Original Article

^{18}F-fluorodeoxyglucose Uptake on Positron Emission Tomography as a Prognostic Predictor in Locally Advanced Hepatocellular Carcinoma

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BACKGROUND: Metabolic activity assessed by ^{18}F-fluorodeoxyglocuse-positron emission tomography (^{18}F-FDG-PET) reflects biological aggressiveness and prognoses in various tumors. The authors present a correlation between tumor metabolic activity and clinical outcomes in patients with hepatocellular carcinoma (HCC). **METHODS:** Over a 3-year period (2005-2008), 135 locally advanced HCC patients were treated with localized concurrent chemoradiotherapy (CCRT; external beam radiotherapy at 45 grays for 5 weeks plus concurrent hepatic arterial infusion of 5-fluorouracil during the first and fifth week) followed by repetitive hepatic arterial infusional chemotherapy with 5-fluorouracil and cisplatin. Among them, the authors studied 107 who received ^{18}F-FDG-PET before CCRT. Maximal standardized uptake values (SUVs) of tumors were calculated. **RESULTS:** The median maximal tumor SUV was 6.1 (range, 2.4-~19.2). Patients with low maximal tumor SUVs (<6.1) had a higher disease control rate than those with high maximal tumor SUVs (≥6.1) (86.8% vs 68.5%, respectively, $P = .023$). Both median progression-free survival (PFS; 8.4 vs 5.2 months; $P = .003$) and overall survival (OS; 17.9 vs 11.3 months; $P = .013$) were significantly longer in the low maximal tumor SUV group than in the high maximal tumor SUV group, respectively. In multivariate analysis, low maximal tumor SUV and objective responses to CCRT remained significant for PFS and OS. The high maximal tumor SUV group was more likely to have extrahepatic metastasis within 6 months than the low maximal tumor SUV group (58.1% vs 26.8%, respectively; $P < .001$). Similar results were obtained for the maximal tumor SUV/normal liver maximal SUV ratio (<2 vs ≥2) concerning progression, death, and extrahepatic metastasis. **CONCLUSIONS:** Metabolic activity may be useful not only in predicting prognosis and treatment responses, but also in establishing optimal treatment plans in locally advanced HCC. ***Cancer* 2011;117:4779–87.** © *2011 American Cancer Society.*

KEYWORDS: hepatocellular carcinoma, fluorodeoxyglucose, standardized uptake value, chemoradiotherapy, tumor response, survival.

Hepatocellular carcinoma (HCC), which accounts for >5% of cancers globally, is ranked as the sixth most common cancer and third leading cause of cancer-related death worldwide.[1] The incidence of HCC is rising in developed countries and continues to be high in endemic areas such as Asia.[1,2] Although surgical resection or local ablative therapies such as radiofrequency ablation and percutaneous ethanol injection achieve the best outcomes, with a 5-year survival rate of 60%-70% in patients treated during early stages, only about 30% are amenable to potentially curative treatments.[3,4] For the majority of HCC patients, these treatment modalities with curative intent are no longer feasible, because of advanced diseases, including extensive tumor burden with portal vein thrombosis and intratumoral/extratumoral spread, or poor liver function at presentation.[3,4]

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To date, several therapeutic options, such as transhepatic arterial chemoembolization, external/internal irradiation, and molecular targeted agents, have been evaluated for advanced HCC, and sorafenib is now recommended as a category 1 drug in such cases owing to its proven survival benefits over the best supportive care.[5-7] However, a treatment of choice has yet to be established in locally advanced HCC without extrahepatic metastasis. Among various treatment modalities, 3-dimensional conformal radiation therapy (3DCRT) has made it possible to escalate the irradiation dose for advanced HCC without undue dose-limiting toxicity, and is now recognized as a potentially curative option.[8] Recently, the combination of intra-arterial chemotherapy and localized 3DCRT has been reported to improve treatment response rates, compared with the poor outcomes experienced with monotherapy for locally advanced solid tumors. This finding supports a beneficial interaction between radiotherapy and chemotherapy.[8-11] So far, localized concurrent chemoradiation therapy (CCRT) followed by repetitive hepatic arterial infusional chemotherapy (HAIC) in locally advanced HCC without extrahepatic metastasis has been attempted at several institutions, with promising results.[9]

Conversely, positron emission tomography (PET) imaging using ^{18}F-fluoro-2-deoxyglucose (^{18}F-FDG) is an imaging technique based on the increased rate of glucose uptake in several kinds of malignant tumors.[12,13] So far, ^{18}F-FDG-PET has been proposed as a prognostic predictor as well as a noninvasive measurement of the biological aggressiveness of the tumor in the field of oncology. Likewise, in HCC, several investigators have reported that ^{18}F-FDG uptake evaluated by preoperative PET scan is associated with tumor differentiation as well as recurrences and survival after resection or transplantation.[14-17] Hence, it is feasible that ^{18}F-FDG uptake on PET scan, like size and number criterion, might be an important prognostic factor in the establishment of treatment and surveillance plans. However, most studies on HCC and ^{18}F-FDG-PET have focused primarily on either tumor detection in preoperative settings or prognostic value in patients treated with resection or transplantations. There are few data on the clinical significance of ^{18}F-FDG-PET in HCC patients who have undergone nonsurgical treatments.[14,15,17-19] Furthermore, to date, there have been no data on the appropriate application of the clinical significance of ^{18}F-FDG-PET in patients who have undergone localized CCRT followed by repetitive HAIC for locally advanced HCCs.

Here, we investigated the value of metabolic activity assessed by ^{18}F-FDG-PET as a prognostic factor in patients who were treated with localized CCRT followed by HAIC for locally advanced HCCs.

MATERIALS AND METHODS

Patient Eligibility

In this study, we consecutively enrolled patients with locally advanced HCC without extrahepatic metastasis who received localized CCRT at Severance Hospital, Yonsei University College of Medicine between January 2005 and June 2008. Diagnosis of HCC was based upon pathologic confirmation or typical appearance of HCC on 2 dynamic imaging examinations (computed tomography [CT] and magnetic resonance imaging [MRI]), or via 1 dynamic technique with elevated serum α-fetoprotein (AFP; >400 ng/mL).[20] ^{18}F-FDG-PET/CT scans were obtained 10 to ~14 days before the initiation of localized CCRT.

Eligible patients for localized CCRT met the following criteria: at least 1 unidimensionally measurable lesion, age 18 to 75 years, an Eastern Cooperative Oncology Group performance status of 0 to 1, life expectancy of at least 3 months, Child-Pugh class A or B, and adequate function in other organs (serum creatinine <1.5mg/dL, aminotransferase <5× the upper limit of normal, absolute neutrophil count ≥1500 cells/μL, platelet count ≥75,000/μL, and hemoglobin ≥10 g/dL). Patients with diffuse or multifocal bilobar tumors were not considered to be eligible for localized CCRT, because whole liver irradiation can cause serious hepatic toxicity. Other exclusion criteria for localized CCRT included extrahepatic or another concurrent malignancy, experience of recent upper gastrointestinal bleeding, and any other underlying serious medical condition interfering with participation in the study. Among patients who underwent localized CCRT according the above criteria, those who underwent ^{18}F-FDG-PET/CT before the initiation of treatment were included in the study. The modified International Union Against Cancer TNM staging system[21] and Barcelona Clinic Liver Cancer staging systems[22] were adopted.

The study protocol was in accordance with the ethical guidelines of the 1975 Declaration of Helsinki. Written, informed consent was obtained from each participant or a responsible family member.

Treatment Protocols

Under the standard localized CCRT protocol, patients received a total radiation dose of 45 grays in 25 fractions

over a period of 5 weeks, with concurrent hepatic arterial infusion of 5-fluorouracil (500 mg/d for 5 hours on 5 consecutive days through an implanted port system) during the first and fifth weeks of radiotherapy.[9] This localized CCRT was followed by repetitive HAIC with 5-fluorouracil (500 mg/m^2 for 5 hours on 3 consecutive days) and cisplatin (60 mg/m^2 for 2 hours on a single day), administered through a port system every 4 weeks for 2 to 12 cycles, depending on the tumor responses.[9] The standard localized CCRT and HAIC protocols were strictly maintained during the study period.

PET Imaging

All patients fasted for at least 6 hours before an ^{18}F-FDG-PET/CT scan. Scanning was performed when the plasma glucose level before administration of ^{18}F-FDG was <130 mg/dL. Scanning was initiated about 1 hour after administration of ^{18}F-FDG. The median time to scanning after injection was 60 minutes (range, 57-61 minutes). A low-dose noncontrast CT scan was obtained for attenuation correction using the following parameters: 120 kVp, 50 mAs, 0.5 seconds rotation time, 5.0 mm scan reconstruction, 60 cm field of view, and a 512 × 512 matrix for the Gemini. Images from the neck to the proximal thighs were obtained using the Phillips Gemini PET scanner (Phillips-ADAC Medical Systems, Hanover, Mass) with a spatial resolution of 5.3 mm in the center of the field of view. Data were acquired in a 3-dimensional (3D) mode after an intravenous administration of 370 to 444 MBq of ^{18}F-FDG. After PET imaging, contrast-enhanced CT images were acquired (intravenously bolus 60% wt/vol at 1.5-2.0 mL/s). The obtained PET images were reconstructed using the 3D row-action maximum likelihood iterative reconstruction algorithm (interation number, 2; relaxation parameter, 0.006).

PET Interpretation

Two experienced nuclear medicine specialists, who were unaware of the clinical information, were responsible for reading the ^{18}F-FDG-PET/CT images. In the cases of discrepancy in determining target tumor lesions, a consensus was reached and was used for analysis. Positive malignant FDG uptake was defined as an abnormal increase in comparison with the background activity in the surrounding tissue. The standardized uptake value (SUV) was assessed by region of interest (ROI) analysis with guidance from the CT or MRI scans and calculated as the activity concentration detected in the lesion divided by the injected activity, with correction for radioactive decay and body weight (μCi/g). The maximal tumor SUV was the peak SUV in 1 pixel with the highest counts within the ROI and in the case of multiple tumors, the maximal tumor SUV was defined as the highest value of the tumors.

For normal liver regions, 3 circular ROIs of about 100 mm^3 each were drawn, 2 in the right lobe and 1 in the left lobe, at a location where tumor was not detected on other images and the maximal SUV of normal liver was defined as the highest of the 3 ROIs drawn on normal liver. Thereafter, another metabolic parameter suggested by the previous investigator,[15] maximal tumor SUV/normal liver maximal SUV ratio was calculated.

Response Evaluation

The response evaluation was carried out with a dynamic CT scan or MRI, if appropriate, first at 1 month after completion of localized CCRT and then after every 2 cycles of HAIC. We adopted the Response Evaluation Criteria in Solid Tumors, as follows: complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD).[23] Objective response was defined as CR or PR, and disease control as CR, PR, or SD. Response was analyzed by intention-to-treat analysis.

Statistical Analysis

The major goals of this study are to investigate clinical outcomes of localized CCRT and to evaluate the prognostic value of metabolic activity assessed by ^{18}F-FDG-PET. Continuous and categorical variables were examined using Student *t* test (or the Mann-Whitney *U* test if appropriate) and the chi-square test, respectively. Progression-free survival (PFS) was assessed from the date of the initiation of localized CCRT until the date of first recurrence or death. Overall survival (OS) was calculated as the time interval between the date of the initiation of localized CCRT and the date of death or last follow-up. Survival time was estimated by the Kaplan-Meier method and the survival difference between groups was assessed by the log-rank test. The Cox proportional hazards model was used for a multivariate analysis of survival. All variables found significant in the univariate analysis were included in the multivariate model.

Statistical analysis was performed using SAS software version 9.1.3 (SAS, Cary, NC), and a 2-sided *P* value <.05 was considered statistically significant.

RESULTS

Patient Characteristics

Of 137 patients who underwent localized CCRT, a total of 107 patients who underwent ^{18}F-FDG-PET/CT

before localized CCRT were included in the study sample. Patients' baseline characteristics are presented in Table 1. The median age was 54 years (range, 20-~75 years) and 79 (73.8%) patients were male. The median body mass index was 22.6 kg/m^2 (range, 17.2-29.8 kg/m^2). The most common etiology was hepatitis B virus infection (81 patients, 75.7%), and 101 were in Child-Pugh class A. Eighty-two (76.6%) patients had stage IVA cancer, and 72 patients (71.0%) had portal vein thrombosis. The median maximal tumor SUV was 6.1 (range, 2.4-~19.2).

Table 1. Baseline Characteristics of the Entire Patient Cohort (n=107)

Characteristic	Value
Age median (range)	54 (20-~75)
Sex, male:female	79:28
Body mass index, median kg/m^2 (range)	22.6 (17.2-29.8)
Etiology	
Hepatitis B/hepatitis C/alcohol/others	81/6/11/9
Biochemical values, median (range)	
White cell count per μL	6000 (2600-15,500)
Hemoglobin, g/dL	13.7 (10.0-17.2)
Platelet count, 10^3/μL	186 (87-526)
Prothrombin time, INR	1.05 (0.7-1.7)
Total bilirubin, mg/dL	0.7 (0.2-3.0)
Albumin, g/dL	4.1 (2.5-4.9)
AST, IU/L	58 (22-145)
ALT, IU/L	42 (6-205)
AFP, ng/mL	485 (1.02-~60,500)
PIVKA-II, mAU/mL (range)	2000 (10-~2000)
Tumor size, median cm (range)	10.0 (3.0-~21)
Tumor number, median (range)	2 (1-~5)
Presence of portal vein thrombosis [main/branch]	72 [33/39]
Tumor stage III/IVA	25/82
BCLC stage B/C	35/72
Child-Pugh classification A/B	101/6

Abbreviations: AFP, α-fetoprotein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; AU, arbitrary unit; BCLC, Barcelona Clinic Liver Cancer; INR, international normalized ratio; PIVKA-II, prothrombin induced by vitamin K absence or antagonist.

Comparison of Clinical Characteristics According to Maximal Tumor SUV

We divided the patients into 2 groups according to the median value of the maximal tumor SUV; the low maximal tumor SUV group (53 patients, maximal tumor SUV <6.1) versus the high maximal tumor SUV group (54 patients, maximal tumor SUV ≥6.1). There were no significant differences in clinical variables between the 2 groups except for the baseline AFP level, which was marginally higher in the high maximal tumor SUV group (Table 2).

Radiologic Responses After Treatments

After localized CCRT, 0 and 31 patients had CR and PR (objective response rate of 28.9%), whereas 52 and 24 had SD and PD, respectively. After subsequent HAIC, 2 and 36 had CR and PR (objective response rate of 35.5%), whereas 45 and 24 had SD and PD, respectively.

Table 3 also shows the detailed radiologic responses to localized CCRT and to localized CCRT plus subsequent HAIC according to the maximal tumor SUV.

Table 2. Comparisons of Baseline Clinical Characteristics According to Maximal Tumor SUV

Variables	Maximal Tumor SUV <6.1, n=53	Maximal Tumor SUV ≥6.1, n=54	*P*
Age, y	55.1 ± 10.9	51.6 ± 10.6	.101
Male sex (%)	45 (84.9)	44 (81.5)	.636
ECOG, 0:1	31:22	26:28	.284
Etiology, HBV:HCV: alcohol: others	36:4:7:6	45:2:4:3	.354
White blood cell count per μL	6430 ± 2137	6313 ± 2650	.853
Hemoglobin, g/dL	13.4 ± 1.61	13.7 ± 1.23	.376
Platelet count, 10^3/μL	186 ± 84	219 ± 98	.064
Prothrombin time, INR	1.049 ± 0.150	1.069 ± 0.102	.421
Bilirubin, mg/dL	0.97 ± 0.61	0.80 ± 0.43	.110
Albumin, mg/dL	4.1 ± 0.47	4.0 ± 0.43	.457
AST, IU/L	112 ± 54.8	94 ± 58.5	.452
ALT, IU/L	73.2 ± 38.9	44.9 ± 32.7	.052
AFP, ng/mL	7313 ± 1787	15440 ± 2200	.040
PIVKA-II, mAU/mL	1478 ± 752	1243 ± 839	.132
Portal vein thrombosis	32, 60.3%	40, 74.1%	.131
TNM stage, III:IVA	13:40	12:42	.778
BCLC stage, B:C	21:32	14:40	.131
Child-Pugh class, A:B	49:4	52:2	.437

Abbreviations: AFP, α-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BCLC, Barcelona Clinic Liver Cancer; ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; HCV, hepatitis C virus; INR, international normalized ratio; PIVKA-II, prothrombin induced by vitamin K absence or antagonist; SUV, standardized uptake value.

Table 3. Responses to Treatments in the 2 Groups

Response	Overall Subjects, No. (%)	Maximal Tumor SUV <6.1	Maximal Tumor SUV ≥6.1
After localized CCRT			
Complete response	0 (0.0)	0	0
Partial response	31 (28.9)	16	15
Stable disease	52 (48.7)	30	22
Progressive disease	24 (22.4)	7	17
After localized CCRT plus HAIC			
Complete response	2 (1.9)	1	1
Partial response	36 (33.6)	19	17
Stable disease	45 (42.1)	26	19
Progressive disease	24 (22.4)	7	17

Abbreviations: CCRT, concurrent chemoradiation therapy; HAIC, hepatic arterial infusional chemotherapy; SUV, standardized uptake value.

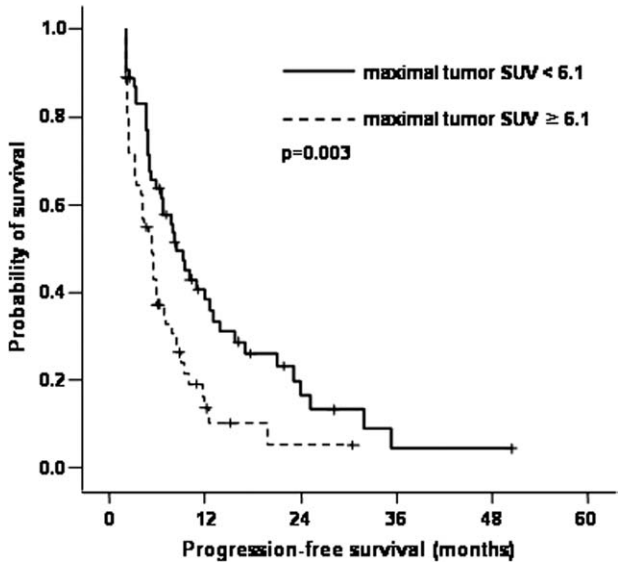

Figure 1. Kaplan-Meier analysis of progression-free survival according to maximal tumor standardized uptake value (tumorSUVmax) is shown.

Patients with the low maximal tumor SUV were more likely to have the higher disease control rate (86.8%) in response to treatments than those with high maximal tumor SUV (68.5%, $P = .023$).

Univariate and Multivariate Analysis for Prognostic Factors Affecting PFS and OS

The median PFS was 6.5 months (95% confidence interval [CI], 4.6-8.4 months). A univariate analysis revealed that a longer median PFS was observed in the low maximal tumor SUV group (8.4 months; 95% CI, 6.0-10.7 months) compared with the high maximal tumor SUV group (5.2 months; 95% CI, 4.0-6.5 months; $P = .003$) (Fig. 1). Furthermore, a longer PFS was also observed in patients with the lower baseline AFP level (8.4 months; 95% CI, 4.9-11.9 months; $P = .030$) and those with objective responses to localized CCRT (12.0 months; 95% CI, 7.1-16.9 months; $P < .001$), compared with those with the higher baseline AFP level (5.1 months; 95% CI, 3.9-6.4 months) and those without objective response to localized CCRT (4.9 months; 95% CI, 4.0-5.8 months), respectively. In a multivariate analysis, the low maximal tumor SUV (adjusted hazard ratio [HR], 0.481; 95% CI, 0.304-0.761; $P = .002$) also remained a significant independent predictor of a lesser risk of progression, along with the objective responses to localized CCRT (adjusted HR, 0.375; 95% CI, 0.223-0.631; $P < .001$) (Table 4).

The median OS was 12.6 months (95% CI, 11.3-13.9 months). Patients with a low maximal tumor SUV (17.9 months; 95% CI, 11.0-24.7 months) had a significantly longer median OS than those with a high maximal tumor SUV (11.3 months; 95% CI, 9.7-12.9 months; $P = .013$) (Fig. 2). In addition, a longer OS was observed in patients without portal vein thrombosis (23.1 months [95% CI, 7.2-39.0 months] vs 11.7 months [95% CI, 10.0-13.5 months]; $P = .021$), and in those with an objective response to localized CCRT (27.0 months [95% CI, 12.0-43.0 months] vs 10.9 months [95% CI, 7.8-14.0 months]; $P < .001$). In a subsequent multivariate analysis, the low maximal tumor SUV also remained a significant independent predictor of a lower risk of death (adjusted HR, 0.545; 95% CI, 0.313-0.947; $P = .031$), along with objective responses to treatments (adjusted HR, 0.317; 95% CI, 0.167-0.599; $P < .001$).

Table 4. Univariate/Multivariate Analysis for Parameters Influencing Cumulative Survival of Patients

Variables	Progression-Free Survival[a]		Overall Survival[a]	
	Univariate Analysis	Multivariate Analysis	Univariate Analysis	Multivariate Analysis
Age, <55 vs ≥ 55 years	.973	—	.381	—
Sex, male vs female	.466	—	.731	—
ECOG, 0 vs 1	.309	—	.014	—
Etiology, HBV vs HCV vs others	.329	—	.549	—
Child-Pugh class, A vs B	.698	—	.193	—
Portal vein thrombosis, yes vs no	.075	—	.021	NS
AFP, <200 ng/mL vs ≥200 ng/mL	.030	NS	.323	NS
PIVKA-II, <600 mAU/mL vs ≥600 mAU/mL	.714	—	.641	—
TNM stage, III vs IVA	.875	—	.961	—
Maximal tumor SUV, <6.1 vs ≥6.1	.003	.002	.013	.031
Objective responses after localized CCRT	<.001	<.001	<.001	<.001

Abbreviations: AFP, α-fetoprotein; CCRT, concurrent chemoradiation therapy; ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; HCV, hepatitis C virus; NS, not significant; PIVKA-II, prothrombin induced by vitamin K absence or antagonist; SUV, standardized uptake value.
[a] Expressed as *P* value.

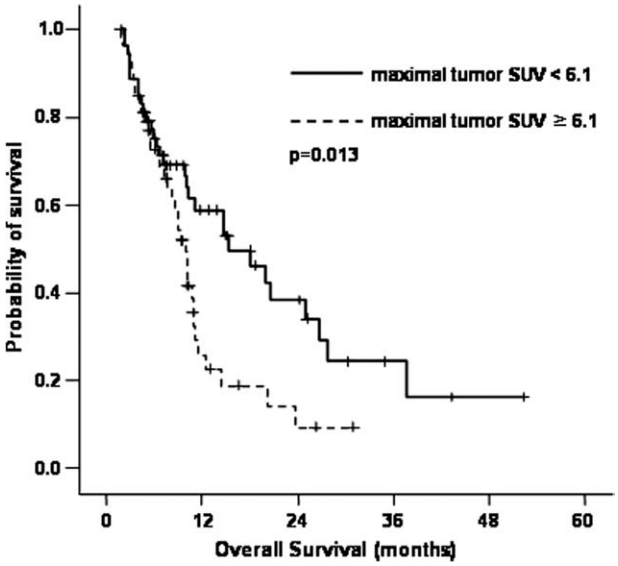

Figure 2. Kaplan-Meier analysis of overall survival according to maximal tumor standardized uptake value (tumorSUVmax) is shown.

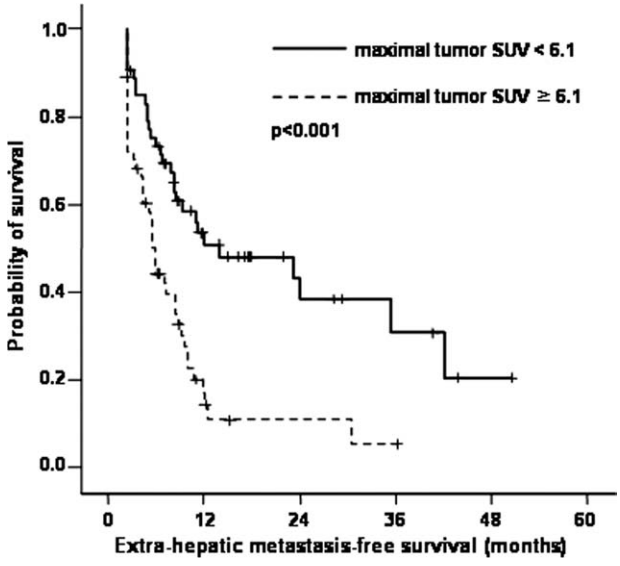

Figure 3. Kaplan-Meier analysis of extrahepatic metastasis-free survival according to maximal tumor standardized uptake value (tumorSUVmax) is shown.

Maximal Tumor SUV and Extrahepatic Metastasis

Patients with a high maximal tumor SUV had a significantly higher incidence of extrahepatic metastasis (14 patients, 25.9%) after completion of localized CCRT than those with a low maximal tumor SUV (4 patients, 7.5%; $P = .018$), with an odds ratio of 4.287 (95% CI, 1.308-14.052). In addition, the high maximal tumor SUV group was more likely to have extrahepatic metastasis within 6 months of the initiation of treatment (58.1%) than the low maximal tumor SUV group (26.8%, $P < .001$), with a HR of 2.544 (95% CI, 1.561-4.145) (Fig. 3). A shorter median extrahepatic metastasis-free survival was observed in the high maximal tumor SUV group (5.7 months; 95% CI, 4.9-6.6 months) compared with the low maximal tumor SUV group (13.8 months; 95% CI, 9.8-17.7 months; $P < .001$) (Fig. 3).

Another Metabolic Parameter, Maximal Tumor SUV/Normal Liver Maximal SUV Ratio

We tested another metabolic parameter suggested by the previous investigator,[15] that is, maximal tumor SUV/

normal liver maximal SUV ratio, which showed consistent results with maximal tumor SUV in this study. There was a significant correlation between the maximal tumor SUV and maximal tumor SUV/normal liver maximal SUV ratio by Pearson correlation test ($r = 0.799$, $P < .001$). By using the suggested cutoff value of 2.0, we observed significantly longer median PFS in those with maximal tumor SUV/normal liver maximal SUV ratio <2.0 (9.4 months [95% CI, 3.5-15.3 months]) compared with those with maximal tumor SUV/normal liver maximal SUV ratio ≥2.0 (5.4 months [95% CI, 4.3-6.4 months]), with a lesser risk of progression (HR, 0.603; 95% CI, 0.390-0.931; $P = .022$). Likewise, longer median OS in those with maximal tumor SUV/normal liver maximal SUV ratio <2.0 (17.9 months [95% CI, 6.7-29.0 months]) was observed compared with those with maximal tumor SUV/normal liver maximal SUV ratio ≥2.0 (11.7 months [95% CI, 10.0-13.5 months]), with a lesser risk of death (HR, 0.586; 95% CI, 0.354-0.970; $P = .038$). In addition, those with maximal tumor SUV/normal liver maximal SUV ratio ≥2.0 were more likely to have extrahepatic metastasis within 6 months of the initiation of treatment (50.9%) than those with maximal tumor SUV/normal liver maximal SUV ratio <2.0 (28.7%), with an HR of 2.269 (95% CI, 1.382-3.726; $P < .001$).

DISCUSSION

Malignant tumors including HCC are known to have increased glycolysis compared with normal tissues.[24] The increased activities of enzymes involved in glucose uptake and intracellular glycolytic metabolism, such as glucose transporter protein, hexokinase, and phosphofructokinase, result in the increased uptake of ^{18}F-FDG in tumor cells.[24,25] However, because the expression of glucose-6-phosphatase enabling ^{18}F-FDG to accumulate in tumor cells varies widely in HCC, only 50% to ~70% of HCC cases have positive ^{18}F-FDG uptake, in contrast to metastatic liver cancer or cholangiocarcinoma.[26,27] Thus, we undertook the current study with the assumption that such metabolic diversity in HCC may lead to differences in biological characteristics, treatment outcomes, and ultimately prognosis. So far, most previous studies of HCC and ^{18}F-FDG-PET have primarily focused on either detection of extrahepatic metastasis in preoperative settings or prognostic significance in patients who were treated with surgical resection or transplantation.[14,15] To our knowledge, this is the first study to evaluate the prognostic value of quantitative metabolic activity and its correlation with clinical outcomes in subjects who have undergone localized external beam radiotherapy along with concurrent intra-arterial chemotherapy infusion performed in homogeneous protocols. Considering the relatively low sensitivity of ^{18}F-FDG uptake in individual HCCs, we selected the ROI of HCC with guidance from dynamic CT or MRI for accurate measurement of the maximal SUV.[28] Because the combination of external beam radiotherapy and intra-arterial chemotherapy infusion has been widely applied at many institutes, the results from our study could help physicians accurately determine disease courses and establish further treatment plans.

In the present study, the localized CCRT showed considerable antitumor effect, with a median PFS of 6.5 months and an OS of 12.6 months, suggesting a benefit over the best supportive care and at least comparable outcomes with reference to sorafenib in patients with locally advanced HCC, although this is not a direct comparative study.[5,7] As a prognostic factor, those with a low maximal tumor SUV had a higher disease control rate, as well as longer PFS and OS. On multivariate analysis, maximal tumor SUV independently affected both PFS and OS along with the objective response to CCRT. In addition, a higher baseline AFP level was significantly associated with worse outcome in univariate analysis of PFS, but not in multivariate analysis. This may be primarily because of the higher baseline AFP levels observed in patients with high maximal tumor SUVs, suggesting that patients with high maximal tumor SUVs may have the more aggressive tumor biology and disease burdens.[27] Regarding OS, the presence of portal vein thrombosis was a significant factor in univariate analysis, but not in multivariate analysis. However, we note that most of our patients had portal vein thrombosis, and even those without it already had highly advanced disease, in terms of number and size. Another metabolic parameter, maximal tumor SUV/normal liver maximal SUV ratio, showed consistent prognostic implications with maximal tumor SUV in this study. Therefore, the metabolic activity assessed by ^{18}F-FDG-PET might be useful in identifying subgroups with differential prognosis before treatment, considering that conventional staging systems such as TNM and Barcelona Clinic Liver Cancer stage cannot discriminate the detailed high-risk groups in patients with locally advanced HCC without extrahepatic metastasis, because most of them fall into the category of TNM IVA and Barcelona Clinic Liver Cancer C stage.

Several factors may explain the prognostic implications of maximal tumor SUV. First, increased glucose

metabolism and resulting relative glucose depletion in intracellular milieu in HCC cells might induce the expression of the multidrug resistance (*MDR*) gene, comprising the treatment outcomes by activating an efflux pump to chemotherapeutic agents.[29] Second, the increased uptake of ^{18}F-FDG reflects the rapid growth of the HCC and poor histologic differentiation associated with aggressive biological behavior.[17,19,26,30] In addition, the higher expression of metalloproteinase-9 in tumor cells with enhanced glucose metabolism might make invasion into surrounding tissues and extrahepatic spread much easier.[31] In the same context, HCC with a high uptake of ^{18}F-FDG exhibited microvascular invasion more frequently, which proved to be an important histopathological parameter, resulting in treatment failures like intrahepatic/extrahepatic dissemination.[32,33] Thus, it is of note that patients with the higher baseline maximal tumor SUV were more likely to have extrahepatic metastasis within 6 months of treatment initiation (more than 2-fold increase of risk) compared with those with low maximal tumor SUV. In particular, patients with high maximal tumor SUV had an approximately 4-fold increase in the incidence of extrahepatic metastasis after completion of localized CCRT. For those high-risk patients, locoregional therapy, either localized radiotherapy or intra-arterial chemotherapy infusion, might be insufficient for prevention of systemic dissemination of the disease. Thus, the addition of other systemic therapy should be considered at an earlier stage of treatment for such patients. Theoretically, sublethal irradiation damage of HCC cells may induce the compensatory activation of multiple intracellular signaling pathway mediators such as PI3K, MAPK, JNK, NF-κB, and VEGF, not only leading to enhanced intratumor angiogenesis, but also ultimately facilitating earlier dissemination of HCC. Recent studies have shown positive results upon maintenance of molecular target agents such as sorafenib, along with chemoradiotherapy.[34,35] Thus, such high-risk patients may benefit from concomitant systemic therapy such as novel agents to block multimolecular pathways.[35-37]

This study has several limitations. First, quantitative assessments of changes in maximal tumor SUV from baseline after completion of chemoradiotherapy were not performed. Further studies investigating metabolic responses as a prognostic factor are warranted. Second, histopathologic examinations on tumor specimens were not included. Future studies covering the clinical correlation between metabolic activity and the expression of various regulatory enzymes and genes on tumor tissues are required to understand the tumor biology. Third, although maximal tumor SUV had a good correlation with the prognosis, considering that the repeatability of the SUV measurement is not high in a single patient, physicians should be cautious in interpreting this metabolic parameter. Therefore, further investigations to develop other metabolic parameters for generating the reproducible results are warranted.

In conclusion, we have shown that tumor metabolic activity before therapy, assessed by ^{18}F-FDG-PET/CT, is an independent prognostic factor in determining survival outcomes in patients with locally advanced HCC who have undergone localized CCRT followed by HAIC. Thus, it could be used as an ancillary method for risk stratification in the treatment of HCC. Further studies are required to investigate whether tumor metabolic activity is similarly significant in other nonsurgical treatment modalities, especially newer targeted agents.

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CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

REFERENCES

1. Pisani P, Ferlay J, Bray F, Parkin DM. Global cancer statistics, 2002. *CA Cancer J Clin*. 2005;55:74-108.
2. El-Serag HB, Rudolph KL. Hepatocellular carcinoma: epidemiology and molecular carcinogenesis. *Gastroenterology*. 2007;132:2557-2576.
3. Llovet JM, Burroughs A, Bruix J. Hepatocellular carcinoma. *Lancet*. 2003;362:1907-1917.
4. Sherman M, Bruix J. Management of hepatocellular carcinoma. *Hepatology*. 2005;42:1208-1236.
5. Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med*. 2008; 359:378-390.
6. Zhu AX, Clark JW. Commentary: sorafenib use in patients with advanced hepatocellular carcinoma and underlying Child-Pugh B cirrhosis: evidence and controversy. *Oncologist*. 2009;14:67-69.
7. Cheng AL, Kang YK, Chen Z, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. *Lancet Oncol*. 2009; 10:25-34.
8. Hawkins MA, Dawson LA. Radiation therapy for hepatocellular carcinoma: from palliation to cure. *Cancer*. 2006; 106:1653-1663.

9. Han K, Seong J, Kim JK, Ahn SH, Lee DY, Chon CY. Pilot clinical trial of localized concurrent chemoradiation therapy for locally advanced hepatocellular carcinoma with portal vein thrombosis. *Cancer*. 2008;113:995-1003.
10. Ben-Josef E, Normolle D, Ensminger WD, et al. Phase II trial of high-dose conformal radiation therapy with concurrent hepatic artery floxuridine for unresectable intrahepatic malignancies. *J Clin Oncol*. 2005;23:8739-8747.
11. Koom WS, Seong J, Han KH, Lee DY, Lee JT. Is local radiotherapy still valuable for patients with multiple intrahepatic hepatocellular carcinomas? *Int J Radiat Oncol Biol Phys*. 2010;77:1433-1440.
12. Rigo P, Paulus P, Kaschten BJ, et al. Oncological applications of positron emission tomography with fluorine-18 fluorodeoxyglucose. *Eur J Nucl Med*. 1996;23:1641-1674.
13. Siemerink EJ, Mulder NH, Brouwers AH, Hospers GA. 18F-Fluorodeoxyglucose positron emission tomography for monitoring response to sorafenib treatment in patients with hepatocellular carcinoma. *Oncologist*. 2008;13:734-735; author reply 736.
14. Seo S, Hatano E, Higashi T, et al. Fluorine-18 fluorodeoxyglucose positron emission tomography predicts tumor differentiation, P-glycoprotein expression, and outcome after resection in hepatocellular carcinoma. *Clin Cancer Res*. 2007;13:427-433.
15. Lee JW, Paeng JC, Kang KW, et al. Prediction of tumor recurrence by 18F-FDG PET in liver transplantation for hepatocellular carcinoma. *J Nucl Med*. 2009;50:682-687.
16. Hatano E, Ikai I, Higashi T, et al. Preoperative positron emission tomography with fluorine-18-fluorodeoxyglucose is predictive of prognosis in patients with hepatocellular carcinoma after resection. *World J Surg*. 2006;30:1736-1741.
17. Kornberg A, Freesmeyer M, Barthel E, et al. 18F-FDG-uptake of hepatocellular carcinoma on PET predicts microvascular tumor invasion in liver transplant patients. *Am J Transplant*. 2009;9:592-600.
18. Higashi T, Hatano E, Ikai I, et al. FDG PET as a prognostic predictor in the early post-therapeutic evaluation for unresectable hepatocellular carcinoma. *Eur J Nucl Med Mol Imaging*. 2010;37:468-482.
19. Kornberg A, Kupper B, Thrum K, et al. Increased 18F-FDG uptake of hepatocellular carcinoma on positron emission tomography independently predicts tumor recurrence in liver transplant patients. *Transplant Proc*. 2009;41:2561-2563.
20. Korean Liver Cancer Study Group and National Cancer Center. Practice guidelines for management of hepatocellular carcinoma 2009 [in Korean]. *Korean J Hepatol*. 2009; 15:391-423.
21. Ueno S, Tanabe G, Nuruki K, et al. Prognostic performance of the new classification of primary liver cancer of Japan (4th edition) for patients with hepatocellular carcinoma: a validation analysis. *Hepatol Res*. 2002;24:395-403.
22. Cillo U, Vitale A, Grigoletto F, et al. Prospective validation of the Barcelona Clinic Liver Cancer staging system. *J Hepatol*. 2006;44:723-731.
23. Gwyther SG, Christian MC, van Oosterom AT, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst*. 2000;92:205-216.
24. Flier JS, Mueckler MM, Usher P, Lodish HF. Elevated levels of glucose transport and transporter messenger RNA are induced by ras or src oncogenes. *Science*. 1987;235:1492-1495.
25. Okazumi S, Isono K, Enomoto K, et al. Evaluation of liver tumors using fluorine-18-fluorodeoxyglucose PET: characterization of tumor and assessment of effect of treatment. *J Nucl Med*. 1992;33:333-339.
26. Torizuka T, Tamaki N, Inokuma T, et al. In vivo assessment of glucose metabolism in hepatocellular carcinoma with FDG-PET. *J Nucl Med*. 1995;36:1811-1817.
27. Trojan J, Schroeder O, Raedle J, et al. Fluorine-18 FDG positron emission tomography for imaging of hepatocellular carcinoma. *Am J Gastroenterol*. 1999;94:3314-3319.
28. Yoon KT, Kim JK, Kim do Y, et al. Role of 18F-fluorodeoxyglucose positron emission tomography in detecting extrahepatic metastasis in pretreatment staging of hepatocellular carcinoma. *Oncology*. 2007;72(suppl 1):104-110.
29. Ledoux S, Yang R, Friedlander G, Laouari D. Glucose depletion enhances P-glycoprotein expression in hepatoma cells: role of endoplasmic reticulum stress response. *Cancer Res*. 2003;63:7284-7290.
30. Burk D, Woods M, Hunter J. On the significance of glucolysis for cancer growth, with special reference to Morris rat hepatomas. *J Natl Cancer Inst*. 1967;38:839-863.
31. Medina RA, Owen GI. Glucose transporters: expression, regulation and cancer. *Biol Res*. 2002;35:9-26.
32. Kim BK, Han KH, Park YN, et al. Prediction of microvascular invasion before curative resection of hepatocellular carcinoma. *J Surg Oncol*. 2008;97:246-252.
33. Vauthey J, Lauwers GY, Esnaola NF, et al. Simplified staging for hepatocellular carcinoma. *J Clin Oncol*. 2002; 20:1527-1536.
34. Zhao JD, Liu J, Ren ZG, et al. Maintenance of sorafenib following combined therapy of 3-dimensional conformal radiation therapy/intensity-modulated radiation therapy and transcatheter arterial chemoembolization in patients with locally advanced hepatocellular carcinoma: a phase I/II study. *Radiat Oncol*. 2010;5:12-18.
35. Chi KH, Liao CS, Chang CC, et al. Angiogenic blockade and radiotherapy in hepatocellular carcinoma. *Int J Radiat Oncol Biol Phys*. 2010;78:188-193.
36. Cheng JC, Chou CH, Kuo ML, Hsieh CY. Radiation-enhanced hepatocellular carcinoma cell invasion with MMP-9 expression through PI3K/Akt/NF-kappaB signal transduction pathway. *Oncogene*. 2006;25:7009-7018.
37. Chung YL, Jian JJ, Cheng SH, et al. Sublethal irradiation induces vascular endothelial growth factor and promotes growth of hepatoma cells: implications for radiotherapy of hepatocellular carcinoma. *Clin Cancer Res*. 2006;12:2706-2715.