Ann Surg Oncol (2012) 19:156–162
DOI 10.1245/s10434-011-1990-y

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – HEPATOBILIARY TUMORS

Preoperative FDG-PET Predicts Recurrence Patterns in Hepatocellular Carcinoma

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ABSTRACT

Purpose. We investigated the usefulness of preoperative fluorine-18 fluorodeoxyglucose positron emission tomography (FDG-PET) as a tool for predicting recurrence patterns to select patients for liver resection as an initial surgical strategy for hepatocellular carcinoma.

Methods. Sixty-three consecutive hepatocellular carcinoma patients undergoing FDG-PET were enrolled. They were classified according to the initial recurrence patterns (beyond the Milan criteria [MC], within the MC, and no recurrence) and the time intervals before initial postoperative recurrence (within 1 year, after 1 year or later, and no recurrence). The tumor-to-nontumor ratio (TNR) obtained by FDG-PET and survival rates were compared among the groups.

Results. TNR in the recurrence within the MC group (1.9 ± 1.6) and no recurrence group (1.3 ± 1.5) was significantly lower than that in the beyond the MC group (2.9 ± 2.6). TNR was an independent predictive factor of recurrence patterns in multivariate analysis. TNR in the groups with recurrence after 1 year or later (1.6 ± 0.8) and no recurrence (1.3 ± 0.5) were significantly lower than that in the within 1-year group (3.1 ± 2.7). TNR was an independent predictive factor of the interval before initial recurrence by multivariate analysis.

Conclusions. Preoperative FDG-PET predicts hepatocellular carcinoma recurrences within the MC or no recurrence and recurrences after 1 year or later. FDG-PET may be useful for selecting appropriate patients for liver resection as an initial surgical strategy.

First Received: 22 April 2011;
Published Online: 18 August 2011

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Orthotopic liver transplantation (OLT) and liver resection (LR) provide the best outcome in well-selected candidates in treating hepatocellular carcinoma (HCC). There has been an intense debate regarding whether OLT or LR is the optimal initial treatment for HCC patients. Some clinicians recommended OLT as the first-line treatment for HCC cases fulfilling the Milan criteria (MC; solitary liver nodule not exceeding 5 cm in maximum diameter, or 2 or 3 tumors not exceeding 3 cm in diameter), given the high 5-year survival rate (>70%).[1–5] OLT for HCC is thought to be the best option because it has the potential to cure both the tumor and the underlying liver disease. However, there are still difficulties, such as limited graft availability, perioperative mortality, and recurrence of underlying diseases. On the other hand, LR also currently results in a relatively high 5-year survival rate (>70%).[6–8] Although LR is associated with a high risk of HCC recurrence, there are many treatment options, including liver transplantation, for HCC recurrence within the MC, and a good prognosis can be expected. Therefore, preoperatively predicting recurrence patters of tumors is important to select the best candidates for LR and plan treatment options for recurrence, including salvage transplantation. Furthermore, predicting recurrence patterns, within or beyond the MC, and time intervals before recurrence is helpful in deciding appropriate initial surgical procedures such as OLT or LR for HCC.

FDG-PET (fluorine-18 fluorodeoxyglucose positron emission tomography) has been utilized as oncologic diagnostic imaging; this method is based on the enhanced

glucose metabolism of cancer cells. We have previously reported that FDG uptake, particularly the tumor-to-nontumor ratio of standardized uptake value (TNR) obtained by preoperative FDG-PET, is associated with prognosis in HCC patients.[9–11] The aim of this retrospective study was to investigate the usefulness of preoperative FDG-PET as a tool for predicting recurrence patterns and selecting appropriate patients for LR as an initial surgical treatment for HCC.

PATIENTS AND METHODS

Patients

This study was performed as a retrospective review of HCC patients who underwent an FDG-PET study during preoperative examination and LR at the Department of Surgery, Kyoto University, between May 2003 and September 2005. Inclusion criteria were as follows: (1) diagnosis of HCC by computed tomography (CT) and magnetic resonance imaging (MRI) with pathological confirmation, and (2) hepatectomy within 2 weeks after the FDG-PET study. Exclusion criteria were as follows: (1) patients with distant metastasis, and (2) patients who received pretreatment for HCC during the preoperative period. All patients were followed up with monitoring of serum alfa-fetoprotein (AFP) and ultrasound and/or contrast-enhanced CT every 3 months. Recurrence was confirmed by several imaging modalities, including CT and MRI.

The Kyoto University Graduate School and Faculty of Medicine Ethics Committee approved this study in accordance with ethics guidelines for epidemiological studies in Japan (E-885). Each patient provided written informed consent for undergoing FDG-PET.

FDG-PET Study

All PET imaging procedures were performed as described in our previous study.[12]

Image Analysis

PET images were interpreted by at least two experienced nuclear medicine physicians (TH and YN) on consensus, by using all available clinical information and correlative conventional imaging for anatomic guidance. Regions of interest were defined on the target lesions in the transaxial tomograms of PET images by the PET-to-CT coregistration method using the automatic rigid/nonrigid body-deformable fusion software Quantiva/BodyGuide (Tomographix IP, Toronto, Ontario, Canada).[12] The maximum standardized uptake value (SUV) was calculated for quantitative analysis of tumor ^{18}F-FDG uptake as follows:

$$\text{SUV} = \text{C(kBq/ml)/ID(kBq)/body weight (kg)},$$

where C represents the tissue activity concentration measured by PET and ID represents the injected dose.

TNR was also calculated as follows:

$$\text{TNR} = \text{tumor SUV/nontumor SUV},$$

where the nontumor SUV is defined as the average of SUVs at 5 points in nontumor liver tissues.

Statistical Analysis

Statistical analysis was performed by SPSS software, version 11.0.1 (SPSS, Chicago, IL). The following statistical analyses of preoperative clinical prognostic factors were performed in all 63 HCC patients. Patients were stratified and analyzed by univariate analysis using age, sex, preoperative serum AFP level, preoperative serum des-gamma carboxy prothrombin (DCP) level, MC at hepatic resection, number of tumors, tumor size, indocyanine green 15, Child-Pugh classification, liver damage, International Union Against Cancer (UICC) T stage, and TNR of tumor. All values are expressed as the means ± standard error of the mean (SEM). Correlations between clinicopathological parameters between each group were assessed by the chi-square test. The statistical significance of the differences between each group was assessed by nonparametric statistical tests (Mann-Whitney *U*-test). Survival time was defined from the date of surgery until the date of death, and recurrence was defined as detected by various modalities, including CT, MRI, and FDG-PET. The cumulative overall survival rate was analyzed by Kaplan-Meier methods, and differences in survival between the groups were compared by a log rank test. A P value of <0.05 was considered statistically significant.

RESULTS

Patient Characteristics

In all, 126 patients with HCCs underwent LR between May 2003 and September 2005 at the Kyoto University Hospital. One hundred thirteen of these patients underwent preoperative FDG-PET, and 50 of them received previous treatment for HCC, including LR ($n = 6$), transarterial chemoembolization ($n = 30$), both LR and transarterial chemoembolization ($n = 10$), or percutaneous ethanol injection therapy ($n = 4$); the remaining 63 patients (mean age 66 years; range 32–80 years; 46 men and 17 women) were enrolled onto this study. HCC was confirmed histologically to be well-differentiated in 12 patients,

moderately differentiated in 33 patients, and poorly differentiated in 18 patients. The TNR ranged from 0.6 to 13.3 (2.2 ± 2.0). The mean follow-up period in the patients was 38 months (range 2.5–66.7 months), and postoperative recurrence developed in 47 (74.6%) patients, including 23 patients within the MC and 24 patients beyond the MC. Five-year disease free and overall survival rates were 20.5 and 50.8%, respectively. The median disease-free time and overall survival time were 17.7 and 51.9 months, respectively.

Cumulative Survival Rates and TNR According to Recurrence Patterns

The survival rate in each group according to the type of recurrence is shown in Fig. 1a. The 5-year survival rate in groups with recurrence within the MC (59.0%) and no recurrence (81.3%) was significantly higher than that in the group with recurrence beyond the MC (23.8%, $P < 0.05$). The mean survival time of the groups with recurrence beyond the MC, recurrence within the MC, and no recurrence were 26.9, 56.3, and 57.2 months, respectively. TNR values in the groups with recurrence within the MC (1.9 ± 1.6; $P < 0.05$) and no recurrence (1.3 ± 0.5; $P < 0.01$) were significantly lower than that in the group with recurrence beyond the MC (2.9 ± 2.6; Fig. 1b). Moreover, the proportion of a high TNR value (cutoff 2) in the groups with recurrence within the MC (26%) and no recurrence (5.6%) was generally lower than that in the group with recurrence beyond the MC (55%; $P < 0.01$; Fig. 1c).

Univariate analysis showed that DCP levels ($P = 0.027$) and TNR values ($P = 0.007$) are significant predictive factors for recurrence patterns (beyond MC vs. within MC and no recurrence) of HCC (Table 1). Multivariate analysis revealed that the TNR value was an independent predictive factor of recurrence patterns (odds ratio 0.262; 95% confidence interval (CI) 0.08–0.85; $P = 0.026$; Table 2).

Cumulative Survival Rates and TNR According to Time Interval Before HCC Recurrence

The survival rate in each group according to the interval before initial HCC recurrence is shown in Fig. 2a. The 5-year survival rates in both groups with recurrence after 1 year or later (69.1%) and no recurrence (81.3%) were significantly higher than that of the group with recurrence within 1 year (19.2%, $P < 0.01$). The mean survival time of the group with recurrence within 1 year and recurrence after 1 year or later were 26.1 and 61.6 months, respectively. The TNR values in the groups with recurrence after 1 year or later (4.4 ± 1.6; $P < 0.05$) and no recurrence (3.8 ± 1.5; $P < 0.01$) were significantly lower than that in the group with recurrence within 1 year (8.4 ± 6.3; Fig. 2b). In addition, the proportion of higher TNR values in groups with recurrence after 1 year or later (20%) and no recurrence (5.9%) were significantly lower than that in the group with recurrence within 1 year (54%; $P < 0.01$; Fig. 2c).

Univariate analysis showed that the T stage (UICC) ($P = 0.047$) and preoperative AFP ($P < 0.001$), DCP ($P = 0.014$), and TNR ($P = 0.001$) values are significant

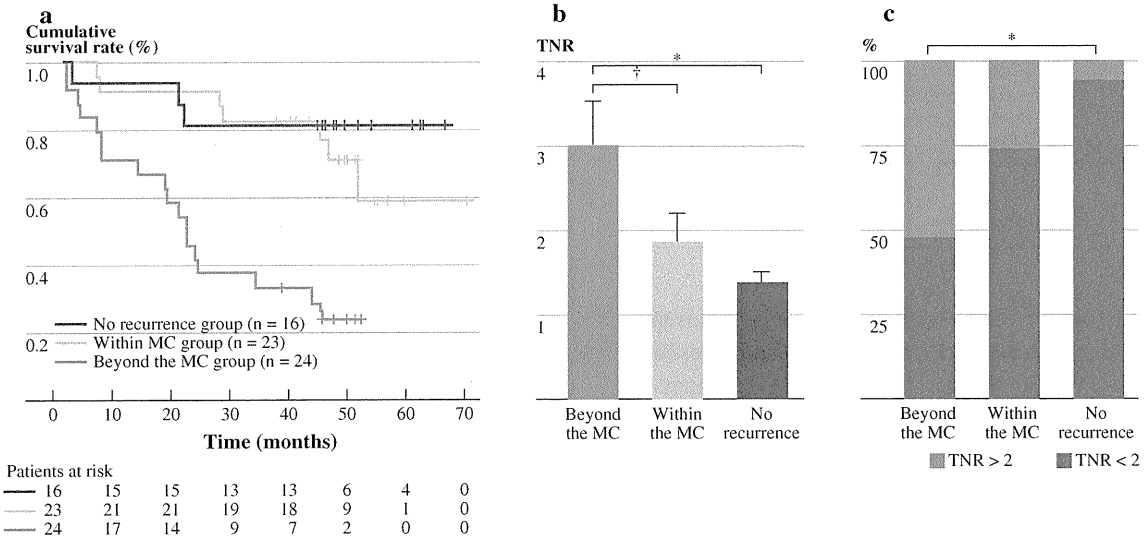

FIG. 1 Cumulative survival rates and TNR according to recurrence patterns. **a** Cumulative overall survival rates of HCC patients included in the 3 groups analyzed by Kaplan–Meier analysis and log rank test. **b** Mean value of tumor TNR with the 3 groups of recurrence patterns. **c** Relationship between TNR and recurrence patterns. *Dark gray*, TNR ≥ 2.0; *light gray*, TNR < 2.0. Data are shown as means ± SEM. *$P < 0.01$, †$P < 0.05$

TABLE 1 Univariate analysis of preoperative clinical factors associated with recurrence patterns (beyond MC vs. within MC and no recurrence) of 63 patients with HCC

Factor	Variable	Recurrence		*P* value
		Beyond MC	Within MC/no recurrence	
Age (years)	<65	13	14	0.144
	≥65	11	25	
Sex	Male	18	28	0.781
	Female	6	11	
MC	Within	2	10	0.089
	Beyond	22	29	
No. of tumors	Single	15	27	0.582
	Multiple	9	12	
Tumor size (cm)	≤5	9	22	0.145
	>5	15	17	
ICG 15	≤15	13	16	0.310
	>15	11	23	
Child-Pugh	A	22	37	0.612
	B	2	2	
Liver damage	A	17	25	0.582
	B	7	14	
UICC T stage[a]	1.2	16	32	0.096
	3.4	8	7	
AFP (ng/ml)	<400	17	33	0.189
	≥400	7	6	
DCP (AU/ml)	<400	5	19	0.027
	≥400	19	20	
TNR	<2.0	12	32	0.007
	≥2.0	12	7	

ICG indocyanine green

[a] Tumor, node, metastasis system classification of the International Union Against Cancer (6th edition)

TABLE 2 Multivariate analysis of predictive factors for recurrence patterns in 63 patients with HCC

Characteristic	Logistic regression analysis		
	Odds ratio	95% CI	*P* value
DCP	0.345	0.10–1.17	0.086
TNR	0.262	0.08–0.85	0.026

predictive factors for the interval before initial recurrences (within 1 year vs. after 1 year or later and no recurrence) of HCC (Table 3). Multivariate analysis revealed that the TNR value was an independent predictive factor of interval before initial recurrence (odds ratio 0.164; 95% CI 0.04–0.72; $P = 0.016$; Table 4).

DISCUSSION

OLT and LR are the possible surgical treatments for the patients with HCC as defined by MC. OLT based on MC has been shown to provide good disease-free survival; thus, it is considered the optimal treatment for small HCC, particularly in patients with underlying chronic liver disease.[1,2] The Barcelona Clinic Liver Cancer classification offers a prognostic stratification of patients with HCC who have increased portal pressure as candidates for OLT as the best surgical strategy.[13–15]

However, LR, which affords the highest controllability among all local treatments as well as good survival, is readily available and may have a positive effect on decreased global availability of donor organs. However, LR is associated with high intrahepatic recurrence rates, and the 5-year recurrence rates range from 77 to 100%, although recurrence was confined to the remnant liver in >80% patients and included either metastasis to the intrahepatic regions or de novo malignancies.[8,16–18] For HCC recurrences within the MC, many treatment options are available, such as liver transplantation, and a good prognosis can be expected. There are several recent reports concerning salvage transplantation.[19–22] Belghiti et al.

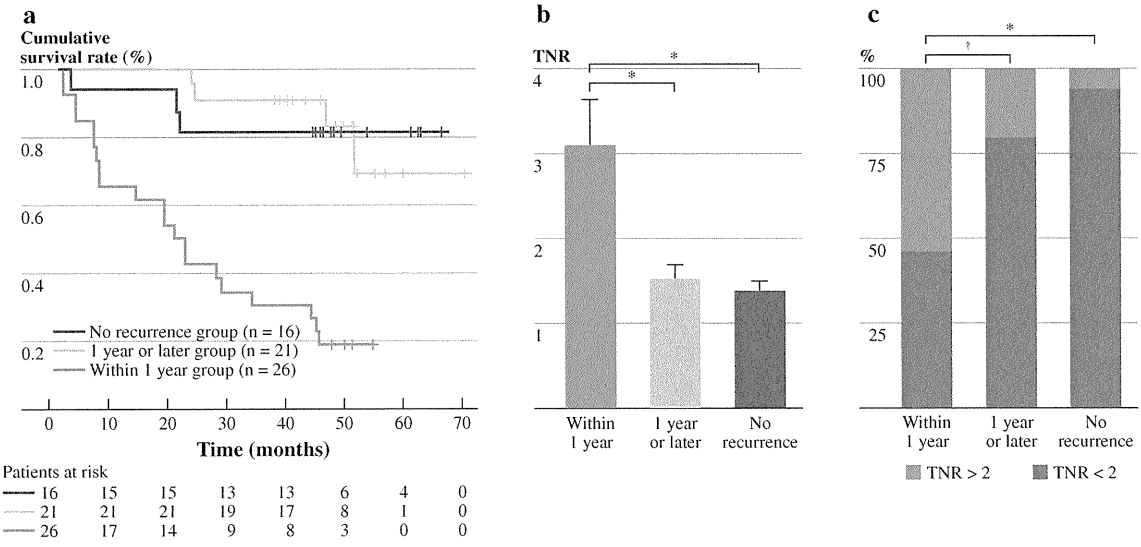

FIG. 2 Cumulative survival rates TNR according to time interval before recurrence. **a** Cumulative overall survival rates of HCC patients included in the 3 groups analyzed by Kaplan–Meier analysis and log rank test. **b** Mean value of tumor TNR with the 3 groups of the time interval before recurrence. **c** Relationship between TNR and the time interval before recurrence. *Dark gray,* TNR $\geq$ 2.0; *light gray,* TNR < 2.0. Data are shown as means $\pm$ SEM. $*P < 0.01$, $\dagger P < 0.05$

reported that LR before transplantation can be performed as an integrated treatment for HCC.[23] Poon et al. reported that primary LR and salvage transplantation may be a feasible and rational strategy for HCC patients.[7] An interesting advantage of LR is that it allows analysis of the entire pathologic tumor specimen and assessment of prognostic factors such as differentiation and microscopic vascular invasion.[22,24–26] These factors have been proposed to select patients as candidates for secondary OLT. In our study, 38% of patients developed recurrent HCC beyond the MC in initial recurrence and consequently lost the opportunity for liver transplantation. In patients with HCC beyond the MC at initial LR, some patients who could meet the MC at recurrence may have been eligible for salvage liver transplantation. Therefore, predicting the recurrence patterns within or beyond the MC is important to select patients as candidates for LR. Results of this study showed that FDG-PET predicts recurrence patterns and can be used as an imaging biomarker for selecting appropriate patients as candidates for LR in initial surgical strategies.

Furthermore, to clarify the optimal treatment strategy for recurrent HCC, predicting the time interval between primary LR and initial HCC recurrence is important. Early recurrence within 1 year after LR was previously confirmed to be one of the most important prognostic indicators in patients with recurrent HCC.[27,28] In our series, early recurrence after primary resection significantly impaired overall survival after resection, consistent with previous reports.[27–29] These results suggest that many cases of recurrence within 1 year were thought to be intrahepatic metastasis from the primary HCC. Therefore, adjuvant therapy, such as Sorafenib, may be necessary to improve outcomes in such patients. In contrast, in our series, the survival rate of the group with recurrence after 1 year or later was not significantly different from that of the group without recurrence. Patients in these groups may be candidates for LR in initial surgical strategies.

In the present study, TNR was shown by multivariate analysis to be a statistically significant preoperative risk factor for both patient survival and recurrence-free survival. Differentiation between the tumor and physiologic noise in the liver is sometimes difficult in FDG-PET because normal liver tissue exhibits heterogeneity in FDG uptake, and physiologic noise in the liver is apparent. Background nontumor liver uptake varied to some extent, and the contrast between the liver tumor and background liver noise may be dependent on the extent of tumor uptake itself as well as on the general liver background. In our series, the SUV of background nontumor liver did not correlate with prognosis of HCC patients (data not shown). For these reason, we measured TNR in addition to the SUV of the tumor. Our previous HCC evaluation showed that TNR has a similar or better prognostic value than SUV in PET diagnosis of HCC.[9–11] On the basis of our results, we propose that HCC patients with a TNR of <2 are candidates for LR as an initial surgical strategy and those with a TNR of $\geq$2 are candidates for OLT or need adjuvant therapy. Further studies would be needed to clarify the usefulness of TNR for liver transplant patients.

There are limitations to our study. First, the study was conducted retrospectively. Second, the SUV of a tumor indicates the value of this parameter over the region of

TABLE 3 Univariate analysis of preoperative clinical factors associated with interval before initial recurrence (within 1 year vs. after 1 year or later and no recurrence) of 63 patients with HCC

Factor	Variable	Recurrence		*P* value
		Within 1 year	After 1 year or later/no recurrence	
Age (y)	<65	15	12	0.046
	≥65	11	25	
Sex	Male	17	29	0.253
	Female	9	8	
MC at hepatic resection	Within	3	9	0.203
	Beyond	23	28	
No. of tumors	Single	16	26	0.469
	multiple	10	11	
Tumor size (cm)	≤5	11	20	0.359
	>5	15	17	
ICG 15	≤15	14	15	0.297
	>15	12	22	
Child-Pugh	A	23	36	0.157
	B	3	1	
Liver damage	A	17	25	0.856
	B	9	12	
UICC T stage[a]	1.2	17	31	0.047
	3.4	9	6	
AFP (ng/ml)	<400	15	35	0.000
	≥400	11	2	
DCP (AU/ml)	<400	6	18	0.014
	≥400	20	19	
TNR	<2.0	12	32	0.001
	≥2.0	14	5	

ICG indocyanine green

[a] Tumor, node, metastasis system classification of the International Union Against Cancer (6th edition)

TABLE 4 Multivariate analysis of predictive factors for interval before initial recurrence in 63 patients with HCC

Characteristic	Cox proportional hazard model		
	Odds ratio	95% CI	*P* value
Age	2.766	0.73–10.5	0.136
UICC T stage[a]	1.428	0.26–7.84	0.682
AFP	0.227	0.03–1.58	0.134
DCP	0.553	0.15–2.09	0.383
TNR	0.164	0.04–0.72	0.016

[a] Tumor, node, metastasis system classification of the International Union Against Cancer (6th edition)

interest, but it does not reflect the heterogeneity of a tumor. Tumor heterogeneity was not taken into account in our study. We conclude that preoperative FDG-PET predicted patterns of HCC recurrences within the MC or no recurrence and recurrences after 1 year or later and could be helpful in selecting appropriate patients for LR, as an initial surgical strategy.

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CASE REPORT

Uptake of gadolinium-ethoxybenzyl-diethylenetriaminepentaacetic acid in metastatic adrenal tumour from hepatocellular carcinoma

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ABSTRACT. We present the case of a metastatic adrenal tumour from hepatocellular carcinoma (HCC) showing the uptake of gadolinium ethoxybenzyl diethylenetriaminepentaacetic acid (Gd-EOB-DTPA) on MRI. To our knowledge, this is the first case of metastatic HCC in which Gd-EOB-DTPA uptake was shown on MRI and this finding facilitated the accurate pre-operative diagnosis of a metastatic adrenal tumour.

Received 11 August 2010
Revised 13 October 2010
Accepted 25 October 2010

DOI: 10.1259/bjr/20594229

Recently, gadolinium ethoxybenzyl diethylenetriaminepentaacetic acid (Gd-EOB-DTPA), a contrast agent with perfusion and hepatoselective properties, has been used for the diagnosis of hepatocellular carcinoma (HCC) on MRI [1–3]. It allows combined dynamic imaging and hepatocyte-specific imaging in one examination. In the hepatobiliary phase, hepatic lesions like HCC lacking normally functioning hepatocytes are imaged as a defect of hepatocyte-selective enhancement compared with normal parenchyma. Some HCCs may show the paradoxical uptake of Gd-EOB-DTPA and are recognised as iso- or hyperintense lesions in the hepatobiliary phase compared with normal parenchyma [3–7]. However, to date there have been no published reports describing the uptake of Gd-EOB-DTPA in a metastatic lesion from HCC. We describe a patient with adrenal metastasis from HCC, showing Gd-EOB-DTPA uptake on MRI.

Case report

A 73-year-old male with a history of hepatitis C was referred from a district hospital for further HCC treatment and suspected left adrenal metastasis. He also had a history of colon cancer, which had been curatively treated 19 years earlier without recurrence, and cholelithiasis, which had been treated with cholecystectomy 7 years previously.

A CT scan with contrast enhancement was performed, which revealed an ill-defined low density area in the segment 4/8 region of the liver accompanied by a filling defect in the enlarged intrahepatic portal vein (Figure 1a). A 28 mm round-shaped left adrenal nodule was also noted; it showed soft-tissue attenuation (>10 HU) on unenhanced CT, homogeneous enhancement in the early phase after the injection of contrast material and washout in the equilibrium phase (Figure 1b–d).

On MRI with Gd-EOB-DTPA injection, the hepatic lesion was depicted as a heterogeneously enhanced ill-defined area during the arterial phase and a heterogeneous low-intensity area during portal and equilibrium phases. It was more clearly depicted as a low-intensity area in the hepatobiliary phase 20 min after contrast medium injection. The adrenal lesion showed low intensity on T_2 weighted fast-spin echo images and no signal drop was demonstrated on in- and opposed-phase T_1 weighted gradient recalled echo images (Figure 2a,b), which suggests a poor fatty component within the lesion. After Gd-EOB-DTPA administration, the lesion showed enhancement in the arterial phase compared with the unenhanced fat-suppressed T_1 weighted image and a washout pattern on portal and equilibrium phase images. On hepatobiliary phase images, the nodule and hepatic parenchyma appeared homogeneously hyperintense compared with a pre-contrast image (Figure 2c–e), which suggests uptake of Gd-EOB-DTPA within the left adrenal lesion.

The serum alpha-fetoprotein (AFP) concentration was 5.1 ng ml^{-1} (normal range (NR) <15 ng ml^{-1}) and the protein level induced by vitamin K antagonist-2 (PIVKA-2) was 2050 mAU ml^{-1} (NR <40 mAU ml^{-1}). The results of other biochemical tests were as follows: total protein 8.8 mg dl^{-1} (NR 6.3–8.1 g dl^{-1}); albumin 3.0 mg dl^{-1} (NR 3.9–5.1 g dl^{-1}); aspartate aminotransferase 66 IU/l

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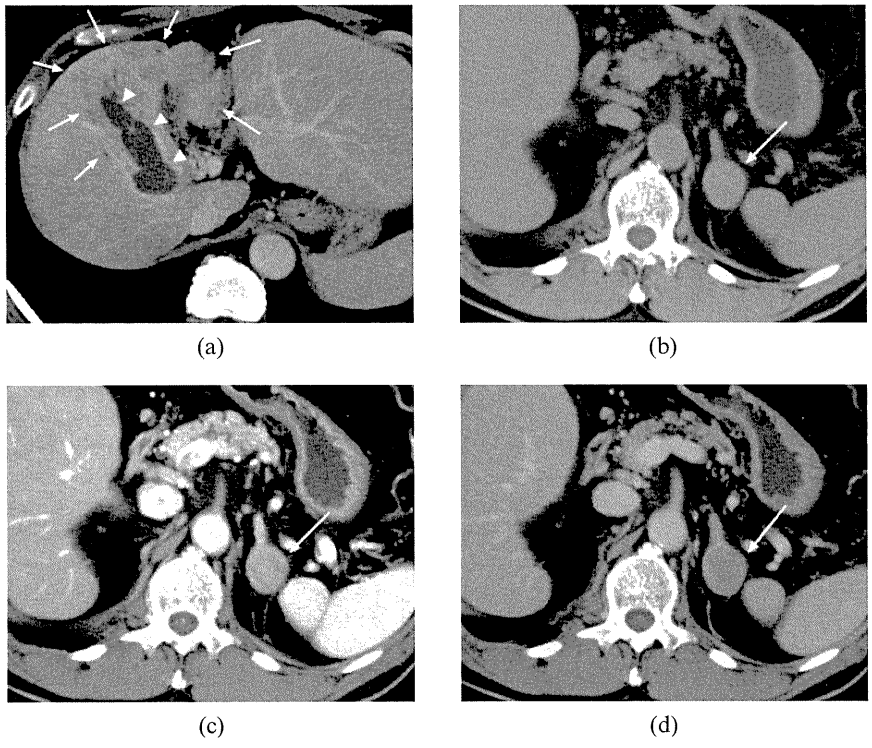

Figure 1. (a) Contrast-enhanced CT shows an ill-defined low density area in the segment 4/8 region of the liver (arrows), accompanied with filling defect in the enlarged intrahepatic portal vein which represents tumour thrombosis (arrowheads). At a more caudal level, a 28 mm round-shaped well-demarcated nodule can be noted; (b) soft-tissue attenuation (>10 HU) on plain CT (arrow), (c) homogeneous enhancement in the early phase after the injection of contrast material (arrow) and (d) washout in the equilibrium phase (arrow).

(NR 13–33 IU l^{-1}); alanine aminotransferase 52 IU l^{-1} (NR 8–42 IU l^{-1}); alkaline phosphatase 990 IU l^{-1} (NR 115–359 IU l^{-1}); γ-glutamyl transpeptidase 300 IU l^{-1} (NR 9–54 IU l^{-1}); lactate dehydrogenase 216 IU l^{-1} (NR 129–241 IU l^{-1}); and total bilirubin 0.4 mg dl^{-1} (NR 0.3–1.3 mg dl^{-1}).

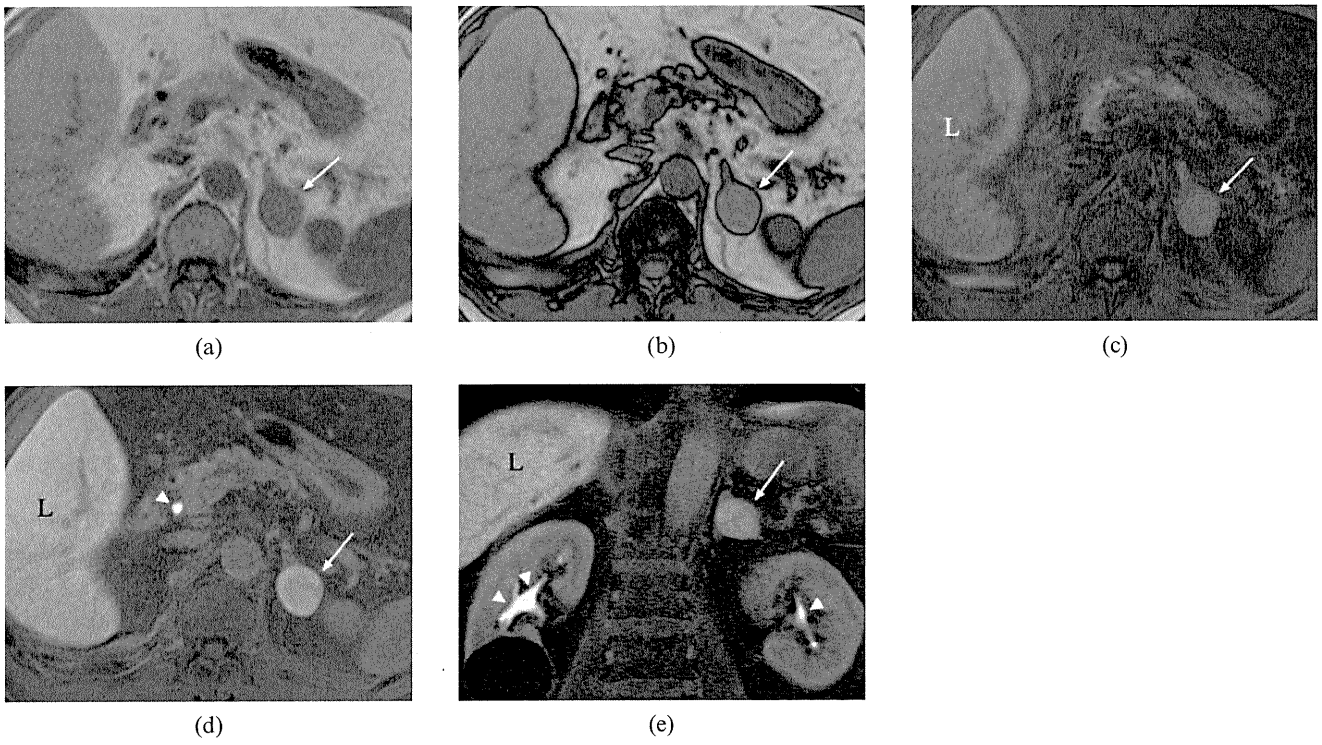

Figure 2. On (a) in- and (b) opposed-phase T_1 weighted gradient recalled echo MRI, no signal drop of the left adrenal nodule is demonstrated (arrows in a,b), which suggests a poor fatty component within the lesion. Compared with a (c) pre-contrast fat-suppressed T_1 weighted image, (d,e) the lesion is depicted as a homogeneously hyperintense nodule as well as hepatic parenchyma in the hepatobiliary phase 20 min after Gd-EOB-DTPA administration (arrows in c–e), which suggests the uptake of Gd-EOB-DTPA within the tumour (L, liver). Note high signal intensity in the common bile duct (arrowhead in d) and bilateral renal pelves (arrowheads in e), which represents contrast material excreted in the bile and urine, respectively.

From the patient's history of hepatitis C, the laboratory data (especially elevated AFP and PIVKA-2) and the imaging findings noted above, a diagnosis of diffuse HCC in the liver with portal vein tumour thrombosis and a metastatic left adrenal tumour from HCC was made.

The continuous administration of 5-fluorouracil (250 mg body^{-1} per day, days 1–5) and cisplatin (10 mg body^{-1} per day, days 1–5) was performed by hepatic arterial infusion through a subcutaneous injection port implanted into the right inguinal region. After 3 weeks, the PIVKA-2 level in serum decreased to 324 mAU ml^{-1} and reduction of the tumour thrombus in the intrahepatic portal vein was confirmed on a follow-up CT. The left adrenal tumour did not change in size and features. Consecutive CT, MRI and PET using 18-fluoro-2-deoxy-D-glucose revealed neither intrahepatic nor distant metastasis other than left adrenal metastasis, and so it was planned for the patient to undergo hepatectomy and left adrenalectomy. After receiving percutaneous transhepatic portal embolisation of the right posterior intrahepatic portal vein to induce hypertrophy of the left lateral lobe, he underwent an extended right lobectomy and left adrenalectomy.

On macroscopic findings, the resected hepatic lesion was a solid pale-yellow tumour and the left adrenal lesion was a solid pale-green tumour. Based on microscopic histopathological analysis, the liver tumour was moderately differentiated HCC, post-chemotherapy, with intrahepatic portal vein tumour thrombosis. The left adrenal tumour showed a highly-to-moderately differentiated metastatic carcinoma, consistent with hepatic origin.

Discussion

Recently, Gd-EOB-DTPA has been used for the diagnosis of HCC on MRI. In the hepatobiliary phase, HCCs are usually imaged as a defect of hepatocyte-selective enhancement compared with normal parenchyma. It is known, however, that some HCCs show the paradoxical uptake of Gd-EOB-DTPA with an incidence of 9–27% [3–7] and are recognised as iso- or hyperintense lesions in the hepatobiliary phase compared with the normal parenchyma. To our knowledge, there has been no report describing the uptake of Gd-EOB-DTPA in metastatic lesions from HCC and our report is the first to describe metastatic HCC in which the uptake of Gd-EOB-DTPA was shown on MRI.

An early report indicated that 50% of well-differentiated HCCs exhibited iso- or hyperintensity to the surrounding liver parenchyma and that moderately or poorly differentiated HCCs exhibited no uptake of Gd-EOB-DTPA [5]. According to more recent reports, however, no relationship between uptake of Gd-EOB-DTPA and tumour grade has been reported [3, 4, 6, 7]. The mechanism of uptake of Gd-EOB-DTPA in HCCs and the characteristics of Gd-EOB-DTPA-positive HCCs have also been gradually clarified. Narita et al [6] showed that the expression of OATP1B3, which is one of the sodium-independent organic anion transporters and is expressed in the human liver in the basolateral membrane of hepatocytes, determines the uptake of Gd-EOB-DTPA in the hepatobiliary phase in HCCs. Tsuboyama et al [7] reported that hepatocyte-selective enhancement is induced by expression patterns of transporters including OATP1B3, OATP1B1 and MRP2. Unfortunately, the expression of these transporters was not investigated in our case, either in the hepatic nor adrenal tumour.

The adrenal gland is a common target organ of haematogenous metastasis from HCC, with an incidence of 11–16.9% in clinical practice [8–10]. There are a few reports describing the CT findings of metastatic adrenal tumours from HCC. Nakamura et al [11] described large (>8 cm) adrenal metastases with a central low density area owing to necrosis and rather smaller ones homogeneously enhanced. Katyal et al [8] reported that many of the adrenal metastases from HCC demonstrated enhancement during the hepatic arterial phase, consistent with our case. The findings on MRI are not well described.

The presence of an enlarged adrenal mass does not always imply malignancy because statistically adrenal adenomas are a more common cause of an enlarged adrenal gland, even in patients with known extra-adrenal primary tumours [12]. If the presence of fat within adrenal tumours is confirmed based on the density on unenhanced CT (<10 HU) or a dropped signal on an opposed phase T_1 weighted MRI, a diagnosis of adenoma can be made [13, 14]. However, lipid-poor adenoma cannot be diagnosed by this procedure and both adenoma and metastatic HCC often show similar findings of early enhancement and washout. $^{99}Tc^{m}$ pyridoxyl–5-methyl tryptophan hepatobiliary scintigraphy is useful for specifically diagnosing metastatic HCC but only when the tumour cells produce bile [15–17]. We estimate that the uptake of Gd-EOB-DTPA in any masses outside the liver is also a specific finding of metastatic lesions from HCC and that this finding is useful for diagnosing metastatic tumours from HCC, although its sensitivity is presumably low.

Conclusion

We have presented a case of a metastatic adrenal tumour from HCC showing the uptake of Gd-EOB-DTPA on MRI. This MR finding enabled us to make the correct pre-operative diagnosis of a metastatic adrenal tumour.

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J Gastroenterol
DOI 10.1007/s00535-011-0511-x

RAPID COMMUNICATION

Early evaluation of transcatheter arterial chemoembolization-refractory hepatocellular carcinoma

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Received: 31 May 2011 / Accepted: 14 November 2011

Abstract
Background There is no standard therapy for patients with transcatheter arterial chemoembolization (TACE)-refractory hepatocellular carcinoma (HCC). This study examined whether evaluating the tumor effect (TE) at 1 week after TACE was useful for predicting refractoriness to TACE.
Methods We performed a historical cohort study involving 54 patients and 119 tumors. TE was evaluated at 1 week and 3 months after TACE, and an overall evaluation was also performed at 3 months based on the response evaluation criteria in cancer of the liver.
Results Among 45 tumors evaluated as TE2 at 1 week, 43 tumors (95.6%) were classified as TE1 or TE2 at 3 months. Of the 24 patients whose tumors were categorized as TE2 at 1 week, none achieved a complete or partial response.
Conclusions Evaluating the TE at 1 week after TACE is useful for the early diagnosis of TACE-refractory HCC and allows alternative treatment options, such as sorafenib, to be employed before the disease progresses.

Keywords Hepatocellular carcinoma · Transcatheter arterial chemoembolization · Tumor effects

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Introduction

Transcatheter arterial chemoembolization (TACE) provides a survival benefit in patients with unresectable or relapsed hepatocellular carcinoma (HCC) [1]. TACE is recommended for HCC patients who have been categorized as A or B on the Child–Pugh classification [2]. The selection criteria for TACE are affected by the patient's history of resection, the location of the recurrent HCC, and portal tumor thrombosis. However, repetitive TACE treatments might reduce liver function and induce stenosis of the hepatic artery. Furthermore, even if liver function is preserved in patients whose disease has been defined as Child–Pugh classification A or B, repetitive TACE treatments become less effective in patients with relapsed HCC. These cases are considered TACE-refractory in clinical practice. No effective treatment for TACE-refractory HCC has been established.

Sorafenib is a molecular-targeted agent that is used to prolong the survival of patients with advanced HCC [3, 4]. Recently, it was suggested that sorafenib has beneficial effects on metastatic or TACE-refractory HCC [5]. According to consensus statements from the Japan Society of Hepatology, TACE-refractory HCC patients belonging to Child–Pugh group A are candidates for sorafenib monotherapy as a second-line treatment option [6].

However, refractoriness to TACE is not well defined. Although it is desirable to assess the tumor effect (TE) at least 1 month after TACE, overall response evaluations are performed 3 months after TACE, according to the response evaluation criteria in cancer of the liver (RECICL) [7]. This delay in performing the evaluation is a major concern because of the risk of recurrence and/or tumor progression. If TACE-refractory HCC could be evaluated early, patients with TACE-refractory HCC could be treated with

Published online: 21 December 2011

alternative treatments, such as sorafenib. Therefore, this study examined whether TE evaluations conducted at 1 week after TACE treatment could be used to predict the TE of TACE and the results of the overall response evaluation in order to provide an early diagnosis of TACE refractoriness.

Methods

Study design and eligibility criteria

The Kyoto University Graduate School and Faculty of Medicine Ethics Committee approved this study (E-1071) in accordance with the ethics guidelines for epidemiologic studies in Japan. All patients gave their informed consent for TACE. We performed a historical cohort study to assess the efficacy of TACE. Patients at Kyoto University Hospital who were diagnosed with HCC and treated with TACE between 1 June 2009 and 31 December 2009 were selected for this study. The clinical variables selected in this study were age, sex, hepatitis B surface antigen, hepatitis C virus antibody, history of resection and local ablation therapy, the number of previous TACE treatments, Child–Pugh classification, platelet count, alpha-fetoprotein levels, levels of prothrombin induced by vitamin K absence or antagonist-II, chemotherapeutic agents administered, and the number of tumors. These variables were measured before TACE therapy.

Treatment

Epirubicin® (Nipponkayaku, Tokyo, Japan) dissolved in contrast medium and then suspended in Lipiodol was injected as selectively as possible into the hepatic segmental artery supplying the HCC. Gelfoam® sponges (Pfizer, NY, USA) were used for the embolization. No repeat TACE treatment was scheduled unless the tumor relapsed.

Assessment of efficacy

The efficacy of TACE was assessed by performing dynamic computed tomography (CT; Aquilion TSX-101A, Toshiba Medical Systems, Japan) or magnetic resonance imaging (MRI; MAGNETOM Skyra, Siemens, Germany) before and 3 months after the TACE treatment. For the early evaluation performed 1 week after the TACE, plain CT was performed to assess the uptake of Lipiodol. CT angiography was not routinely performed during TACE. MRI was used for patients that displayed an allergic reaction to the contrast medium and patients who did not demonstrate a typical target lesion on dynamic CT. The tumors targeted in the TE assessment were selected during the CT or MRI conducted before the TACE. The response to TACE was calculated according to RECICL [7]. The tumor-necrotizing effect and tumor size reduction rate were assessed on the basis of the reduction in tumor size or the disappearance of hypervascularity from the nodule using bi-dimensional measurements. The rate of reduction of the necrotic area was estimated from the Lipiodol accumulation observed on CT after TACE. The TE for each targeted tumor was defined as follows: TE4, the disappearance of the tumor or a 100% tumor-necrotizing effect; TE3, a $\geq$50% reduction in tumor size or a $\geq$50% tumor-necrotizing effect; TE1, a $\geq$25% increase in tumor size regardless of the necrotizing effect; and TE2, cases that did not qualify as TE4, TE3, or TE1. The TE determined at 1 week after the TACE treatment was defined as the early TE in this study.

The CT or MR images obtained at 3 months after the TACE treatment were used for the overall evaluation, which was performed according to the RECICL [7]. When there were more than 5 tumors, only 5 tumors were targeted. The overall evaluation was defined using the total tumor load of all the targeted tumors as follows: complete response (CR), disappearance of the tumor or a 100% tumor-necrotizing effect in all tumors; partial response (PR), $\geq$50% reduction in tumor size or a $\geq$50% tumor-necrotizing effect; progressive disease (PD), $\geq$25% increase in tumor size or the emergence of a new tumor; and stable disease (SD), the cases that were not classified as CR, PR, or PD.

Statistical analysis

We examined the relationship between early TE and TE at 3 months. To calculate the sensitivity and specificity of early TE for each tumor, we divided TE into two categories, TE3/4 and TE1/2. Furthermore, we examined the relationship between early TE and the results of the overall evaluation. We also divided the overall evaluation into two categories, CR/PR and SD/PD, to calculate the sensitivity and specificity of early TE. In patients with multiple tumors, we used the lowest TE in our analysis.

Results

Patients

Among the 80 consecutive patients treated with TACE for HCC, the patients who did not undergo any radiological imaging at 3 months after TACE ($n = 10$), who were administered sorafenib ($n = 1$), who underwent TACE with additional percutaneous ethanol injection therapy or radiofrequency ablation ($n = 10$), who underwent TACE

without embolization ($n = 4$), or who underwent TACE using cisplatin instead of epirubicin ($n = 1$) were excluded from this study. Thus, 54 patients with 119 tumors were enrolled in this study. The characteristics of the patients are shown in Table 1.

Relationship between early TE and TE at 3 months after TACE

Early TE1, early TE2, early TE3, and early TE4 were observed in 0, 45, 34, and 40 tumors, respectively. As for the TE observed at 3 months after TACE, TE1, TE2, TE3, and TE4 were observed in 32, 35, 6, and 46 tumors, respectively (Table 2). The sensitivity and specificity of early TE for predicting the TE at 3 months were 64.2 and 96.2%, respectively. Among the 45 tumors evaluated as early TE2, 19 and 24 tumors were evaluated as TE1 and TE2, respectively, at 3 months after TACE. Thus, the positive predictive value of early TE was 95.6%.

Relationship between early TE and the results of the overall evaluation

In the overall evaluation, CR, PR, SD, and PD were observed in 11, 1, 5, and 37 patients, respectively (Table 3). Compared with the response rate achieved in other studies [8], the CR (22%) and disease control rates (31%) were relevant. The sensitivity and specificity of early TE for predicting the results of the overall evaluation were 57.1 and 100%, respectively. Among the 24 patients whose tumors were evaluated as early TE2, 20 patients were evaluated as PD and 4 patients were categorized as SD. Thus, the positive predictive value of early TE was 100%, suggesting that the designation "early TE2" indicates reduced TACE effectiveness.

Discussion

HCC is staged on the basis of the Barcelona Clinic Liver Cancer (BCLC) staging system, and TACE is considered to be effective for patients with intermediate stage HCC [9]. However, TACE failure or TACE-refractory HCC is often observed after repeated TACE treatments. The response rate for TACE has been reported to be 15–55% [8]. TACE failure is defined by the following circumstances: an inability to select the feeding artery of the HCC because of arterial devastation, a deterioration of liver function due to repeated TACE treatments, and/or tumor thrombosis of the portal vein. TACE refractoriness is defined using four factors: repetitive tumor recurrence in the liver, the appearance of vascular invasion, the appearance of distant metastasis, and a continuous increase in tumor marker levels after TACE. Repetitive recurrence is diagnosed according to the RECICL, which indicate that the assessment should be performed at least 1 month after TACE. Furthermore, a time interval of 2 or 3 months is usually required between TACE treatments. Therefore, the time period between the initial TACE therapy and the next TACE treatment needs to be more than 3 months.

According to a subanalysis performed as part of the sorafenib HCC assessment randomized protocol (SHARP) study [3], it is expected that treatment with sorafenib in combination with TACE will markedly prolong the overall survival of HCC patients [6]. Several clinical trials such as the global sorafenib placebo in combination with TACE (SPACE) trial and the Japanese TACE therapy in combination with sorafenib (TACTICS) trial have been conducted to analyze the effect of combining TACE therapy with sorafenib. However, in a phase III study conducted in Japan and Korea of sorafenib treatment in patients with advanced HCC, who were administered the drug after

Table 1 Patient characteristics

Characteristics		Number of patients (%)
Age	Median (range)	72 (49–84)
Sex	Male	45 (83)
Hepatitis B surface antigen	Positive	6 (11)
Hepatitis C virus antibody	Positive	24 (44)
History of resection		35 (64)
History of local ablation therapy		25 (46)
No. of previous TACEs	Median (range)	2 (0–9)
Child–Pugh classification	A/B	48/6 (89/11)
Platelet count ($\times 10^9$/L)	Median (range)	9.2 (4.4–40)
Alpha-fetoprotein (ng/dL)	Median (range)	14.9 (2.0–9,282)
PIVKA-II (mAU/mL)	Median (range)	61 (11–33,000)
Chemotherapeutic agent	Median (range)	28.5 (10–45)
Tumor diameter (cm)	≤2/>2	38/16 (70/30)
Number of tumors	Single/multiple	21/33 (39/61)

PIVKA-II prothrombin induced by vitamin K absence or antagonist-II, *TACE* transcatheter arterial chemoembolization

Table 2 Relationship between early TE and TE after TACE

Number of tumors	TE (3 months)				Total
	1	2	3	4	
Early TE (1 week)					
2	19	24	2	0	45
3	9	8	3	14	34
4	4	3	1	32	40
Total	32	35	6	46	119

TE tumor effect

Table 3 Relationship between early TE and overall evaluation

Number of patients	Overall evaluation				Total
	PD	SD	PR	CR	
Early TE (1 week)					
2	20	4	0	0	24
3	8	0	1	6	15
4	9	1	0	5	15
Total	37	5	1	11	54

TE tumor effect, *PD* progressive disease, *SD* stable disease, *PR* partial response, *CR* complete response

TACE [10], the time to progression was not significantly prolonged in HCC patients treated with sorafenib. This negative result was considered to have been caused by the increased number of discontinuations and shorter treatment duration that they experienced, as well as the long time period required between TACE treatment and the start of sorafenib therapy (median 9.3 weeks). Additionally, ineffective TACE is considered to induce a neoangiogenic reaction early after TACE [11]. Therefore, treating TACE-refractory HCC patients with sorafenib earlier might have beneficial effects, even in patients with advanced HCC.

There were some limitations to this study. Early TE displayed sensitivities of 64.2 and 57.1% for predicting TE at 3 months and the results of the overall evaluation, respectively. Therefore, early TE was not very accurate at predicting the TE at 3 months and the results of the overall evaluation. However, we think that assessing early TE is useful because it would allow 57.1% of patients to be treated with alternative options earlier. We are currently conducting a prospective trial regarding the effectiveness of the early evaluation of TACE-refractory HCC (UMIN 000005847). Furthermore, an inability to select the feeding artery of a target HCC is one of the causes of TACE failure, although no tumors with extra feeding arteries were detected by angiography after TACE in this cohort. Chemotherapeutic agents such as cisplatin might affect TE [12, 13], although it is unclear whether the selection of chemotherapeutic agents influences the efficacy of embolization [9].

In conclusion, tumors in which an early evaluation classifies the TE as TE2 tend to display a TE of TE1 or TE2 at 3 months after TACE and so a CR or PR will probably not be achieved in these cases. Thus, conducting early evaluations at 1 week after TACE is useful for predicting TACE-refractory HCC. An early diagnosis of TACE-refractory HCC will allow alternative treatment options, such as sorafenib, to be employed before the disease progresses.

Conflict of interest The authors declare that they have no conflict of interest.

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J Gastroenterol (2011) 46:92–100
DOI 10.1007/s00535-010-0293-6

ORIGINAL ARTICLE—LIVER, PANCREAS, AND BILIARY TRACT

Alpha-fetoprotein above normal levels as a risk factor for the development of hepatocellular carcinoma in patients infected with hepatitis C virus

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Received: 4 August 2009 / Accepted: 6 July 2010 / Published online: 14 August 2010

Abstract

Background Noninvasive risk factors are required for predicting the development of hepatocellular carcinoma (HCC) not only in patients with cirrhosis but also in those with chronic hepatitis who are infected with hepatitis C virus (HCV).

Methods A total of 707 patients with chronic HCV infection without other risks were evaluated for the predictive value of noninvasive risk factors for HCC, including age, sex, viral load, genotype, fibrosis stage, aspartate and alanine aminotransferase levels, bilirubin, albumin, platelet count, and alpha-fetoprotein (AFP) at entry to the study, as well as interferon (IFN) therapy they received.

Results The ten-year cumulative incidence rates of HCC for patients with fibrosis stages F0/F1, F2, F3, and F4 were 2.5, 12.8, 19.3, and 55.9%, respectively. Multivariate analysis identified age ≥57 years [hazard ratio (HR) 2.026, $P = 0.004$], fibrosis stage F4 (HR 3.957, $P < 0.001$), and AFP 6–20 ng/mL (HR 1.942, $P = 0.030$) and ≥20 ng/mL (HR 3.884, $P < 0.001$), as well as the response to IFN [relative risk (RR) 0.099, $P < 0.001$], as independent risk factors for the development of HCC. The ten-year cumulative incidence rates of HCC in the patients with AFP levels of <6, 6–20, and ≥20 ng/mL at entry were 6.0, 24.6, and 47.3%, respectively.

Conclusions Not only high (>20 ng/mL), but also even slightly elevated (6–20 ng/mL) AFP levels, could serve as a risk factor for HCC to complement the fibrosis stage. In contrast, AFP levels <6 ng/mL indicate a low risk of HCC development in patients infected with HCV, irrespective of the fibrosis stage.

Keywords Alpha-fetoprotein · Hepatitis C virus · Hepatocellular carcinoma

Introduction

Worldwide, an estimated 170 million people are persistently infected with hepatitis C virus (HCV) [1, 2], and they are at high risk of developing hepatocellular carcinoma (HCC) [1, 3–5]. Several factors have been identified that increase the risk of HCC, including, age, male gender, and alcohol intake, as well as cirrhosis and the duration of infection [3, 5]. Of these factors, the stage of liver fibrosis parallels the risk for HCV-associated HCC. The annual incidence of HCC in patients with HCV-related cirrhosis ranges from 1 to 7% [6, 7]. Although liver biopsy is the gold standard for the assessment of hepatic fibrosis [8, 9], it is too invasive a procedure to be acceptable as a routine test [10, 11]. In place of liver biopsy, the platelet count is used to estimate the degree of fibrosis [12–14], and low platelet counts have been shown to be a risk factor for the development of HCC in cirrhotic patients [13, 15, 16]. In this study, we tried to identify noninvasive markers for predicting the development of HCC in a large cohort of

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patients with chronic HCV infection during a long observation period.

Patients and methods

Study design

Between January 1992 and December 2003, 832 patients were identified who were positive for both anti-HCV, by a second or third-generation enzyme-linked immunosorbent assay (ELISA), and for HCV RNA by polymerase chain reaction (PCR). These patients underwent liver biopsy guided by ultrasonography (US) at the National Nagasaki Medical Center. Of the 832 patients, 125 (15.0%) were excluded according to the following criteria: (1) positive for hepatitis B surface antigen (HBsAg) ($n = 12$); (2) heavy habitual drinking defined as an average daily consumption of >100 g ethanol ($n = 26$); (3) presence of autoimmune hepatitis (AIH), primary biliary cirrhosis, or idiopathic portal hypertension ($n = 8$); (4) positive antinuclear antibody (defined as a titer of >320×) without a diagnosis of AIH ($n = 8$); or (5) a short follow-up period (<180 days) ($n = 71$). The remaining 707 patients were analyzed retrospectively for the incidence of HCC. Their medical histories had been recorded, with the results of routine tests for blood cell counts, liver biochemical parameters, and markers for HCV infection at the time of US-guided liver biopsy at regular intervals. Complete blood cell counts and biochemical tests were performed, using automated procedures, at the clinical pathology laboratories of the National Nagasaki Medical Center. Iinformed consent was obtained from each patient included in the study, and the study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a-priori approval by the institution's human research committee.

Staging of hepatic fibrosis

Liver biopsy was taken by fine-needle aspiration (18G or 16G sonopsy) guided by US. Liver tissue specimens were fixed in 10% formalin, embedded in paraffin, and stained with hematoxylin and eosin. They were evaluated for the stage of hepatic fibrosis by a pathologist according to the criteria of Desmet et al. [17].

HCV RNA, HCV core antigen, and HCV genotypes

HCV RNA was determined by reverse transcriptase (RT)-PCR using a commercial kit (Amplicor HCV; Roche Diagnostic Systems, Basel, Switzerland). HCV core antigen was determined using the lumispot EIKEN HCV antigen assay (Eiken Chemicals, Tokyo, Japan). HCV core antigen levels were classified as low or high with the cutoff at 1,000 fmol/L [18, 19]. Genotypes of HCV were determined by RT-PCR with genotype-specific primers (HCV RNA core genotype; Roche Diagnostics, Tokyo, Japan) [20, 21].

Interferon therapy

During the observation period, 373 of the 707 (52.8%) patients received interferon (IFN) monotherapy, pegylated (PEG)-IFN monotherapy, combination therapy with IFN and ribavirin, or PEG-IFN and ribavirin. Sustained virological response (SVR) was defined as the absence of detectable HCV RNA by the end of treatment that persisted for longer than 6 months thereafter, while failure in meeting these criteria was judged as non-SVR. There was no relapse of viremia after 6 months among SVR patients.

Diagnosis of hepatocellular carcinoma

Patients were followed up with hematological and biochemical tests at intervals of 1–12 months. Liver imaging was performed by US at 6- to 12-month intervals in most patients at fibrosis stages F0–F2, while computed tomography (CT), magnetic resonance imaging (MRI), or US was performed at 3- to 6-month intervals in patients at fibrosis stages F3 and F4. HCC was diagnosed by typical vascular patterns on CT, MRI, or angiography, or by fine-needle biopsy of space-occupying lesions detected in the liver.

Statistical analysis

Continuous variables [platelet counts, albumin, total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alpha-fetoprotein (AFP), HCV core antigen] were dichotomized with respect to the median value or clinically meaningful values in a multivariate analysis. To estimate the cumulative risk of developing HCC, the Kaplan–Meier method and the log-rank test were used. Cox proportional hazards regression analysis was performed to evaluate risk factors for HCC. Analysis was performed by Bonferroni's correction and data analysis was performed with SPSS ver. 11.0 (SPSS, Chicago, IL, USA).

Results

Characteristics at enrollment

Table 1 lists the characteristics of the 707 patients at enrollment. The median age was 57.0 years; 120 (17.0%)

Table 1 Demographic, clinical, and virological characteristics of 707 patients persistently infected with hepatitis C virus (HCV)

Age (years)	57.0 (19–79)
Male	351 (49.6%)
Observation period (years)	8.2 ± 4.4[a]
Interferon therapy	373 (52.8%)
Habitual alcohol intake	135 (19.1%)
Fibrosis stage	
F0/F1	273 (38.6%)
F2	193 (27.3%)
F3	121 (17.1%)
F4	120 (17.0%)
Platelet count ($\times 10^3/mm^3$)	156 (30–391)
Albumin (g/dL)	4.2 (2.7–5.3)
Total bilirubin (mg/dL)	0.7 (0.1–2.5)
Aspartate aminotransferase (AST; IU/L)	53 (11–422)
Alanine aminotransferase (ALT; IU/L)	82 (1–1,057)
Alpha-fetoprotein (AFP; ng/mL)	6 (1–510)
HCV core antigen	
≥1,000 fmol/L	539 (76.2%)
HCV genotype	
1b	510 (72.1%)
2a/2b	195 (27.6%)
Unknown	2 (0.3%)

Values are medians with ranges in parentheses, or means with SD in parentheses

[a] Mean ± SD

patients were diagnosed histologically with liver cirrhosis (fibrosis stage: F4) and the remaining 587 had chronic hepatitis (fibrosis stage F0, F1, F2, or F3). The median value of AFP was 6 ng/mL. The average follow-up period was 8.2 years. The patients were classified into three categories by the level of AFP; 350 patients (49.5%) had AFP levels of <6 ng/mL, 254 (35.9%) had levels between 6 and 20 ng/mL, and the remaining 103 (14.6%) had levels of ≥20 ng/mL.

IFN therapy and IFN response

Of the 120 patients with cirrhosis (fibrosis stage F4), 46 (38.3%) received IFN while the remaining 74 (61.7%) did not. The proportions of IFN-treated patients showing an SVR were 40.8% (56/137) in patients with F1; 37.6% (44/117) in those with F2; 32.8% (24/73) in those with F3; and 32.6% (15/46) in those with F4.

Risk factors for HCC

Cox regression analysis was performed on several variables, including age, sex, alcohol consumption, IFN therapy during the observation period, and biochemical as well as virological parameters. The following factors were identified as showing an increased risk for HCC by the univariate analysis: age; IFN therapy; fibrosis stage; platelet count; albumin; AST, ALT, and AFP levels; and HCV genotype (Table 2). Multivariate analysis was performed on these factors (Table 3), and the following were identified as independent risk factors: fibrosis stage (F4), AFP (6–20 and ≥20 ng/mL), age (≥57 years), and IFN therapy (SVR).

Development of HCC

During the follow-up period, HCC developed in 110 (15.6%) patients. Of the 110 patients with HCC, 58 (52.7%) were diagnosed with the disease by histological examination of biopsy-obtained or resected liver specimens. Of these 58 patients, 24 (41.3%) had hypovascular HCC.

Among the patients with HCC, only eight (7.2%) had AFP <6 ng/mL at the time of diagnosis of HCC. Figure 1 shows Kaplan–Meier estimates of the cumulative risk of HCC with respect to fibrosis stage at entry. The 10-year cumulative incidence rates of HCC for stages F0/F1, F2, F3, and F4 were 2.5, 12.8, 19.3, and 55.9%, respectively.

There were significant differences in cumulative incidence rates among the three groups of patients with different AFP levels. The 10-year cumulative risk of HCC was 6.0% in the 350 patients with AFP <6 ng/mL at the study entry, 24.6% in the 254 patients with AFP 6–20 ng/mL, and 47.3% in the 103 patients with AFP ≥20 ng/mL ($P < 0.001$) (Fig. 2). Of the 350 patients with AFP <6 ng/mL, 21 eventually developed HCC during the observation period. Fourteen of these 21 patients were ≥57 years old and 10 had fibrosis stage F3 or F4. In remarkable contrast, HCC ultimately developed in 84.5% of the patients with AFP ≥20 ng/mL.

The 10-year cumulative incidence rates of HCC were 3.1% in patients with SVR to IFN, 14.6% in patients with non-SVR, and 29.5% in the patients without IFN therapy (Fig. 3). Of the 139 patients with SVR, three (2.2%) eventually developed HCC during the observation period. These three patients had advanced fibrosis stages at the study entry (1 with F3 and 2 with F4). Figure 4 shows the cumulative incidence of HCC in the patients with different AFP levels, stratified by the fibrosis stage. In the patients with fibrosis stage F4, there were significant differences in HCC incidence between those with AFP levels of <6 and those with levels of ≥20 ng/mL.

Figure 5 shows the proportions of patients with different AFP levels stratified by the fibrosis stage. The proportion of patients with AFP <6 ng/mL decreased with the advance of fibrosis stage, and conversely, the proportion of patients with AFP ≥20 ng/mL increased with the advance of fibrosis stage. There was a strong correlation between AFP levels and the fibrosis stage.

Table 2 Factors increasing the risk for hepatocellular carcinoma (HCC), determined by univariate analysis

Features	Hazard ratio	*P* value
Age		
<57 years	1	
≥57 years	3.889	<0.001
Sex		
Female	1	
Male	1.146	0.475
Alcohol intake		
None	1	
Habitual	1.012	0.962
Interferon therapy		
None	1	
Non-SVR	0.523	0.002
SVR	0.063	<0.001
Fibrosis stage		
F0/F1	1	
F2	1.863	0.096
F3	3.985	<0.001
F4	13.045	<0.001
Platelet count		
≥150 × 10^3/mm^3	1	
<150 × 10^3/mm^3	4.644	<0.001
Albumin		
≥4.2 g/dL	1	
<4.2 g/dL	2.952	<0.001
Total bilirubin		
<0.7 mg/dL	1	
≥0.7 mg/dL	1.438	0.065
AST		
<53 IU/L	1	
≥53 IU/L	2.501	<0.001
ALT		
<82 IU/L	1	
≥82 IU/L	1.514	0.035
AFP		
<6 ng/mL	1	
6–20 ng/mL	4.628	<0.001
≥20 ng/mL	10.335	<0.001
HCV core antigen		
<1,000 fmol/L	1	
≥1,000 fmol/L	1.112	0.645
HCV genotype		
2a/2b	1	
1b	1.730	0.027

SVR sustained virological response

Table 3 Factors increasing the risk for HCC, determined by multivariate analysis

Features	Hazard ratio (95% CI)	*P* value
Fibrosis stage		
F0/F1	1	
F2	1.030 (0.471–2.253)	0.942
F3	1.682 (0.632–3.713)	0.198
F4	3.957 (1.861–8.411)	<0.001
AFP		
<6 ng/mL	1	
6–20 ng/mL	1.942 (1.066–3.538)	0.030
≥20 ng/mL	3.884 (2.014–7.433)	<0.001
Age		
<57 years	1	
≥57 years	2.026 (1.261–3.255)	0.004
Interferon therapy		
None	1	
Non-SVR	0.704 (0.453–1.094)	0.119
SVR	0.099 (0.029–0.334)	<0.001

CI confidence interval

Discussion

In the present study, four variables were identified as risk factors for HCC in patients with chronic HCV infection: fibrosis stage, AFP level, age, and IFN therapy. Previous reviews have analyzed risk factors for the development of HCC [3, 22–25]. Yoshida et al. [6] have reported that the annual incidence increases with the stage of liver fibrosis, from 0.5% in patients with stage F0 or F1 to 7.9% in patients with stage F4 (cirrhosis). In our study, the cumulative incidence of HCC increased along with the advance of fibrosis stage. AFP is used as a serological marker of HCC, and is employed in combination with US for screening HCC [3]. Several reports have shown an elevated AFP level as a risk factor for the development of HCC among patients infected with HCV [16, 25–32]. Most of the studied patients had cirrhosis that was not definitely diagnosed by clinical symptoms and ultrasonographic findings. There have been few studies on patients with chronic hepatitis C, in addition to those with cirrhosis [27]. Thus, it has been unclear whether elevated AFP levels are a risk factor for the development of HCC in patients infected with HCV. Against this background, we were prompted to analyze the utility of AFP as a risk factor for the development of HCC in patients who had been histologically diagnosed by US-guided liver biopsy. In the present study,