Fluorine-18 Fluorodeoxyglucose Positron Emission Tomography Predicts Tumor Differentiation, P-glycoprotein Expression, and Outcome after Resection in Hepatocellular Carcinoma

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Abstract

Purpose: To investigate the diagnostic value of fluorine-18 fluorodeoxyglucose positron emission tomography (FDG-PET) for prediction of tumor differentiation, P-glycoprotein (P-gp) expression, and outcome in hepatocellular carcinoma (HCC) patients.

Experimental Design: Seventy HCC patients who underwent curative resection were prospectively enrolled in the study. FDG-PET was done 2 weeks preoperatively, and the standardized uptake value (SUV) and the tumor to nontumor SUV ratio (TNR) were calculated from FDG uptake. Tumor differentiation and P-gp expression were examined with H&E and immunohistochemical staining, respectively.

Results: SUV and TNR were significantly higher in poorly differentiated HCCs than in well-differentiated ($P = 0.001$ and 0.002) and moderately differentiated HCCs ($P < 0.0001$ and $P < 0.0001$). The percentage P-gp–positive area was significantly higher in well-differentiated HCCs than in poorly differentiated ($P < 0.0001$) and moderately differentiated HCCs ($P = 0.0001$). Inverse correlations were found between SUV and P-gp expression ($r = -0.44$; $P < 0.0001$) and between TNR and P-gp expression ($r = -0.47$; $P = 0.01$). Forty-three (61.4%) patients had postoperative recurrence. The overall and disease-free survival rates in the high TNR (≥ 2.0) group were significantly lower than in the low TNR (<2.0) group ($P = 0.0001$ and 0.0002). In multivariate analysis, a high α-fetoprotein level (risk ratio, 5.46; $P = 0.003$; risk ratio, 8.78; $P = 0.006$) and high TNR (risk ratio, 1.3; $P = 0.03$; risk ratio, 1.6; $P = 0.02$) were independent predictors of postoperative recurrence and overall survival.

Conclusions: The results suggest that preoperative FDG-PET reflects tumor differentiation and P-gp expression and may be a good predictor of outcome in HCC.

Hepatocellular carcinoma (HCC) is a common tumor that ranks fifth in frequency of occurrence worldwide (1). Treatment of HCC using hepatic resection and liver transplantation gives the best outcome in well-selected candidates; however, the 5-year survival rate is still only 60% to 70%. In addition, 70% of patients complicate with tumor recurrence within 5 years after hepatic resection (2), and prediction of early recurrence before treatment may be useful for choice of alternative therapeutic modalities, such as percutaneous ablation therapy. For example, we have found that percutaneous ablation therapy for intrahepatic recurrence is a major contributory factor for improving survival after recurrence as well as for overall survival (3). Several predictors of intrahepatic recurrence have been identified, including the presence of microvascular invasion, poor histologic differentiation, and satellite lesions (2, 4), but these factors cannot be used preoperatively to predict recurrence.

The high rates of tumor recurrence and cancer-related mortality after potentially curative therapy for HCC have led to development of alternative therapies, including adjuvant systemic or hepatic-arterial infusion chemotherapy. However, chemotherapy and chemoembolization have not improved overall or disease-free survival after resection of HCC (5), and HCC is known for its poor chemosensitivity to anticancer agents, which is mainly due to multidrug resistance (MDR). MDR is often associated with the ATP-binding cassette transporter family, which mediates transport-based MDR mechanisms (6, 7). The best-characterized member of this protein family is P-glycoprotein (P-gp), and a significant correlation between P-gp overexpression and chemoresistance has been reported in neuroblastoma (8), lymphoma (9), and osteosarcoma (10). In HCC, P-gp expression inversely correlates with chemotherapeutic response to etoposide or doxorubicin (11) and is associated with tumor differentiation (12). Therefore, determination of P-gp expression by a noninvasive imaging modality may be useful as an *in vivo* marker of chemosensitivity.

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Increased uptake of fluorine-18 fluorodeoxyglucose (^{18}F-FDG) based on enhanced glucose metabolism in cancer cells is a sensitive marker of tumor viability. The detection of increased ^{18}F-FDG uptake by positron emission tomography (PET) has been used in diagnostic imaging for several tumors, including HCC (13, 14), and studies in liver tumors have shown that FDG-PET is useful for tumor characterization and for assessment of therapeutic response and outcome (15–17). However, other reports suggest that the positive predictive rate of FDG-PET is not sufficiently high (50-55%) in patients with HCC (18–21). FDG uptake has also been associated with P-gp expression and tumor differentiation in lung cancer (22), but the relationship between P-gp expression and FDG uptake in HCC has not been examined. Therefore, the purpose of this study was to investigate the diagnostic value of FDG-PET prospectively as an *in vivo* marker for tumor differentiation, P-gp expression, and postoperative recurrence in patients with HCC.

Patients and Methods

Study population. From May 2003 to May 2005, 188 patients with HCC were admitted to our unit in Kyoto University Hospital, and 140 were identified by computed tomography (CT) and magnetic resonance imaging as candidates for curative surgery. Ultimately, 93 patients underwent FDG-PET in a preoperative examination; the remaining 47 patients did not give their consent to the FDG-PET procedure. The entry criteria for the study were as follows: (*a*) diagnosis of HCC by CT and magnetic resonance imaging, (*b*) no distant metastasis, and (*c*) no previous treatment. Twenty-three patients were excluded for the following reasons: distant metastases were detected in 2 patients by FDG-PET, transcatheter arterial chemoembolization has been done in 18 patients, and radiofrequency ablation has been done in 3 patients. Finally, 70 patients (52 males and 18 females; mean age, 65 years old; range, 32-80 years old) were included in the prospective analysis. Before enrollment in the study, each patient gave written informed consent. All patients underwent hepatectomy within 2 weeks after the FDG-PET study and HCC was confirmed histologically (well differentiated in 13 patients, moderately differentiated in 39 patients, and poorly differentiated in 18 patients). Serologically, 19 patients were positive for hepatitis B virus surface antigen, 28 patients were positive for hepatitis C virus antibody, and 23 patients were negative for both. Fifty patients had a single lesion, and 20 patients had multiple lesions. The size of the tumors was determined from the resected specimens and ranged from 11 to 174 mm in diameter. After resection, all patients were followed up with monthly monitoring of serum α-fetoprotein (AFP) and ultrasonography and/or contrast-enhanced CT every 3 months. Recurrence was confirmed by several imaging modalities, including CT and magnetic resonance imaging.

PET study. ^{18}F was produced by a ^{20}Ne (d, α) ^{18}F nuclear reaction, and ^{18}F-FDG was synthesized by nucleophilic substitution using an F-100 ^{18}F-FDG synthesis instrument (Sumitomo Heavy Industries Co. Ltd., Tokyo, Japan) and a CYPRIS-325R cyclotron (Sumitomo Heavy Industries). All patients were examined with a high-resolution, whole-body PET scanner with an 18-ring detector arrangement (Advance, General Electric Medical Systems, Milwaukee, WI).

The patients fasted for >4 h before i.v. injection of ^{18}F-FDG (296 ± 74 MBq), and acquisition of whole-body PET images started 50 min after the injection. The patients lay supine on the PET table with their arms positioned beside their bodies and were held in place by a holding belt fitted around the abdomen. Data acquisition (emission and transmission scans) was done in two-dimensional imaging mode with septae in place. Emission images were acquired for 3 min per bed position and each postemission transmission scan was obtained for 1 min per position. A whole-body scan (from face to upper thigh) was done in each patient using five or six bed positions according to the height of the patient. Data were reconstructed using the ordered subsets expectation maximization method using 16 subsets, 3 iterations, and a 128 × 128 array size.

Image analysis. PET images were interpreted by at least three experienced nuclear medicine physicians, using all available clinical information and correlative conventional imaging for anatomic guidance. For semiquantitative analysis of ^{18}F-FDG uptake, regions of interest were manually defined on transaxial tomograms. In patients for whom no significant high uptake was detectable by PET, the region of interest was drawn based on images from abdominal CT scans. The maximum standardized uptake value (SUV) was calculated for quantitative analysis of tumor ^{18}F-FDG uptake as follows: SUV = C (kBq/mL) / ID (kBq) / body weight (kg), where C represents the tissue activity concentration measured by PET and ID represents the injected dose. The tumor to nontumor SUV ratio (TNR) was also calculated as follows: TNR = tumor SUV / nontumor SUV, where the nontumor SUV was defined as the average of SUVs at five points in nontumor liver tissues.

Histologic examination and immunohistochemical staining for P-gp. The specimens were fixed in 10% formalin and embedded in paraffin. Serial 5-μm sections were prepared for conventional light microscopic examination with H&E staining and immunohistochemical analysis. Based on histologic grade, tumors were divided into low-grade (well differentiated and moderately differentiated) and high-grade HCCs (poorly differentiated and undifferentiated). Samples from 29 patients were subjected to immunohistochemical staining for P-gp, which was done using the avidin-biotin-peroxidase technique with tyramide signal amplification. In brief, after the deparaffinization procedure, specimens were treated with microwaves for 30 min for antigen retrieval followed by blocking of endogenous peroxidase with 3% H_2O_2/methanol and endogenous biotin using a biotin-blocking system kit (Vector Laboratories, Burlingame, CA). Specimens were then incubated with mouse monoclonal P-gp antibody C219 (diluted at 1:100 in PBS with 5% nonfat skimmed milk; Signet, Dedham, MA) overnight at 4°C. For signal amplification, a TSA Biotin System kit (NEN Life

Table 1. Patient characteristics

Age (y)	
Mean ± SD	65 ± 10.6
Range	32-80
Sex, *n* (%)	
Male	52 (74)
Female	18 (26)
Tumor differentiation, *n* (%)	
Well	13 (19)
Moderately	39 (56)
Poorly	18 (25)
Postoperative recurrence, *n* (%)	
Absent	27 (39)
Present	43 (61)
Remnant liver	35 (81)
Lung	6 (15)
Bone	1 (2)
Lymph node	1 (2)
SUV	
Mean ± SD	5.7 ± 4.4
Range	1.1-30
TNR	
Mean ± SD	2.1 ± 1.9
Range	0.4-13.3
Disease-free survival (d)	
Mean ± SD	408 ± 276
Range	30-1030
Overall survival (d)	
Mean ± SD	596 ± 239
Range	75-1125

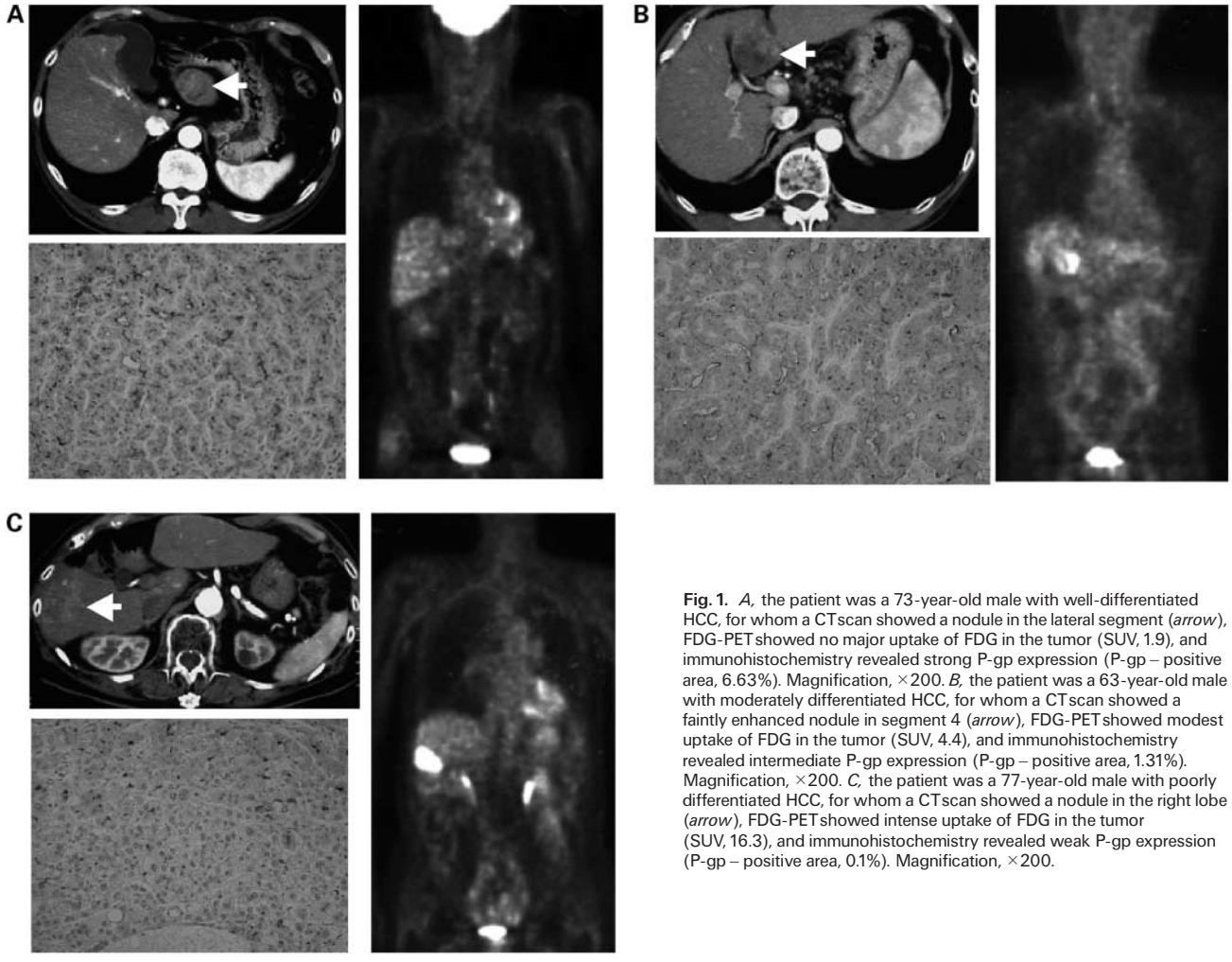

Fig. 1. *A,* the patient was a 73-year-old male with well-differentiated HCC, for whom a CT scan showed a nodule in the lateral segment (*arrow*), FDG-PET showed no major uptake of FDG in the tumor (SUV, 1.9), and immunohistochemistry revealed strong P-gp expression (P-gp – positive area, 6.63%). Magnification, ×200. *B,* the patient was a 63-year-old male with moderately differentiated HCC, for whom a CT scan showed a faintly enhanced nodule in segment 4 (*arrow*), FDG-PET showed modest uptake of FDG in the tumor (SUV, 4.4), and immunohistochemistry revealed intermediate P-gp expression (P-gp – positive area, 1.31%). Magnification, ×200. *C,* the patient was a 77-year-old male with poorly differentiated HCC, for whom a CT scan showed a nodule in the right lobe (*arrow*), FDG-PET showed intense uptake of FDG in the tumor (SUV, 16.3), and immunohistochemistry revealed weak P-gp expression (P-gp – positive area, 0.1%). Magnification, ×200.

Science, Boston, MA) and biotinylated rabbit anti-mouse IgG (diluted at 1:250; DAKO, Glostrup, Denmark) were used according to the manufacturers' protocols. Horseradish peroxidase activity was developed using 3,3′-diaminobenzidine solution (DAKO) as the chromogen. Nuclear counterstaining was done using Mayer's hematoxylin. Negative controls were established with nonimmunized mouse IgG (DAKO). To estimate P-gp expression, the positively stained area was evaluated using NIH image in 10 randomly chosen fields from each specimen. The percentage P-gp – positive area was calculated as the ratio of the pixel number of the P-gp – positive area to the pixel number of the whole area.

Statistical analysis. All values are expressed as means ± SD. Differences between two groups were analyzed using Student's *t* test for unpaired data (StatView PowerPC version). Patients were stratified and analyzed by univariate analysis using the following factors: age, gender, history of blood transfusion, hepatitis B virus surface antigen status, hepatitis C virus antibody status, histologic presence of liver cirrhosis, preoperative serum AFP level, maximal tumor dimension, number of tumors, histologic grade, presence of intrahepatic metastasis, Child-Pugh classification, macroscopic presence of portal vein thrombus, SUV, and TNR. Survival time was defined from the date of surgery until the date of death, and the end point for disease-free survival was defined as the date when recurrence was detected by CT. The disease-free survival rate and overall cumulative survival rate were analyzed using the Kaplan-Meier method, and differences in survival between the groups were compared using a log-rank test. Variables that showed significance in univariate analysis of factors affecting survival were included in a subsequent multivariate analysis using Cox's proportional hazard model. A P value <0.05 was considered statistically significant.

Results

Patient characteristics. Patient characteristics are summarized in Table 1. Based on a cutoff value for the TNR of 1.2, 43 of 70 (61.4%) patients were positive in the FDG-PET study. The mean follow-up period was 596 days (range, 75-1,125 days), and 43 (61.4%) patients showed postoperative recurrence: 35 patients with local recurrence, 6 patients with lung metastases, 1 patient with bone metastasis, and 1 patient with lymph node metastasis.

Correlations among FDG uptake, tumor differentiation, and P-gp expression. CT scans, FDG-PET images, and P-gp expression are shown in Fig. 1 for cases of well-, moderately, and poorly differentiated HCC. SUVs were significantly higher in poorly differentiated HCC (n = 18; 10.1 ± 6.5) than in well-differentiated HCCs (n = 13; 3.4 ± 1.4; P = 0.001) and moderately differentiated HCCs (n = 39; 4.5 ± 1.8; P < 0.0001;

Fig. 2A). TNRs were significantly higher in poorly differentiated HCCs (n = 18; 3.9 ± 2.9) than in well-differentiated HCCs (n = 13; 1.1 ± 0.4; P = 0.002) and moderately differentiated HCCs (n = 39; 1.6 ± 0.7; P < 0.0001). TNRs were also significantly higher in moderately differentiated HCCs compared with well-differentiated HCCs (P = 0.006; Fig. 2B). In contrast, the percentage P-gp–positive area was significantly higher in well-differentiated HCCs (n = 9; 4.6 ± 2.5%) than in poorly differentiated HCCs (n = 6; 0.2 ± 0.1%; P < 0.0001) and moderately differentiated HCCs (n = 14; 1.64 ± 0.9%; P = 0.0001; Fig. 2C). There was an inverse correlation between SUV and P-gp expression (r = −0.44; P = 0.018; Fig. 2D) and between TNR and P-gp expression (r = −0.47; P = 0.01; Fig. 2E). Using the mean values as cutoffs, patients were classified into low SUV (<5.0) and high SUV (≥5.0) groups and low TNR (<2.0) and high TNR (≥2.0) groups.

SUV and TNR as a predictor of survival and postoperative recurrence. The 1-year and 2-year overall survival rates for patients with HCC were 84.2% and 77.1%, respectively. The overall survival rate was significantly lower in the high SUV group compared with the low SUV group (P = 0.002; Fig. 3A) and was also significantly lower in the high TNR group compared with the low TNR group (P = 0.0001; Fig. 3B). In univariate analysis, there were significant differences in overall survival among groups stratified by age (P = 0.002), preoperative serum AFP level (P < 0.0001), histologic grade (P < 0.0001), portal vein thrombus (P = 0.01), SUV (P = 0.001), and TNR (P = 0.0001; Table 2). In multivariate analysis using a Cox proportional hazards model, serum AFP level (risk ratio, 8.78; P = 0.006) and TNR (risk ratio, 1.6; P = 0.02) were independent predictors of survival in HCC patients (Table 3).

Forty-three (61.4%) patients had postoperative recurrence. The disease-free survival rate was significantly lower in the high SUV group compared with the low SUV group (P = 0.0005; Fig. 3C) and was also significantly lower in the high TNR group compared with the low TNR group (P = 0.0002; Fig. 3D). In univariate analysis, there were significant differences in disease-free survival among groups stratified by preoperative serum AFP level (P = 0.0006), maximal tumor dimension (P = 0.03),

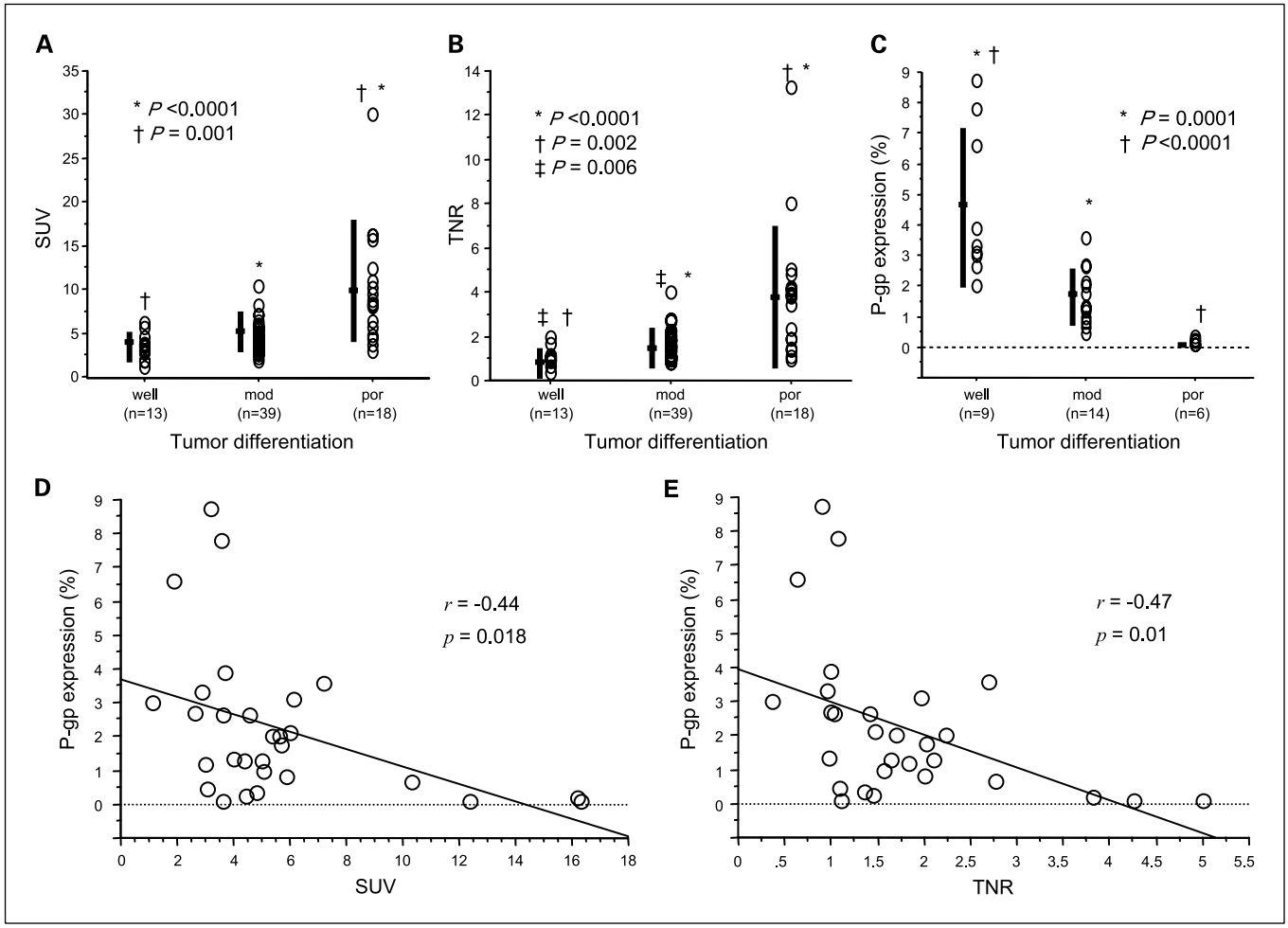

Fig. 2. *A,* SUVs were significantly higher in poorly differentiated HCCs (n = 18; 10.1 ± 6.5) than in well-differentiated HCCs (n = 13; 3.4 ± 1.4; †, P = 0.001) and moderately differentiated HCCs (n = 39; 4.5 ± 1.8; *, P < 0.0001). *B,* TNRs were significantly higher in poorly differentiated HCCs (n = 18; 3.9 ± 2.9) than in well-differentiated HCCs (n = 13; 1.1 ± 0.4; †, P = 0.002) and moderately differentiated HCCs (n = 39; 1.6 ± 0.7; *, P < 0.0001). TNRs were also significantly higher in moderately differentiated HCCs than in well-differentiated HCCs (‡, P = 0.006). *C,* the P-gp – positive area was significantly higher in well-differentiated HCCs (n = 9; 4.58 ± 2.46%) than in poorly differentiated HCCs (n = 6; 0.18 ± 0.11%; †, P < 0.0001) and moderately differentiated HCCs (n = 14; 1.64 ± 0.89%; *, P = 0.0001). *D,* there was an inverse correlation between SUV and P-gp expression (r = −0.44; P = 0.018). *E,* there was an inverse correlation between TNR and P-gp expression (r = −0.47; P = 0.01). well, well-differentiated HCC; mod, moderately differentiated HCC; por, poorly differentiated HCC.

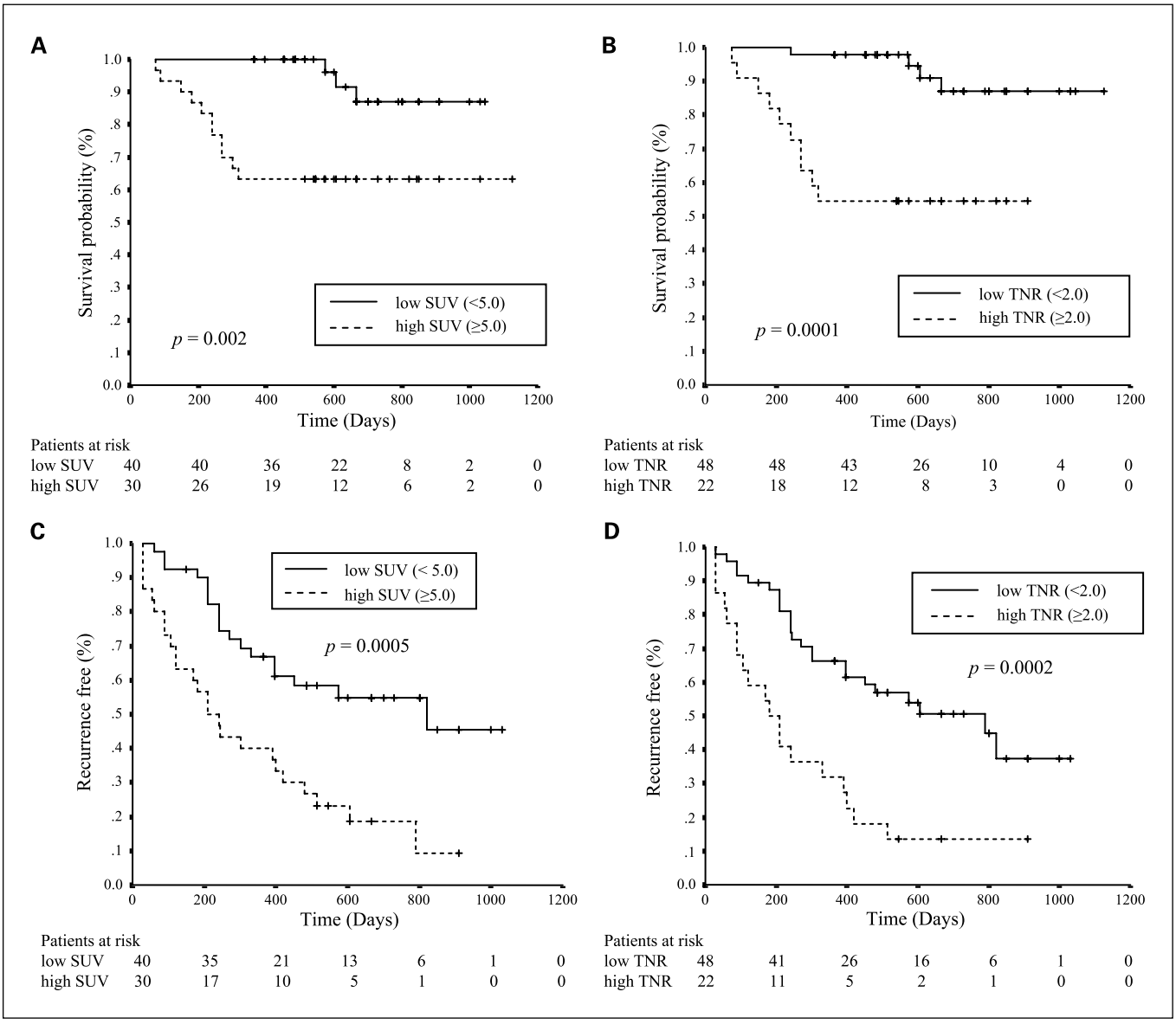

Fig. 3. *A,* the overall survival rate was significantly lower in the high SUV group than in the low SUV group ($P = 0.002$). *B,* the overall survival rate was significantly lower in the high TNR group compared with the low TNR group ($P = 0.0001$). *C,* the recurrence-free rate was significantly lower in the high SUV group compared with the low SUV group ($P = 0.0005$). *D,* the recurrence-free rate was significantly lower in the high TNR group compared with the low TNR group ($P = 0.0002$).

histologic grade ($P = 0.03$), macroscopic portal vein thrombus ($P = 0.002$), SUV ($P = 0.0005$), and TNR ($P = 0.0002$; Table 2). In multivariate analysis, model serum AFP level (risk ratio, 5.46; $P = 0.003$), macroscopic portal vein thrombus (risk ratio, 4.65; $P = 0.008$), and TNR (risk ratio, 1.3; $P = 0.03$) were independent predictors of postoperative recurrence in HCC patients (Table 3).

Discussion

FDG-PET is a well-established noninvasive diagnostic tool for detection of malignant tumors (13, 14) and for staging and monitoring of chemotherapeutic response (23, 24) in several cancers. FDG-PET is also a useful diagnostic method for metastatic liver tumors because it can detect these lesions with high sensitivity (15, 18); however, several investigators have reported that the sensitivity of FDG-PET is low in detection of HCC (15, 18–21). The difference in accumulation of FDG between metastatic liver tumors and HCC is due to a difference in the activity of enzymes involved in glucose metabolism. The activity of glucose-6-phosphatase, which converts FDG-6-P to FDG, is high in normal liver and nearly zero in metastatic liver tumors (15, 25). In contrast, this enzyme activity varies widely in different types of HCC: well-differentiated HCC cells exhibit FDG metabolism similar to that of normal liver tissue, whereas undifferentiated HCC cells do not do so (15, 25). Therefore, well-differentiated HCC cells tend to accumulate a similar amount of FDG as normal liver, which results in the SUV being relatively low. The current study showed that the SUV and TNR were significantly higher in poorly differentiated HCCs than in well-differentiated and moderately differentiated HCCs as found in previous studies (15, 25). Thus, FDG-PET does not

Table 2. Univariate analysis of prognostic factors for disease-free and overall survival

Variable	*n*	Mean disease-free survival (d)	*P*	Mean survival (d)	*P*
Age (y)					
<60	20	236	0.42	260	0.002
≥60	50	490		691	
Gender					
Male	52	479	0.58	655	0.28
Female	18	406		524	
History of blood transfusion					
Present	14	184	0.56	588	0.18
Absent	56	481		603	
Hepatitis B surface antigen					
Positive	19	447	0.91	264	0.10
Negative	51	467		672	
Hepatitis C virus antibody					
Positive	28	466	0.85	632	0.14
Negative	42	455		611	
Liver cirrhosis					
Positive	27	339	0.09	590	0.51
Negative	43	516		645	
AFP (ng/mL)					
<400	52	529	0.0006	698	<0.0001
≥400	18	211		428	
Maximal tumor dimension					
<5 cm	35	551	0.03	625	0.09
≥5 cm	35	292		603	
Tumor no.					
Single	50	505	0.17	659	0.53
Multiple	20	298		272	
Histologic grade					
Low grade	52	514	0.03	693	<0.0001
High grade	18	157		433	
Intrahepatic metastasis					
Positive	24	293	0.09	285	0.18
Negative	46	521		675	
Child-Pugh classification					
A	67	468	0.52	644	0.38
B	3	230		240	
Portal vein thrombus					
Positive	24	241	0.002	559	0.01
Negative	46	548		631	
SUV					
<5.0	40	669	0.0005	990	0.002
≥5.0	30	338		791	
TNR					
<2.0	48	633	0.0002	1,051	0.0001
≥2.0	22	291		592	

detect well-differentiated HCC effectively but can be used as an indicator of the degree of HCC differentiation.

P-gp is an ATP-dependent plasma membrane transporter that is responsible for innate and/or acquired drug resistance in tumor cells due to its drug efflux function (26, 27). Immunohistochemical studies have shown that 40% to 80% of HCC tumors are P-gp positive and that HCC response to chemotherapy is inversely related to P-gp expression in HCC patients (11, 28–31). The current study showed that the P-gp–positive area was significantly higher in well-differentiated HCCs than in poorly differentiated and moderately differentiated HCCs. Considering the role of P-gp in drug resistance, these results support previous data showing that well-differentiated HCC tumors are more resistant to doxorubicin compared with poorly differentiated tumors (32).

In an animal study, Lorke et al. (33) reported that FDG uptake of a P-gp–positive tumor was lower than that of a P-gp–negative tumor, and Bentley et al. (34) showed that 2-deoxy-D-glucose accumulation *in vitro* is reduced in MDR

Table 3. Multivariate analysis of prognostic factors for disease-free and overall survival

Variable	Risk ratio (95% CI)	*P*
Disease-free survival		
AFP level	5.46 (1.82-16.4)	0.003
Maximal tumor dimension	1.01 (0.99-1.02)	0.31
Histologic grade	0.79 (0.3-2.14)	0.65
Portal vein thrombus	4.65 (1.49-14.5)	0.008
SUV	0.66 (0.17-2.5)	0.54
TNR	1.3 (1.03-1.62)	0.03
Overall survival		
Age	1.04 (0.97-1.11)	0.32
AFP level	8.78 (1.89-40.9)	0.006
Histologic grade	1.52 (0.37-6.2)	0.56
Portal vein thrombus	1.2 (0.37-3.83)	0.76
SUV	1.69 (0.34-8.24)	0.52
TNR	1.6 (1.07-2.38)	0.02

Abbreviation: 95% CI, 95% confidence interval.

cell lines with strong P-gp expression and reduced GLUT-1 expression. Our results indicated an inverse correlation between SUV and P-gp expression and also between TNR and P-gp expression; these findings are compatible with the *in vitro* and animal findings and suggest that FDG-PET data can be used as a potential marker for P-gp expression *in vivo*. Furthermore, our findings suggest that P-gp may act as an efflux pump to reduce FDG accumulation; in this context, it is of note that a recent study showed that FDG may be a substrate of MDR proteins in some melanoma cells and that MDR may influence melanoma imaging by FDG-PET (35). However, further work will be necessary to explain the basis of the inverse correlation between SUV (TNR) and P-gp expression.

The outcomes of patients with a high SUV and a high TNR were worse than those with a low SUV and a low TNR, which suggest that the SUV and TNR may be predictors of postoperative early recurrence. In non–small cell lung cancer, the maximal SUV is a more powerful independent predictor than the TNM stage for recurrence and survival (36). The current report is the first to suggest a prognostic usefulness of FDG-PET in patients with HCC, and our data indicate that HCC with a higher SUV and TNR tends to have more aggressive malignant potential; therefore, patients with such tumors should be carefully observed postoperatively, even if curative surgery is accomplished. We believe that the TNR will serve as a more accurate index than the SUV because SUV is affected by liver function. In addition, to avoid recurrence, adjuvant chemotherapy might be appropriate for patients with a high TNR and low P-gp because patients with low P-gp expression are likely to be responders to chemotherapy. In conclusion, FDG-PET is a good predictor of tumor differentiation, P-gp expression, and postoperative recurrence in HCC and may also be useful in patient management, such as in identification of patients at high risk for recurrence.

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