI	P-value
AFP-L3 (≥15%)	1.644	0.510-5.308	0.405
PIVKA-II (≥200 mAU/ml)	2.113	0.481-9.275	0.322
Tumor size (≥5 cm)	1.157	0.271-4.935	0.843
R-SUV (≥1.5)	8.137	1.027-64.466	0.047

CI, confidence interval; AFP-L3, fucosylated α-fetoprotein; PIVKA-II, protein induced by vitamin K absence or antagonist II; R-SUV, ratio of accumulations of FDG in HCC and non-HCC areas of the liver.

Patients with HCC nodules rated as Edmondson III (13) had a higher R-SUV value (3.0±1.8) than those rated as I

Table III. Clinical background of the patients.

	Low R-SUV group (n=19)	High R-SUV group (n=34)	P-value
Age (years)	68.2±14.1	69.5±10.5	0.705
Anti-HCV (positive:negative)	13:6	15:19	0.092
Gender (male:female)	15:4	25:9	0.705
Aspartate transferase (IU/l)	49.4±32.2	50.2±25.8	0.308
Alanine transferase (IU/l)	40.5±25.4	41.5±27.8	0.934
Total bilirubin (mg/dl)	0.79±0.49	0.66±0.28	0.085
Albumin (g/dl)	4.0±0.6	4.0±0.5	0.555
Prothrombin time (%)	80.1±12.2	81.2±9.9	0.127
Platelets (x10^4 cells/μl)	13.0±4.7	16.0±5.7	0.696
Child-Pugh class (A:B)	15:4	29:5	0.528
AFP (ng/ml)	371.2±1,199.4	2,306.5±12,657.9	0.201
AFP-L3 (%)	1.6±5.1	16.9±23.9	<0.001
PIVKA-II (mAU/ml)	424.4±1,123.6	8,436.2±17,683.6	0.001
Tumor size (<5 cm:≥5 cm)	14:5	17:17	0.077
No. of tumors	1.4±0.7	1.4±0.7	0.819
Score of up to 7 criteria	5.0±1.7	7.4±3.4	0.013
TNM stage (I:II:III:IV)	1:13:5:0	0:22:9:3	0.320
Mean R-SUV	1.23±1.45	2.73±1.65	<0.001

HCV, hepatitis C virus; AFP, α-fetoprotein; AFP-L3, fucosylated AFP; PIVKA-II, protein induced by vitamin K absence or antagonist II; TNM stage, tumor node metastasis stage; R-SUV, ratio of accumulations of FDG in HCC and non-HCC areas of the liver.

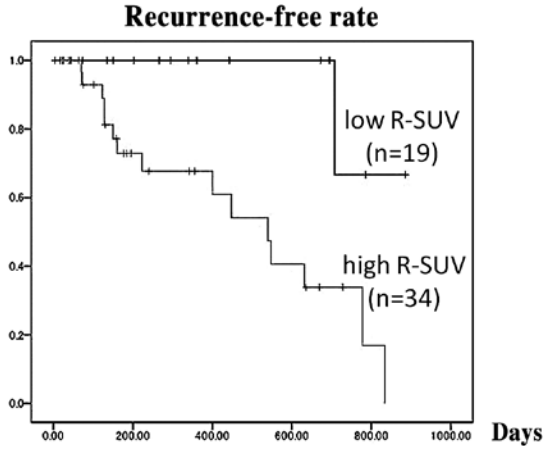

Figure 1. Recurrence rates in both patient groups. A higher level of early recurrence after resection was observed in the high R-SUV group (P<0.01).

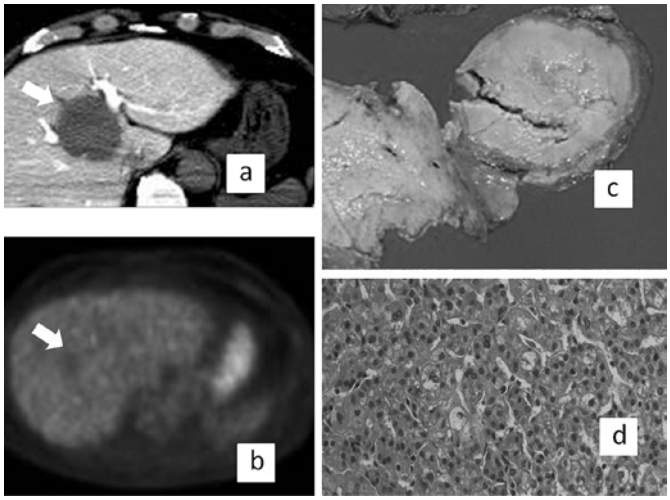

Figure 2. Accumulations of FDG (SUV) in both the HCC and non-HCC areas of the liver. The ratio (R-SUV) was calculated using FDG PET/CT findings. Representative case with HCC in the 4th segment of the liver (5.1 cm in diameter). (a) The tumor is observable as a defect in the CT arterial portography findings. (b) A low R-SUV value (1.4) was revealed by FDG PET/CT. (c) Resected specimen showing the tumor as a single nodular type. (d) The tumor was diagnosed as a well-differentiated HCC (Edmondson I) from the histological findings.

and II (1.4±0.3 and 1.9±0.9, respectively; P<0.01). Patients with nodules showing vp(+) and im(+), and with non-boundary type of nodules (single nodular type with extranodular growth, confluent multinodular or invasive type) had higher R-SUV values than those with vp(-), im(-) or boundary type (vaguely nodular or single nodular type) (3.6±2.4 vs. 2.0±0.9, 3.5±2.3 vs. 1.9±0.8 and 2.9±1.8 vs. 1.6±0.5, respectively; P<0.01). Throughout the observation period, extrahepatic metastasis was observed in 2 cases of stage II; these cases had high R-SUV (2.3 and 2.4, respectively). Fig. 2 shows representative results of a patient with low R-SUV (1.4) whose pathological findings were single nodular type, Edmondson I, and who was negative for both vp and im. By contrast, Fig. 3 presents the results of a representative patient with high R-SUV (1.9) whose pathological findings were confluent multinodular type, Edmondson III and positive for vp, though the tumor size was small (2.5 cm in diameter).

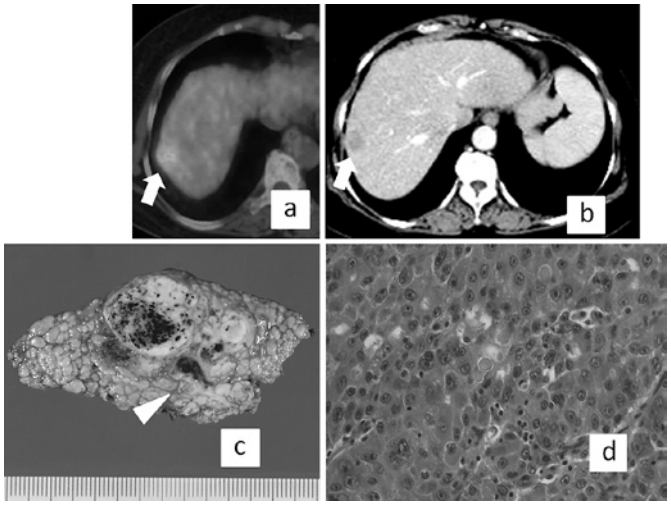

Figure 3. Representative case with HCC in the 8th segment of the liver (2.5 cm in diameter). (a) The tumor is noted as a defect in the CT arterial portography findings. (b) The tumor had a high R-SUV value (1.9) as shown by FDG PET/CT. (c) Resected specimen showing the tumor as a confluent multinodular type with macroinvasion to the 8th portal vein (arrowhead). Invasion of the portal vein was not detected in an imaging examination conducted 2 weeks before surgical resection. (d) The tumor was diagnosed as a poorly differentiated HCC (Edmondson III) upon histological examination.

Discussion

In Japan, the shortage of donors for liver transplantation is a major obstacle to the treatment of HCC, thus hepatic resection is often performed as curative therapy (4,5). FDG-PET/CT is a functional imaging modality that is used to measure the glucose metabolism of malignant tumors, although its clinical efficacy has not been established. The ability of PET to detect HCC in the liver was found to be less effective than that of contrast enhanced CT (14). On the other hand, Yoon *et al* (15) and Sugiyama *et al* (16) reported that PET is useful for the screening of extrahepatic metastasis from HCC. Recently, the usefulness of FDG-PET for predicting HCC recurrence following liver transplantation was proposed (17,18). However, few reports have described FDG-PET as useful for predicting prognosis after resection (1,2). Kawamura *et al* found that even in patients diagnosed in the early phase of HCC, a high R-SUV value among other prognostic scores may indicate poor prognosis or the need for radical treatment (3). The present results are similar to past reports, which showed that a high R-SUV value is capable of predicting early recurrence after resection, and that the relationship between a high R-SUV and pathological malignant potential is associated with positive findings for im or vp (19), higher Edmondson grade and worse gross type (11,12) in resected specimens. Since the average R-SUV of Edmondson I was <1.5, we set 1.5 as the cut off; this cut off value predicted the early recurrence of HCC.

Full body scanning with PET/CT is useful for the screening of extrahepatic metastasis and staging in patients with large HCC (15). An FDG-PET/CT examination is non-invasive and useful for predicting the malignant pathological potential of HCC before resection without the need for a biopsy. However, patients with high R-SUV values must be followed carefully with imaging modalities after resection.

In conclusion, we found that HCC patients with a high R-SUV value (≥1.5) had an elevated risk of early recurrence after resection, while R-SUV was also shown to be related with pathological findings. Thus, R-SUV is proposed as a useful predictive marker for the early recurrence of HCC before surgical resection.

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