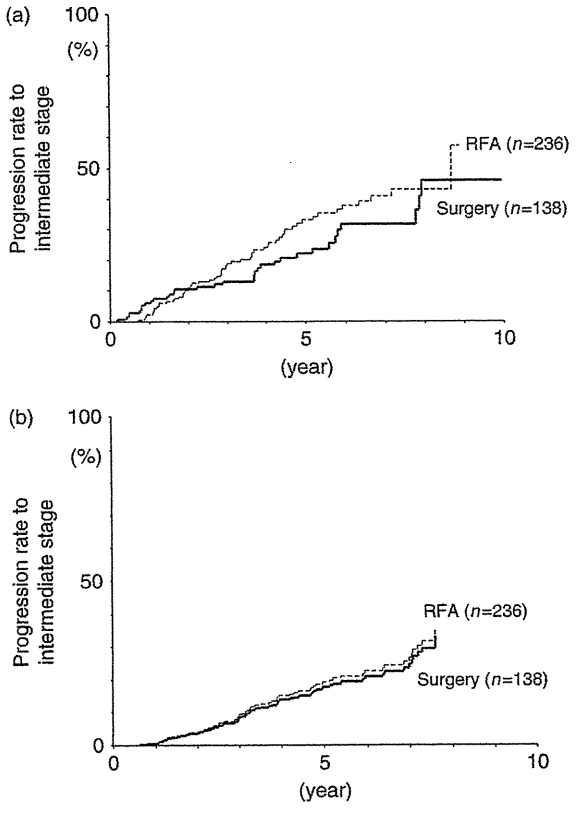

Fig. 3. (a) Crude development rates to the intermediate stage of hepatocellular carcinoma according to initial therapy. (b) Adjusted development rates to the intermediate stage, using proportional hazard analysis. RFA, radiofrequency ablation.

did not affect the eventual survival rate (hazard ratio 1.09, $P = 0.70$) (Table 3).

Cumulative progression curves from the early stage to the intermediate stage were drawn from the multivariate analysis in an imaginary RFA group and an imaginary surgery group, with an average positive rate of HBsAg and an average platelet count (Fig. 3b). Five-year progression rates to the intermediate stage were 19% in the RFA group and 18% in the surgery group. The differences in the progression rates were considered as a 'pure' impact of the difference in the initial mode of therapy on future stage progression, which was adjusted with significant covariates assuming a standardized study group.

Survival rates and predictive factors

A total of 87 (23.3%) died during the observation: 60 (25.4%) in the RFA group and 27 (19.6%) in the surgery group.

The crude survival rates in the RFA group and the surgery group were 88.5 and 92.6% in the third year, 71.7 and 80.9% in the fifth year and 60.6 and 74.6% in the seventh year respectively (Fig. 4a). The survival rate of the surgical therapy group was higher but statistical significance was not obtained ($P = 0.071$).

Table 3. Independent factors associated with the progression rate from an early stage to an intermediate stage of hepatocellular carcinoma

Factors	Category	Hazard ratio (95% confidence interval)	*P*
HBsAg	1: negative	1	
	2: positive	0.41 (0.20–0.82)	0.012
Platelet count	1: ≥ 100 000/mm^3	1	
	2: < 100 000/mm^3	1.58 (1.04–2.39)	0.032
Initial therapy	1: surgery	1	
	2: RFA	1.09 (0.69–1.71)	0.70

RFA, radiofrequency ablation.

Independent factors associated with survival were explored in all the patients. Multivariate hazard analysis indicated that the survival rate is independently associated with a positive HBsAg ($P = 0.038$), a low indocyanine green retention rate at 15 min (ICG R15) ($P < 0.001$) and a low AFP value ($P = 0.021$). The factor of initial therapy did not affect the eventual survival rate (hazard ratio 1.26, $P = 0.35$) (Table 4).

Overall survival curves in patients with an early stage of HCC were drawn from the multivariate analysis in an imaginary RFA group and an imaginary surgery group, using an average positive rate of HBsAg, an average ICG R15 value and an average AFP value (Fig. 4b). Five-year survival rates were estimated as 80% in the RFA group and 81% in the surgery group, and 7-year rates were 71 and 72% respectively. Among 87 deaths during the observation, 70 (80.5%) died from progression of HCC, 14 (16.1%) died from liver failure without progression of HCC and the remaining three patients died from causes other than liver disease

Probabilities for transition among four disease states of hepatocellular carcinoma

The Markov model for the progression of HCC depended on the probabilities for transition among the four states at one time interval that was set at 1 year. Yearly transition probabilities were calculated based on 1892 person-year data from the 374 patients with an early stage of HCC. Figure 5 illustrates a probability diagram of the long-term progression of HCC calculated from the Markov model. All patients were at an early stage initially, but intermediate and advanced stages gradually increased with time. Approximately half of the patients died, and < 40% of the patients remained at early stage at the end of the 10th year.

The results are shown in Table 5 as a matrix of the transition probabilities for three subsets composed of three decades of their lives (< 60, 60–69 and ≥ 70 years) stratified by four states (early stage, intermediate stage, advanced stage and death).

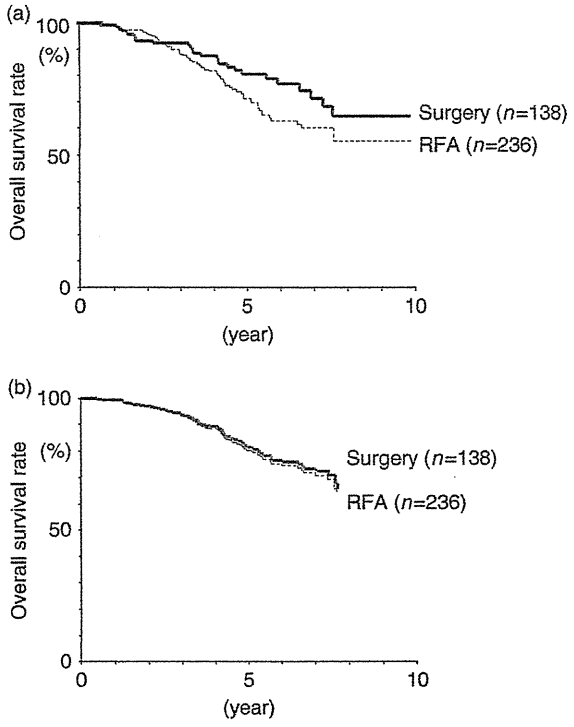

Fig. 4. (a) Crude survival rates in patients receiving radiofrequency ablation and those undergoing surgery as the initial therapy. (b) Adjusted survival rates in the radiofrequency group and surgery group, using proportional hazard analysis. RFA, radiofrequency ablation.

Table 4. Independent factors associated with the survival rate after the initial treatment for hepatocellular carcinoma

Factors	Category	Hazard ratio (95% confidence interval)	*P*
HBsAg	1: negative	1	
	2: positive	0.43 (0.19–0.94)	0.034
ICG R15*	1: < 30%	1	
	2: ≥30%	1.96 (1.20–3.20)	0.0070
α-fetoprotein	1: < 40 mg/ml	1	
	2: ≥40 mg/ml	1.71 (1.09–2.68)	0.020
Prothrombin time	1: < 80%	1	
	2: ≥80%	0.60 (0.37–0.96)	0.035
Initial therapy	1: surgery	1	
	2: RFA	1.09 (0.66–1.81)	0.73

*ICG R15, indocyanine green retention rate at 15 min.
RFA, radiofrequency ablation.

In the matrix of age of < 60 years, 2.34% of the patients in the early stage developed to the intermediate stage annually, 1.40% to the advanced stage and 0.93% died. The remaining 95.33% of the patients remained in the early stage after 1 year. The probability for the transition from an early stage to an intermediate stage

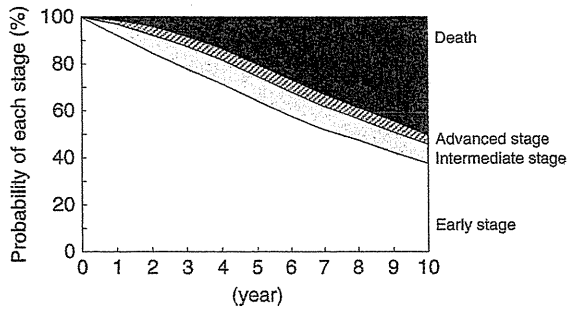

Fig. 5. Illustrated transition probabilities of patients, from the early stage of hepatocellular carcinoma, to the intermediate stage, the advanced stage and to death.

Table 5. One-year state-transition probability matrices for subsets of hepatocellular carcinoma*

	Early	Intermediate	Advanced	Death
All Patients of all age groups				
Early	92.17	4.81	1.73	1.29
Intermediate		69.32	27.27	3.41
Advanced			24.77	75.23
Death				100.00
Age < 60 years				
Early	95.33	2.34	1.40	0.93
Intermediate		58.33	37.50	4.17
Advanced			23.53	76.47
Death				100.00
Age 60–69 years				
Early	91.40	5.90	1.35	1.35
Intermediate		68.18	30.30	1.52
Advanced			22.21	78.79
Death				100.00
Age ≥70 years				
Early	90.68	5.49	2.33	1.50
Intermediate		74.42	22.09	3.49
Advanced			27.91	72.09
Death				100.00

*Early stage, solitary or multiple up to three nodules 3 cm or less each; Intermediate stage, four nodules or more, or larger than 3 cm; Advanced stage, portal vein invasion, extrahepatic metastasis, or Child–Pugh score C.

was significantly lower in young patients < 60 years of age (2.34%) than that in patients 60 years of age or older (5.70%)($\chi^2 = 7.76$, $P = 0.0053$). From the matrix stratified by three age groups, the transition probability from an intermediate to an advanced stage decreased with age: 37.50% in patients < 60 year of age, 30.30% in patients 60–69 year of age and 22.09% in patients 70 year of age or older ($\chi^2 = 10.57$, $P = 0.0011$).

Probabilities for transition according to the initial treatment

We also evaluated the transition probabilities among the four states in the subgroups of RFA and surgery as the initial mode of therapy.

In the matrix of patients receiving RFA therapy, the transition probability from early to intermediate stage was 5.40%, probability to the advanced stage was 1.63% and to death was 1.73%. In the patients undergoing surgery, the transition probability from an early to an intermediate stage was 3.90%, probability to an advanced stage was 1.87% and to death was 0.62%.

The probability for the transition from an early stage to an intermediate stage was slightly higher in the RFA group (5.40%) than that in the surgery group (3.90%), but statistical significance was not found ($\chi^2 = 1.90$, $P = 0.17$).

Discussion

Radiofrequency ablation has been considered as a less curative mode of therapy than surgical resection, because local tumour progression sometimes occurs after conservative treatment with relatively small ablative margins. As those patients with loco-regional therapy are generally followed up for tumour recurrence with a short time interval of 3–6 months using CT or MRI, we can usually ablate a newly appeared or a locally progressed tumour within a small size and few numbers. In order to elucidate the efficacies and usefulness of RFA compared with surgical resection, we analysed many HCC patients receiving RFA or surgical therapy regarding tumour progression and survival.

Fortunately, in Japan, where highly socialized medicine is practiced with everyone covered by some form of health insurance, almost all of the patients can receive any extensive medical services including surgery, RFA, embolization and repeated imaging diagnosis, regardless of the cost. Under intensive check-up and treatment repetition, the Markov model showed the probability of remaining at the early stage as 92.17% per year: the transition rate from the early to the intermediate stage was 4.81%, to the advanced stage 1.73 and to death 1.29% respectively. Similarly, the probabilities of remaining at the intermediate and advanced stages were 69.32 and 24.77% per year respectively.

Because young patients with HCC usually have better liver function and a relatively low carcinogenesis rate, younger patients are more likely to undergo radical methods of therapy for a recurrent tumour repeatedly. The reason for the low transition rate from the early to the intermediate stage was convincingly explained in the young patient group (Table 4). In contrast, the transition rate from the intermediate to the advanced stage was significantly higher in the young patient group. Although the exact reason was not known, multiple tumours of younger patients possibly progressed rapidly or were resistant to TACE. Hence, the Markov model would be eligible for simulating the outcomes of patients with the early stage of HCC. It is also helpful in planning strategies for the management of small HCC, for the eventual prolongation of a patient's life and for ideal cost-effective guidelines on a national basis, not only in Japan but also elsewhere in the world where the prevalence of HCC is increasing. Although we once generated a 'five-state model' consisting of no tumour, early stage, intermediate stage, advanced stage and death, we finally adopted the current 'four-state model' because of good mathematical fit and statistical robustness. Molinari and Helton (20) and Cho *et al.* (21) described a progression model of HCC after RFA and/or hepatectomy by the Markov model. Both authors performed a meta-analysis-like study using heterogeneous sources of patients from varied published articles, and estimated progression models of HCC in hypothetical patient cohorts. We analysed the actual clinical courses of patients in a single institution, where the same diagnostic and therapeutic procedures were adopted for every patient. Sufficient medical procedures and resources under a universal medical insurance system of the country seemed to give rise to better outcomes and survival, but an exact comparison cannot be carried out using the current data and the previous literatures.

In this study, we also compared RFA and surgery as an initial therapy for the early stage of HCC. Understandably, older patients, patients with severe cirrhosis and those with a concomitant disease other than liver disease tended to undergo non-surgical therapy. In addition, young patients with HBV-related HCC were likely to receive surgery because of good liver function, relatively low potential of recurrence and young age. Although the crude recurrence rate and the crude progression rate from the early stage to the intermediate stage were higher in patients receiving RFA therapy, multivariate analysis with adjustment of background biases showed that the initial mode of therapy did not affect the progression rate and did not affect the overall survival rate. When a regular check-up of imagings with an interval of 3–4 months was conducted, an additional ablation therapy was usually performed successfully for a small locally progressed tumour. Under intensive medical care for liver disease, the initial mode of therapy therefore did not affect the overall survival of a patient with an early stage of HCC. When a careful check-up with imagings and adequate application of repeated ablative procedures for HCC were performed, the choice of ablative manners was insignificant compared with the background liver features of aetiology of liver disease (hepatitis virus) and severity of liver disease (platelet count). The choice of ablative therapy for small-sized HCC should also be assessed from the viewpoints of conservation of liver function, cost-effectiveness and quality of life (9, 10, 12, 22).

Since it seemed to require at least 5 years to obtain a statistical difference in the recurrence rates and survival rates between RFA-treated and surgically treated groups, a prospective randomized trial is actually difficult to perform from both ethical and medical viewpoints. One of the significant results of the current study is that highly socialized medical circumstances with sufficient medical practice can attain a high survival rate of 71–80% at the end of the fifth year in patients at an early stage.

Further studies are required to determine the relationship between patient's age and stage transition. Because HCV-related chronic hepatitis often progresses to HCC during the clinical course, this kind of staging model with analyses of medical intervention will be necessary in the future from the viewpoints of epidemiological assessment and medical politics, together with patient's quality of life and feeling of satisfaction.

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Original Article

Efficacy and safety in sitagliptin therapy for diabetes complicated by chronic liver disease caused by hepatitis C virus

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Aim: Diabetes is present in patients with chronic liver disease caused by hepatitis C virus (HCV). The aim of this case–control study is to assess the efficacy and safety of dipeptidyl peptidase-4 inhibitor (sitagliptin) for type 2 diabetes mellitus (T2DM) with chronic liver disease caused by HCV.

Methods: Sixteen HCV positive patients with T2DM treated by sitagliptin were retrospectively enrolled. These patients were given sitagliptin between December 2009 and January 2010. Another 16 HCV patients with T2DM treated only with diet and excise for 48 weeks were selected as the control group. Serum levels of fasting plasma glucose (FPG), hemoglobin A1C (HbA1C), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were measured before and 12, 24, 36 and 48 weeks after the initiation of treatment.

Results: In the sitagliptin group, the average HbA1C level decreased approximately 0.8% at 48 weeks after the initiation of sitagliptin. Next, the average FPG level decreased approximately 20 mg/dL during follow up after the initiation of sitagliptin. All the patients were able to take sitagliptin of 50 mg/day without reduction because of sitagliptin-related side-effects. On the other hand, in the control group, the average HbA1C and FPG level did not change with statistical significance during follow up of 48 weeks. Regarding aminotransferase, there were no significant changes of average AST and ALT level during follow up of 48 weeks in both the sitagliptin group and control group.

Conclusion: Our results indicate that sitagliptin is effective and safe for the treatment of T2DM complicated with HCV positive chronic liver disease.

Key words: hepatitis C virus, sitagliptin, type 2 diabetes mellitus

INTRODUCTION

HEPATITIS C VIRUS (HCV) is one of the more common causes of chronic liver disease in the world. Chronic hepatitis C is an insidiously progressive form of liver disease that relentlessly but silently progresses to cirrhosis in 20–50% of cases over a period of 10–30 years.[1,2] In addition, HCV is a major risk for hepatocellular carcinoma (HCC).[3–7] Lately, it has been reported that chronic HCV infection is associated with type 2 diabetes mellitus (T2DM)[8–14] Moreover, T2DM has been suggested to enhance with the development of HCC and poor prognosis of liver transplantation.[15–19] Thus, in patients with chronic liver diseases, the management of T2DM is very important to improve the prolonged prognosis.

However, most oral hypoglycemic agents are metabolized in the liver and often induce the liver damage. Thus, it is difficult to treat the patients who have T2DM complicated with chronic liver disease.[20] A new oral hypoglycemic agent, dipeptidyl peptidase-4 (DPP-4)

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inhibitor (sitagliptin), is minimally metabolized.[21,22] Hence, sitagliptin raises the possibility for use in patients with T2DM complicated with chronic liver disease.

With this background in mind, the case–control study was initiated to investigate the efficacy and safety of DPP-4 inhibitors for T2DM patients with HCV positive chronic liver disease.

METHODS

Patients

SIXTEEN PATIENTS WITH T2DM complicated with HCV positive chronic liver disease started the treatment with oral DPP-4 inhibitor (sitagliptin; MDS, Tokyo, Japan) of 50 mg/day from December 2009 to January 2010 in the Department of Hepatology, Toranomon Hospital, Tokyo, Japan. These 16 consecutive patients treated with sitagliptin of 50 mg/day were regarded as the sitagliptin group. Inclusion criteria of DPP-4 inhibitor administration were as follows: (i) evidence of diabetes mellitus (i.e. plasma glucose concentration of ≥126 mg/dL [6.9 mM) in the fasting state, ≥200 mg/dL [11.0 mM] in casual state and/or 2 h after a 75-g oral glucose load; (ii) a diabetic history of less than 2 years; (iii) features of chronic hepatitis or cirrhosis diagnosed by ultrasonography and/or computed tomography; (iv) positive for serum HCV RNA; (v) negativity for hepatitis B surface antigens (HBsAg), antinuclear antibodies or anti-mitochondrial antibodies in serum, as determined by radioimmunoassay or spot hybridization; (vi) no evidence of HCC nodules as shown by ultrasonography and/or computed tomography; and (vii) no underlying systemic disease, such as systemic lupus erythematosus and rheumatic arthritis. The distinction between chronic hepatitis and liver cirrhosis in patients was done by discriminant function using platelet, hyaluronic acid, and γ-globulin.[23] Patients with either of the following criteria were excluded from the study: (i) they were taking medicines except DPP-4 inhibitors known to alter glucose tolerance; and/or (ii) they had illnesses that could seriously reduce their life expectancy or their ability to participate in the trial. Patients in the sitagliptin group exercised and participated in diet therapy in addition to administration of sitagliptin. In the same period, 303 patients with T2DM and chronic liver disease type C were not treated with antidiabetic drugs. These patients exercised and participated in diet therapy for T2DM. Seventy-three of these 303 patients were applied with seven inclusion criteria and two exclusion criteria as described above. Sixteen subjects in the control group were selected from these 73 patients by matching 1:1 with the sitagliptin group for age and sex. Patients who belonged to the control group or sitagliptin group had been subjected to lifestyle intervention of diet and physical exercise after the diagnosis of T2DM. The diet prescription included daily calorie intake of 125.6 kJ/ideal body-weight (kg), a protein energy fraction of 15% and a fat energy fraction of 25%. Physical activity was recommended as at least 120 min of aerobic exercise a week. The physicians in charge explained the methods and side-effects of sitagliptin therapy to each patient and/or patient's family before sitagliptin therapy. Informed consent was obtained from 16 patients of the sitagliptin group before the initiation of sitagliptin therapy. All of the studies in the control group were performed retrospectively by collecting and analyzing data from the patient records. This study was approved by the Institutional Review Board of Toranomon Hospital.

Outcome measures

Type 2 diabetes mellitus was diagnosed by the 2003 criteria of the American Diabetes Association:[24] (i) casual plasma glucose of 200 mg/dL or more; (ii) fasting plasma glucose (FPG) of 126 mg/dL or more; and/or (iii) 2-h post-glucose (oral glucose tolerance test) of 200 mg/dL or more. Hemoglobin A1c (HbA1c) was measured using a high-performance liquid chromatography method.

Laboratory investigation

Anti-HCV was detected using a second-generation enzyme-linked immunosorbent assay (ELISA II) (Abbott Laboratories, North Chicago, IL, USA). HCV RNA was determined by the Amplicor method (Cobas Amplicor HCV Monitor Test v2.0; Roche, Tokyo, Japan). HBsAg was tested by radioimmunoassay (Abbott Laboratories, Detroit, MI, USA). The value for HbA1c (%) was estimated as a National Glycohemoglobin Standardization Program (NGSP) equivalent value (%) calculated by the formula HbA1c (%) = HbA1c (Japan Diabetes Society, JDS) + 0.4%, considering the relational expression of HbA1c (JDS) (%) measured by the previous Japanese standard materials and measurement methods and HbA1c (NGSP).[25] Height and weight were recorded at baseline and the body mass index (BMI) was calculated as weight (kg) / height (m^2).

Follow up

The starting time of follow up in the sitagliptin group was the initiation of sitagliptin therapy. That is, the time

Table 1 Clinical characteristics at the starting time of follow up

	Sitagliptin group	Control group	*P*-value
n	16	16	
Age (years)	65.3 ± 9.1	65.2 ± 9.5	1.0
Sex (male/female)	8/8	8/8	1.0
Chronic hepatitis/liver cirrhosis	13/3	13/3	1.0
BMI	23.0 ± 3.5	23.5 ± 2.9	0.713
BMI (post-intervention)	22.4 ± 2.4	22.6 ± 2.3	1.0
AST (IU/L)	43 ± 34	34 ± 21	0.170
ALT (IU/L)	45 ± 31	40 ± 31	0.423
Albumin (g/dL)	3.8 ± 0.4	3.9 ± 0.4	0.873
Total bilirubin (mg/dL)	0.9 ± 0.5	0.8 ± 0.3	0.167
Platelets ($\times 10^4/mm^3$)	15.1 ± 5.3	17.0 ± 6.7	0.208
Hyaluronic acid (ng/mL)	132 ± 80	112 ± 62	0.637
HbA1c (NGSP value)	7.4 ± 0.8	7.2 ± 0.9	0.552
FPG (mg/dL)	142.1 ± 24.1	140.0 ± 25.7	0.951

Data are number of patients or mean ± standard deviation.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; HCV, hepatitis C virus; NGSP, National Glycohemoglobin Standardization Program.

was from December 2009 to January 2010. The starting time of follow up in the control group was the same as that in the sitagliptin group. Patients were followed up monthly to tri-monthly in our hospital. Physical examination and biochemical tests were conducted at each examination together with regular check up. An overnight (12 h) fasting blood sample and HbA1C sample were taken for routine analyses. These included transaminase activities.

Statistical analysis

Clinical differences between the sitagliptin group and control group were evaluated by Wilcoxon rank sum test or Fisher's exact test. Changes in serum HbA1C and FPG level between the sitagliptin group and control group during follow up were analyzed by one-way repeated measurement ANOVA. Next, predictive factors for responders were assessed. A $P < 0.05$ was considered to be statistically significant. SPSS ver. 11.5 for Windows was used to perform statistical analysis.

RESULTS

Patients' characteristics

TABLE 1 SHOWS the characteristics before follow up in the 32 patients with T2DM and HCV positive chronic liver disease. There were no significant differences in clinical profiles between the sitagliptin group and control group.

Change of HbA1c and FPG

Change of average HbA1C and FPG level are plotted in Figures 1 and 2 in the sitagliptin group and control group. In the sitagliptin group, average HbA1C level decreased from 7.4% to 6.5% at 48 weeks after the initiation of sitagliptin. Moreover, average FPG level could be deduced at approximately 20 mg/dL during follow up after the initiation of sitagliptin. The HbA1C and FPG level in the sitagliptin group were statistically lower than those in the control group.

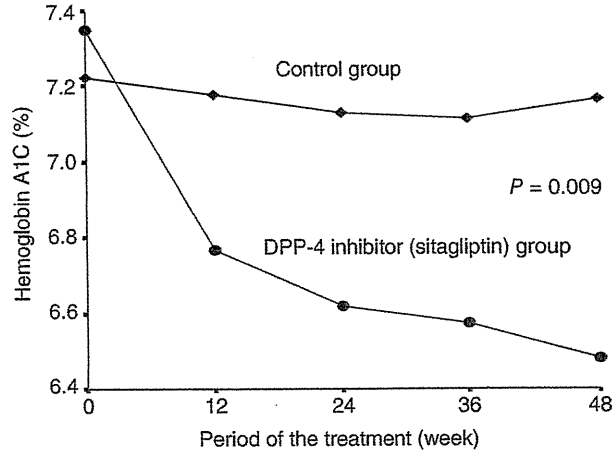

Figure 1 Change of average hemoglobin A1c (HbA1c) level during follow up was plotted in both the dipeptidyl peptidase-4 (DPP-4) inhibitor group and control group.

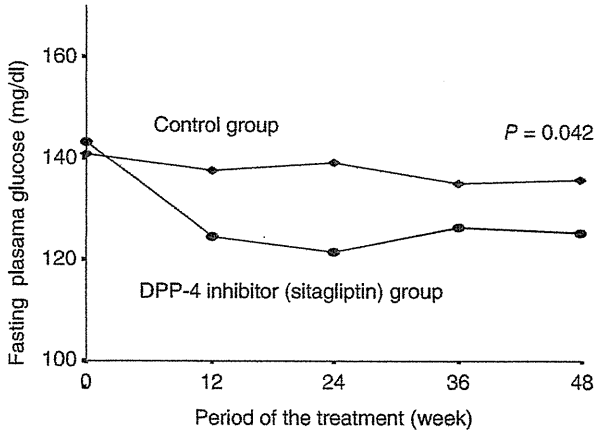

Figure 2 Change of average fasting plasma glucose during follow up was plotted in both the dipeptidyl peptidase-4 (DPP-4) inhibitor group and control group.

Adverse events of sitagliptin

Regarding side-effects, none of the patients treated with DDP-4 inhibitor had sitagliptin-related episodes severe enough to stop the treatment of sitagliptin. Thus, all the patients were able to take sitagliptin 50 mg/day for 48 weeks without reduction. Next, changes of average AST and ALT level during follow up are plotted in Figure 3. There were no significant changes of average AST and ALT level during follow up in either the sitagliptin or control group.

DISCUSSION

WE HAVE DESCRIBED the efficacy and side-effects of sitagliptin for T2DM patients with HCV positive chronic liver disease in the present study. The present study was limited by being a case–control study. Another limitation of the study was that patients were treated with different types of diet and different excise. This heterogeneity makes it slightly difficult to interpret the results of the study.

On the other hand, the present study shows several findings with regard to the efficacy and side-effects of sitagliptin for T2DM patients with HCV positive chronic liver disease. First, in the sitagliptin group, average HbA1C and FPG levels after the initiation of sitagliptin were statistically lower than those at the starting time of DPP-4 inhibitor. It is suggested that sitagliptin increases active glucagon-like peptide-1, stimulates insulin secretion and inhibits glucagon secretion.[21,22] Thus, it is accepted that sitagliptin could improve both HbA1C and glucose level in patients with T2DM and HCV positive chronic liver disease.

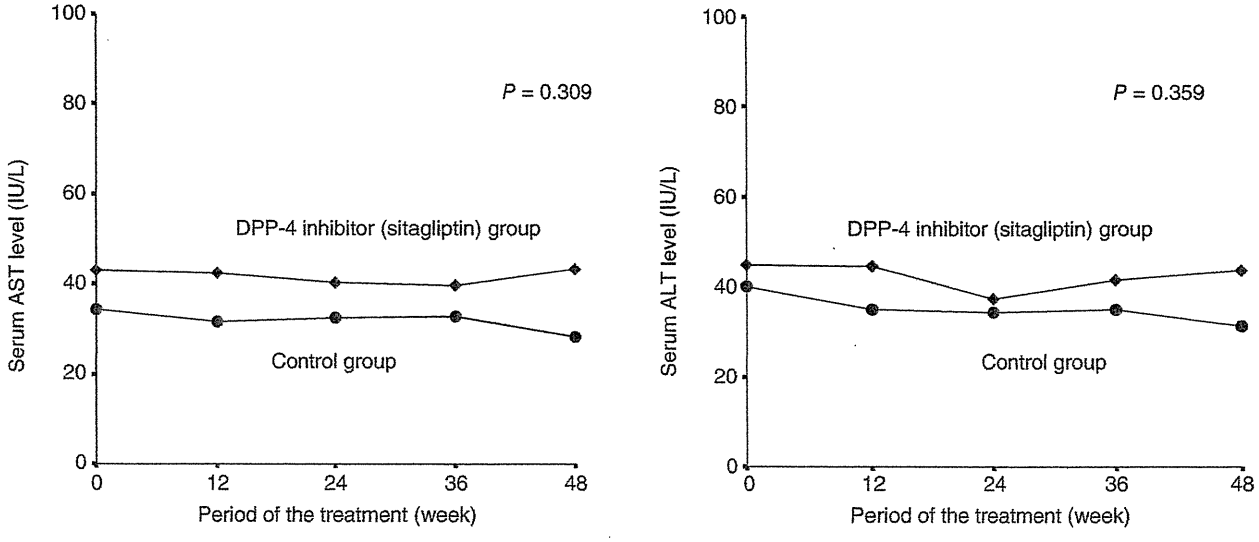

Figure 3 Change of average aminotransferase level during follow up was plotted in both the dipeptidyl peptidase-4 (DPP-4) inhibitor group and control group. (a) Change of average aspartate aminotransferase (AST) level during follow up was plotted in both the DPP-4 inhibitor group and control group. (b) Change of average alanine aminotransferase (ALT) level during follow up was plotted in both the DPP-4 inhibitor group and control group. Patients who belonged to the control group or sitagliptin group were subjected to lifestyle intervention of diet and physical exercise. The diet prescription included daily calorie intake of 30 kcal/ideal bodyweight, a protein energy fraction of 15% and a fat energy fraction of 25%.

Second, administration of sitagliptin is minimal risk and highly tolerable for T2DM patients with HCV positive chronic liver disease. In the present study, none of the patients treated with DDP-4 inhibitor had sitagliptin-related episodes severe enough to stop the sitagliptin therapy. Thus, all the patients could take sitagliptin of 50 mg/day over 48 weeks without reduction or stopping. This new oral hypoglycemic agent, sitagliptin, is minimally metabolized and over 80% of it is excreted in the urine. It seems not to alter pharmacokinetics in hepatic insufficiency.[22] Thus, sitagliptin has few possibilities to cause the aggravation of the chronic liver damage. In fact, in the present study, three patients with liver cirrhosis did not have elevation of aminotransferase during the treatment by sitagliptin. This result indicates that sitagliptin is valuable for treating T2DM with HCV positive liver cirrhosis.

Type 2 diabetes mellitus has been increasing dramatically in many nations including Japan over the past decades.[26] It is widely accepted that approximately 7–8 million people are affected by DM in Japan. Approximately 8–10% of adults in Japan have T2DM. Recently, it has been reported that T2DM has occurred in HCV positive chronic liver disease.[8–13] Moreover, HCV patients with T2DM are at major risk for HCC.[15–17] So, in patients with T2DM and HCV positive chronic liver diseases, the management of DM is very important to improve the prolonged prognosis. However, most oral hypoglycemic agents (thiazolidines, sulfonylurea and biguanides) are metabolized in the liver. Thus, it is suggested that most oral hypoglycemic agents often induce liver damage. The new oral hypoglycemic agent, DPP-4 inhibitor (sitagliptin), is minimally metabolized. Hence, this drug raises the possibility of being used for T2DM patients with HCV positive chronic liver disease.

In conclusion, our retrospective study suggests that sitagliptin is effective and safe for the treatment of T2DM complicated with HCV positive chronic liver disease.

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Heterogeneous Type 4 Enhancement of Hepatocellular Carcinoma on Dynamic CT Is Associated With Tumor Recurrence After Radiofrequency Ablation

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OBJECTIVE. The aim of this study was to predict recurrence of hepatocellular carcinoma (HCC) from baseline dynamic CT images.

MATERIALS AND METHODS. This retrospective study included 191 consecutive patients who underwent surgical resection or radiofrequency ablation (RFA) between January 2005 and September 2009 for the treatment of HCC. Enhancement on pretreatment arterial and portal phase dynamic CT images was classified into one of the four following enhancement patterns: Types 1 and 2 are homogeneous enhancement patterns without or with increased arterial blood flow, respectively; type 3 is a heterogeneous enhancement pattern with septations; and type 4 is an irregularly shaped ring structure enhancement pattern. Predictive factors for tumor recurrence including dynamic CT enhancement pattern were also evaluated. Moreover, risk factors including recurrence type (i.e., tumor number ≥ 10, portal vein invasion, or both) were evaluated in RFA-treated cases.

RESULTS. Among 60 patients who underwent surgical resection, no statistical association was observed between dynamic CT enhancement patterns and recurrence rate. In contrast, in the 131 patients who underwent RFA, cumulative recurrence rates for each enhancement pattern were significantly different: Recurrence rates 2 years after RFA for patients with type 1, 2, 3, and 4 were 26.6%, 46.9%, 38.6%, and 77.8%, respectively ($p = 0.042$). Recurrence, which was defined as the presence of 10 or more nodules, portal vein invasion, or both occurred in nine of 131 patients (6.9%) in the RFA group. A multivariate Cox proportional hazards analysis revealed that the type 4 dynamic CT enhancement pattern is an independent factor for HCC recurrence (hazard ratio, 27.68; 95% CI, 6.82–112.33; $p < 0.001$).

CONCLUSION. The pretreatment type 4 dynamic CT enhancement pattern can potentially be used to predict recurrence of HCC after RFA treatment.

Keywords: dynamic CT, hepatocellular carcinoma, radiofrequency ablation, recurrence, surgical resection

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WEB
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Hepatocellular carcinoma (HCC) is a common malignancy worldwide, and the incidence rate is increasing in Japan as well as in the United States [1–3]. Chronic viral hepatitis and liver cirrhosis after infection with hepatitis B virus (HBV) and hepatitis C virus (HCV) play important roles in the development of HCC [4, 5]. The incidence of HCC in patients with HCV-related cirrhosis is estimated to be 5–10% per annum in Japan, and HCV-related cirrhosis is one of the major causes of death particularly in Asian countries [5]. Among the available treatment options for HCC, surgical resection is generally considered to be a local eradication method that can provide a satisfactory long-term outcome [6–13]. Advances in imaging procedures have led to the increased detection of early stage HCC and have improved survival because more patients in whom hepatic resection is possible are being identified [14, 15].

For patients who are not eligible for surgical treatment for various reasons (e.g., lack of sufficient liver function for surgical resection), percutaneous local therapy is a viable therapeutic option. A number of local ablation therapies are available including percutaneous ethanol injection, percutaneous acetic acid injection, cryotherapy, percutaneous microwave coagulation therapy, and radiofrequency ablation (RFA). In addition to surgical resection, local ablation therapies, particularly RFA, are considered to be local eradication methods for HCC that can provide good long-term outcomes [16]. However, despite the high complete necrosis rate in RFA-treated HCC, some patients experience tumor recurrence within 1 year of RFA, either as local recurrence or new tumor formation. A series of studies have

identified factors predictive of HCC tumor recurrence and seeding including tumor size, tumor location relative to the hepatic capsule (presence or absence of tumor on subcapsular portion), α-fetoprotein (AFP) level, tumor stage, and histopathologic grade [17, 18]. For the reasons stated earlier, it is important to determine the histopathologic grade of HCC before administering local ablation therapy.

We previously reported that a "heterogeneous enhancement pattern with irregular ring-like structures" [19] in the arterial phase of dynamic CT analysis accurately predicts the histopathologic grade of poorly differentiated HCC, and we named this enhancement pattern "type 4" [19]. Therefore, one aim of the current study was to examine the risk factors for tumor recurrence after local eradication, including differences between treatment procedure (surgical resection vs RFA) and dynamic CT enhancement pattern. Moreover, in a previous study, investigators reported an association between tumor seeding after RFA and histopathologic grade of HCC [17, 18]. Therefore, the other aim of the current study was to evaluate the relationship between the type 4 dynamic CT enhancement pattern and HCC recurrence in patients who undergo RFA.

Materials and Methods

Study Population

From January 2005 to September 2009, 705 patients were diagnosed with HCC and underwent surgical resection or RFA as the initial treatment in the Department of Hepatology, Toranomon Hospital, Tokyo, Japan. Among the 705 patients, 191 patients satisfied the following criteria for inclusion in our study: triple-phase dynamic CT study performed before surgical resection or RFA; pretreatment diagnosis of a solitary HCC with a maximum tumor diameter of 30 mm or less; no evidence of extrahepatic metastases as confirmed on pretreatment imaging studies (CT, sonography, or chest radiography); no history of other malignancies; and no pretreatment chemotherapy, including transcatheter arterial chemoembolization (TACE). Accordingly, these 191 patients were retrospectively evaluated for an association between arterial and portal phase dynamic CT enhancement pattern and recurrence of HCC. The observation starting point was the time of the first surgical resection or RFA session for HCC.

Contrast Infusion and CT Protocol

All patients received nonionic contrast material with an iodine concentration of 350 mg I/mL (iomeprol [Iomeron 350, Bracco-Eisai]). CT was performed with a 64-MDCT scanner (Aquilion 64, Toshiba Medical Systems) with the following scanning parameters: rotation time, 0.5 second; beam collimation, 64 × 0.5 mm; section thickness and interval, 5 mm; beam pitch, 0.83; tube voltage, 120 kV; and tube current, 150 mAs. All helical scans were started at the top of the liver and proceeded in a cephalocaudal direction. Unenhanced and three-phase contrast-enhanced helical scans of the whole liver were obtained. Patients were instructed to hold their breath with exhalation during scanning.

An automatic bolus-tracking program (Sure Start, Toshiba Medical Systems) was used to time the start of acquisition in each phase after contrast injection. The attenuation at the axis of the celiac artery level was monitored by one radiology technician; the region-of-interest cursor (1 cm^2) was placed in the abdominal aorta. Real-time low-dose (120 kV, 25 mAs) serial monitoring studies were initiated 5 seconds after the start of contrast injection. The trigger threshold level was set at 100 HU. A double arterial phase acquisition was started 15 and 20 seconds after triggering, and portal phase and delayed phase acquisitions were started 70 and 180 seconds after the start of the contrast injection, respectively.

Diagnosis of HCC

Diagnosis of HCC was predominantly based on image analysis. If a hepatic nodular lesion was identified on screening sonography, the patient underwent dynamic CT, dynamic MRI, or both. Furthermore, when a liver nodule either showed hyperattenuation in the arterial phase of the dynamic study and washout in the portal or delayed phase or showed typical hypervascular staining on digital subtraction angiography, the nodule was diagnosed as HCC. In accordance with the American Association for the Study of Liver Diseases guidelines [20], we obtained at least two dynamic images before treatment. When a nodule did not appear to show the mentioned typical imaging features, fine-needle aspiration biopsy was performed followed by histologic examination and diagnosis.

Imaging Analysis of Hepatocellular Carcinoma and Definition of Enhancement Pattern

Before treatment was administered, triple-phase contrast-enhanced CT was performed of all patients. The enhancement pattern on the arterial and portal phases of dynamic CT was classified into one of four types, and the four enhancement types on the original images were converted into simplified images (Fig. 1 [19]). The type 1 pattern represented a homogeneous enhancement pattern with no increase in arterial blood flow; the entire image was uniform during the arterial phase and portal phase. The type 2 pattern represented a homogeneous enhancement pattern with increased arterial blood flow; the entire image was uniform during the arterial phase and portal phase. The type 3 pattern represented a heterogeneous enhancement pattern with septations with heterogeneous enhancement and septations in the arterial phase, whereas the septations resembled a near-uniform tumor tissue periphery in the portal phase. The type 4 pattern represented a heterogeneous enhancement pattern with irregular ring-like structures; the arterial phase was marked by the presence of irregularly shaped ring areas of enhancement and areas of little blood flow relative

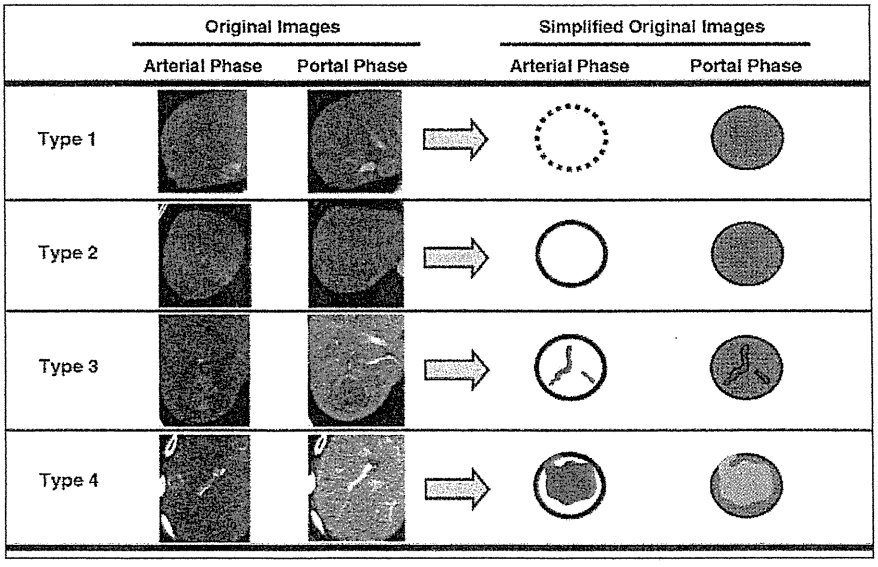

Fig. 1—Sample of original dynamic CT images and simplified images for each enhancement pattern. (Reprinted and modified with permission from John Wiley and Sons [19])

to the periphery of the tumor tissue, and the portal phase was characterized by areas of reduced blood flow.

The enhancement pattern on the arterial and portal phases of dynamic CT was determined by consensus of three expert hepatologists who were blinded to the pathologic results.

Treatment Methods

Physicians and surgeons generally discussed the preferred choice of therapy in individual patients. Hepatic resection was performed under intraoperative sonographic monitoring and guidance. For small and superficial HCCs, arterial and portal vein clamping at the hepatic hilum was not usually required to maintain liver perfusion. RFA was performed using three different devices: a multitined expandable electrode with a 3-cm array with a 150-W radiofrequency generator (model 1500 series, RITA Medical Systems), an internally cooled electrode with a 3-cm active tip with a 200-W radiofrequency generator (Cool-tip Radiofrequency System, Covidien), and a multitined expandable electrode with a 200-W radiofrequency generator (LeVeen Needle Electrode and Radiofrequency 3000 Generator, RTC System, Boston Scientific Japan). For the first two systems, treatment procedures were performed according to the protocols recommended by the manufacturers. However, treatment using the RTC System was performed by adopting the "stepwise hook extension technique" [21].

The needle was inserted into the tumor percutaneously under sonographic guidance. In the case of RFA, dynamic CT was performed 1–3 days after therapy, and the ablated area was evaluated. The goal of treatment was to obtain an ablative margin larger than the original tumor, with a surrounding treatment margin of 5 mm or greater in all directions. When this margin was not achieved or a residual tumor was found, additional ablation was considered.

In this study, 93 of 131 procedures (71%) were performed using the multitined expandable electrode (LeVeen), 28 of 131 procedures (21%) were performed using the internally cooled electrode (Cool-tip), and 10 of 131 procedures (8%) were performed using the multitined expandable electrode (RITA).

Definition of Multinodular Recurrence of HCC

In this study, we defined "multinodular" as follows: the appearance of 10 or more lesions at the time of first recurrence after surgical resection or RFA.

Follow-Up Protocol

Physicians examined the patients every 4 weeks after treatment, and liver function tests and tumor

TABLE 1: Clinical Profile and Laboratory Data of 191 Patients With Hepatocellular Carcinoma Treated by Surgical Resection or Radiofrequency Ablation (RFA)

Parameter	Surgical Resection	RFA	*p*
Patient characteristics			
No. of patients	60	131	
Sex (no. of patients)			0.922
M:F ratio	38:22	82:49	
Age (y)			0.021
Median	66	69	
Range	35–80	37–83	
Background liver disease (no. of patients)			0.003
Hepatitis C virus	34	100	
Hepatitis B virus	22	19	
Others	4	12	
Laboratory data			
Platelet count ($\times 10^4/\mu L$)			0.153
Median	13.3	11.8	
Range	5.1–27.2	2.7–39.6	
Albumin (g/dL)			0.019
Median	3.7	3.7	
Range	2.9–4.7	2.7–4.4	
Total bilirubin (mg/dL)			0.030
Median	0.8	0.9	
Range	0.3–2.2	0.3–2.7	
Prothrombin activity (%)			0.218
Median	94.5	89.9	
Range	60.4–124.0	56.7–124.0	
AST (IU/L)			0.423
Median	41	48	
Range	16–163	16–191	
AFP (μg/L)			0.561
Median	12.0	10.5	
Range	1.6–5541.0	1.0–993.7	
DCP (AU/L)			0.137
Median	20.5	17.0	
Range	9.0–556.0	6.0–314.0	
Tumor characteristics			
Diameter (mm)			< 0.001
Median	20.0	16.0	
Range	10.0–30.0	7.0–30.0	
Tumor location (no. [%] of patients)			
Subcapsular	48/60 (80)	52/131 (40)	< 0.001
Subphrenic	24/60 (40)	58/131 (44)	0.579
Dynamic CT enhancement pattern (no. [%] of patients)			< 0.001
Type 1	4 (7)	46 (35)	
Type 2	27 (45)	52 (40)	
Type 3	21 (35)	24 (18)	
Type 4	8 (13)	9 (7)	

Note—AFP = α-fetoprotein, AST = aspartate aminotransferase, DCP = des-γ-carboxy prothrombin.

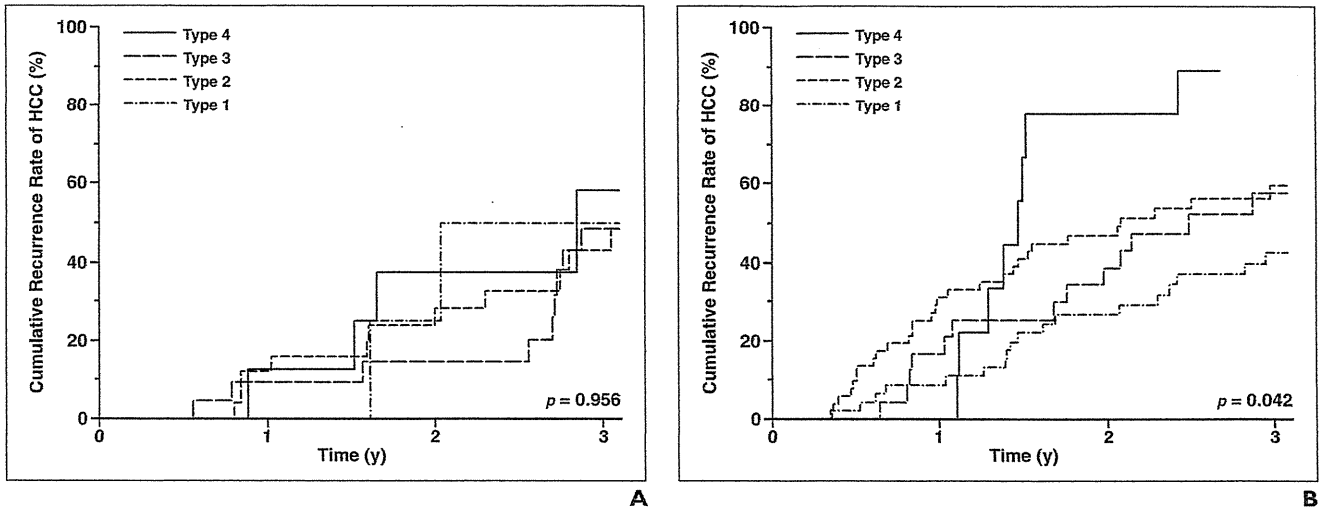

Fig. 2—Correlation between cumulative recurrence rates and enhancement patterns of pretreatment dynamic CT after each treatment procedure.
A and **B**, Graphs show associations between cumulative hepatocellular carcinoma (HCC) recurrence rate after surgical resection (**A**) and after radiofrequency ablation (**B**) and pretreatment dynamic CT enhancement pattern.

markers were also measured once every month. After completion of HCC treatment, patients underwent contrast-enhanced three-phase CT survey every 3 months for recurrence. Local tumor progression was defined as tumor recurrence adjacent to the resected or ablated area.

Statistical Analysis and Ethical Considerations

Differences in background features and laboratory data between the surgical resection and RFA groups were analyzed by the chi-square test and Mann-Whitney *U* test. Recurrence was analyzed using the Kaplan-Meier technique, and differences in curves were tested using the log-rank test. Independent factors associated with overall recurrence and recurrence characterized by multiple nodules, portal vein invasion, or both were studied using stepwise Cox regression analysis. Potential risk factors for overall recurrence after surgical resection and RFA included the following 15 variables: age, sex, cause of background liver disease, serum albumin level, bilirubin level, aspartate aminotransferase (AST) level, platelet count, prothrombin time, AFP level, des-γ–carboxy prothrombin (DCP) level, diameter of the HCC, tumor location relative to the hepatic capsule (presence or absence of tumor on subcapsular portion), tumor location relative to the diaphragm (presence or absence of tumor on subphrenic portion), treatment procedure, and enhancement pattern of pretreatment dynamic CT analysis.

Potential risk factors for recurrence characterized by multiple nodules, portal vein invasion, or both after RFA included the following 15 variables: age, sex, cause of background liver disease, serum albumin level, bilirubin level, AST level,

TABLE 2: Predictors of Tumor Recurrence in Patients With Hepatocellular Carcinoma Treated by Surgical Resection or Radiofrequency Ablation (RFA)

	Univariate Analysis		Multivariate Analysis	
Category	Hazard Ratio (95% CI)	*p*	Hazard Ratio (95% CI)	*p*
Sex				
1: Female	1			
2: Male	1.26 (0.84–1.89)	0.274		
Age				
1: < 65 y	1		1	
2: ≥ 65 y	1.50 (0.10–2.26)	0.050	1.85 (1.16–2.94)	0.010
Background liver disease				
1: Hepatitis C virus	1			
2: Hepatitis B virus	0.84 (0.51–1.39)	0.503		
3: Others	1.29 (0.66–2.49)	0.458		
Platelet count				
1: ≥ 10 ´ 10^4/μL	1		1	
2: < 10 ´ 10^4/μL	1.65 (1.10–2.49)	0.016	1.61 (1.04–2.48)	0.033
Albumin				
1: ≥ 3.5 g/dL	1			
2: < 3.5 g/dL	1.72 (1.15–2.58)	0.008		
Total bilirubin				
1: < 1.0 mg/dL	1			
2: ≥ 1.0 mg/dL	1.64 (1.11–2.42)	0.013		
Prothrombin activity				
1: ≥ 70%	1			
2: < 70%	1.95 (1.01–3.75)	0.046		
AST				
1: < 40 IU/L	1		1	
2: ≥ 40 IU/L	1.65 (1.09–2.49)	0.018	1.66 (1.04–2.66)	0.035

(Table 2 continues on next page)

TABLE 2: Predictors of Tumor Recurrence in Patients With Hepatocellular Carcinoma Treated by Surgical Resection or Radiofrequency Ablation (RFA) (continued)

Category	Univariate Analysis		Multivariate Analysis	
	Hazard Ratio (95% CI)	p	Hazard Ratio (95% CI)	p
AFP				
1: < 100 μg/L	1		1	
2: ≥ 100 μg/L	2.21 (1.40–3.50)	0.001	2.25 (1.30–3.89)	0.004
DCP				
1: < 30 AU/L	1		1	
2: ≥ 30 AU/L	1.82 (1.15–2.88)	0.011	1.77 (1.05–2.99)	0.032
Tumor diameter				
1: < 20 mm	1			
2: ≥ 20 mm	1.13 (0.76–1.67)	0.544		
Tumor on subcapsular portion				
1: Yes	1		1	
2: No	1.37 (0.93–2.00)	0.115	1.72 (1.10–2.70)	0.019
Tumor on subphrenic portion				
1: No	1			
2: Yes	1.01 (0.68–1.49)	0.984		
Treatment				
1: Surgical resection	1			
2: RFA	1.52 (0.98–2.36)	0.062		
Dynamic CT enhancement pattern				
1: Type 1	1			
2: Type 2	1.33 (0.81–2.18)	0.261		
3: Type 3	1.15 (0.66–2.01)	0.628		
4: Type 4	1.95 (0.98–3.89)	0.058		

Note—AFP = α-fetoprotein, AST = aspartate aminotransferase, DCP = des-γ-carboxy prothrombin.

platelet count, prothrombin time, AFP level, DCP level, tumor diameter, tumor location relative to capsule (subcapsular portion), tumor location relative to diaphragm (subphrenic portion), type of RFA device, and dynamic CT enhancement pattern. Several variables were transformed into categoric data consisting of two to four simple ordinal numbers for univariate and multivariate analyses. All factors that were at least marginally associated with overall recurrence and recurrence characterized by multiple nodules, portal vein invasion, or both ($p < 0.15$) in univariate analysis were entered into a stepwise Cox regression analysis. Significant variables were selected by the stepwise method. A two-tailed $p < 0.05$ was considered to be statistically significant. Data analysis was performed using statistics software (SPSS, version 11.0, SPSS Inc.).

The study protocol was approved by the Human Ethics Review Committee of Toranomon Hospital.

Results

Clinical Background, Laboratory Data, and Distribution of Enhancement Patterns on Pretreatment Dynamic CT

Table 1 summarizes the clinical profile and laboratory data of 191 HCC patients who were treated by surgical resection or RFA. The RFA group included significantly older individuals and significantly more patients with less preserved liver function compared with the surgical resection group. The cause of background liver disease was also significantly different between the two treatment groups: Patients in the surgical resection group had larger tumors that were more likely to have a subcapsular location.

The type 2, 3, and 4 enhancement patterns were more commonly observed in the surgical resection group than the type 1 enhancement pattern. In contrast, in the RFA group, the type 1 enhancement pattern was more commonly observed than the type 2, 3, or 4 pattern. In addition, the distribution of enhancement patterns on pretreatment dynamic CT was significantly different for each treatment procedure.

Distribution of Each Enhancement Pattern and Frequency of Poorly Differentiated Hepatocellular Carcinoma by Histologic Examination in the Surgical Resection Group

In 60 surgical resection patients, four patients (7%) had the type 1 enhancement pattern, 27 patients (45%) had the type 2 pattern, 21 patients (35%) had the type 3 pattern, and eight patients (13%) had the type 4 pattern. Pathologic HCC diagnoses by enhancement pattern were as follows: type 1 enhancement pattern, all patients had well-differentiated HCC; type 2 enhancement pattern, five of 27 patients (19%) had well-differentiated HCC and 21 of 27 (78%) patients had moderately differentiated HCC; type 3 enhancement pattern, one of 21 patients (5%) had well-differentiated HCC and 19 of 21 (90%) patients had moderately differentiated HCC; and type 4 enhancement pattern, five of eight patients (63%) had moderately differentiated HCC. Rates of poorly differentiated HCC by enhancement pattern were as follows: type 1 enhancement pattern, zero of four patients (0%); type 2 enhancement pattern, one of 27 patients (4%); type 3 enhancement pattern, one of 21 patients (5%); and type 4 enhancement pattern, three of eight patients (38%).

Correlation Between Cumulative Recurrence Rates and Enhancement Patterns on Pretreatment Dynamic CT After Each Treatment Procedure

In the surgical resection group, cumulative recurrence rates were not significantly different between each pretreatment dynamic CT enhancement pattern (types 1, 2, 3, and 4: 0.0%, 12.0%, 9.5%, and 12.5% at the first year after treatment, respectively, and 25.0%, 28.2%, 14.6%, and 37.5% at the second year) (Fig. 2A). However, in the RFA group, the cumulative recurrence rate was significantly different between each enhancement pattern (types 1, 2, 3, and 4: 8.7%, 31.1%, 16.7%, and 0.0% at the first year, respectively, and 26.6%, 46.9%, 38.6%, and 77.8% at the second year, respectively; $p = 0.042$) (Fig. 2B).

Predictive Factors for Initial Recurrence After Surgical Resection or Radiofrequency Ablation

Multivariate Cox proportional hazards analysis revealed that the following independent

factors are predictive for recurrence of HCC treated by surgical resection or RFA: AFP ≥ 100 μ g/L (hazard ratio [HR], 2.25; 95% CI, 1.30–3.89; p = 0.004), age ≥ 65 years (HR, 1.85; 95% CI, 1.16–2.94; p = 0.010), DCP ≥ 30 AU/L (HR, 1.77; 95% CI, 1.05–2.99; p = 0.032), tumor not present in subcapsular portion (HR, 1.72; 95% CI, 1.10–2.70; p = 0.019), AST ≥ 40 IU/L (HR, 1.66; 95% CI, 1.04–2.66; p = 0.035), and platelet count < 10×10^4/μL (HR, 1.61; 95% CI, 1.04–2.48; p = 0.033) (Table 2).

Association Between the Frequency of Recurrence Characterized by Multiple Nodules, Portal Vein Invasion, or Both and Clinical Features for Each Treatment Procedure

The frequency and clinical features of recurrence characterized by multiple nodules, portal vein invasion, or both are presented in Table 3. Such recurrences occurred in 10 of 191 patients (5.2%). In the surgical resection group, recurrence occurred in one of 60 patients (1.7%), and in the RFA group, recurrence occurred in nine of 131 patients (6.9%). Notably, in the RFA group, six of nine patients (66.7%) had a pretreatment type 4 enhancement pattern. Among the type 4 patients, recurrence of HCC occurred more than 1 year after treatment in six of six patients (100%) after RFA.

Regarding the needles used for RFA of HCC in these nine patients, an internally cooled electrode (Cool-tip) was used in case 2 (Table 3), a RITA multitined expandable electrode was used in case 4, and a LeVeen multitined expandable electrode was used in the other seven patients.

Figure 3 shows a case of recurrence after RFA (case 7 in Table 3). Figures 3A and 3B show that the pretreatment dynamic CT and digital subtraction angiography (DSA) images revealed a type 4 dynamic CT enhancement pattern. In Figures 3C and 3D, dynamic CT and DSA images acquired at the time of recurrence after RFA are shown: Multiple hepatic tumors are apparent surrounding the previously ablated area.

Association Between Cumulative Hepatocellular Carcinoma Recurrence Rate After Radiofrequency Ablation and Pretreatment Dynamic CT Enhancement Patterns: Type 4 Versus Other Enhancement Patterns

In the RFA group, the cumulative recurrence rate was significantly higher in tumors displaying a pretreatment type 4 dynamic CT enhancement pattern than in tumors showing other enhancement patterns (type 4 vs other enhancement patterns, 0.0% vs 2.8% at the first year, 74.6% vs 2.8% at the second year; $p < 0.001$).

Predictive Factors for Hepatocellular Carcinoma Recurrences Characterized by Multiple Nodules, Portal Vein Invasion, or Both After Radiofrequency Ablation

The Multivariate Cox proportional hazards analysis revealed that the type 4 pretreatment dynamic CT enhancement pattern is an independent predictive factor for HCC recurrence characterized by multiple nodules, portal vein invasion, or both in patients with HCC treated by RFA (HR, 27.68; 95% CI, 6.82–112.33; $p < 0.001$) (Table 4).

Discussion

A number of local eradication therapies are currently available for HCC. However, with the exception of surgical resection, the potential risk of tumor dissemination always exists in patients who receive such therapies. Therefore, to properly select the most suitable therapy for an individual patient, it is important to predict the potential risk of HCC before treatment.

As others have previously reported [17, 18], identification of poorly differentiated HCC is particularly important for making good therapeutic

TABLE 3: Frequency of Hepatocellular Carcinoma Recurrence Characterized by 10 or More Nodules, Portal Vein Invasion, or Both by Treatment Procedure and Clinical Features

	At the Time of First Treatment[a]					At the Time of Tumor Recurrence						
Case No.	Age (y)	Type of Enhancement Pattern	Tumor Diameter (mm)	AFP (μg/L)	DCP (AU/L)	AFP (μg/L)	DCP (AU/L)	Treatment of Recurrence	First Recurrence Period (y)	Survival Period (y)	Patient Status at End of Follow-Up Period
1[b]	72	Type 3	26	3	12	8	14	Radiation	2.7	4.1	Alive
2[c]	65	Type 4	9	37	12	34	12	TAI	1.4	1.5	Dead
3	53	Type 4	13	117	94	10	978	TACE and radiation	1.3	2.9	Alive
4	70	Type 4	16	3	14	3	10	TACE	1.5	4.0	Dead
5	77	Type 4	20	4	33	5	19	TACE and RFA	1.1	5.0	Alive
6	60	Type 4	20	27	32	23	4313	TACE	1.5	1.9	Dead
7	83	Type 4	21	6	34	6	70	TACE	1.5	3.0	Alive
8	53	Type 3	10	64	8	141	10	TACE	0.8	4.3	Alive
9	69	Type 2	18	55	10	85	16	TACE	0.6	5.3	Alive
10	73	Type 2	21	7	12	3	34	TACE	0.8	4.0	Alive

Note—AFP = α-fetoprotein, DCP = des-γ-carboxy prothrombin, TACE = transcatheter arterial chemoembolization, and TAI = transcatheter arterial infusion chemotherapy, RFA = radiofrequency ablation.

[a]Disease was Child-Pugh class A in all 10 patients.

[b]For surgical resection, advanced recurrence occurred in one of 60 patients (1.7%) (case 1).

[c]For RFA, advanced recurrence occurred in nine of 131 patients (6.9%) (cases 2–10).

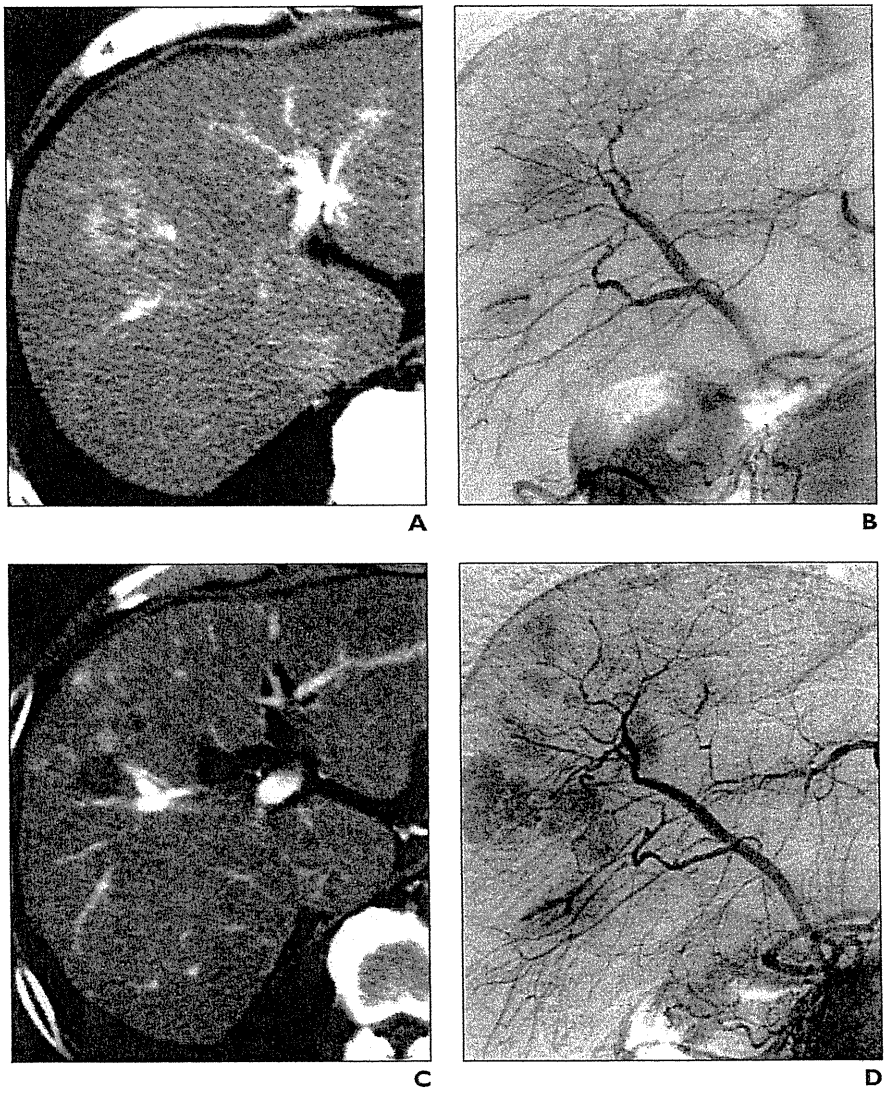

Fig. 3—83-year-old man with hepatocellular carcinoma (case 7 in Table 3).
A, Pretreatment dynamic CT (arterial phase) image. Tumor shows heterogeneous enhancement pattern with irregular ringlike structures—that is, type 4 enhancement pattern.
B, Pretreatment digital subtraction angiography (DSA) image shows single hypervascular nodule, so radiofrequency ablation (RFA) was performed.
C, Dynamic CT study (arterial phase) image obtained at time of recurrence after RFA (1.5 years after treatment) shows multiple hepatic tumors are observed around previously ablated area.
D, DSA image at time of recurrence shows multiple hepatic tumors are observed around original tumor.

progress. In one of our previous studies, we identified the type 4 enhancement pattern as an independent factor that is predictive of poorly differentiated HCC [19]. The results of that study revealed that the risk of a pathologic diagnosis of poorly differentiated HCC in patients with a preoperative type 4 dynamic CT enhancement pattern is approximately 13 times higher than that of patients with a type 1 or 2 enhancement pattern.

Therefore, the first aim of this study was to evaluate the clinical outcomes of patients with HCC treated by surgical resection and of those with HCC treated by RFA in association with dynamic CT enhancement patterns. In the surgical resection group, no significant differences in recurrence rates were observed between patients with different enhancement patterns. We presume that no significant differences were observed because surgical resection is the most effective local eradication therapy for HCC. In contrast, in the RFA group, significant differences in recurrence rates were observed between patients with different enhancement patterns. This result is surmised to reflect the association between each enhancement pattern and histopathologic diagnosis based on the results of these associations in the surgical resection group. However, in multivariate analysis, pretreatment dynamic CT enhancement pattern was not identified as an independent factor predictive for recurrence of HCC. Therefore, a larger-scale examination is required in the future; depending on the results of that study, it may be necessary to reclassify these enhancement patterns.

The second aim of this study was to investigate the relationship between recurrence characterized by 10 or more nodules, portal vein invasion, or both and pretreatment dynamic CT enhancement pattern in the RFA group. Significant differences between the enhancement patterns and recurrence rates were observed, and in multivariate analysis, a pretreatment type 4 dynamic CT enhancement pattern was identified as an independent factor predictive of this type of HCC recurrence after RFA treatment. The risk of this type of recurrence in patients with a pretreatment type 4 dynamic CT enhancement pattern was approximately 28 times higher than that of other enhancement patterns. Based on these results, this new classification of dynamic CT enhancement pattern—particularly the type 4 enhancement pattern—appears to be very useful for avoiding RFA treatment likely to recur.

In addition, among the six patients with a pretreatment type 4 dynamic CT enhancement pattern who underwent RFA, this type of HCC recurrence occurred more than 1 year after treatment in all six patients (100%). Histopathologic tumor features and adhesion molecules may have contributed to this long interval between the initial treatment and this type of recurrence after RFA. However, in this study, we were not able to perform tumor biopsies of nodules in patients with the type 4 enhancement pattern. Further studies, including histopathologic and molecular biologic examinations, are required to confirm this hypothesis.

This study has some limitations. First, there were more HCC patients with HCV in the RFA group than in the surgical resection group; this difference might have been a potential source of bias. This difference may be because patients with HBV-related HCC usually have a better liver reserve than those with HCV-related HCC at the time of initial hepatocarcinogenesis and that patients with

TABLE 4: Predictors of Recurrence Characterized by Multiple Nodules, Portal Vein Invasion, or Both in Patients With Hepatocellular Carcinoma Who Underwent Radiofrequency Ablation (RFA)

Category	Univariate Analysis		Multivariate Analysis	
	Hazard Ratio (95% CI)	*p*	Hazard Ratio (95% CI)	*p*
Sex				
1: Female	1			
2: Male	0.50 (0.14–1.87)	0.305		
Age				
1: < 65 y	1			
2: ≥ 65 y	1.31 (0.33–5.24)	0.703		
Background liver disease				
1: Hepatitis C virus	1			
2: Hepatitis B virus	0.41 (0.05–3.30)	0.405		
3: Others	1.23 (0.15–9.87)	0.843		
Platelet count				
1: ≥ 10×10^4/μL	1			
2: < 10×10^4/μL	0.58(1.17–2.86)	0.499		
Albumin				
1: ≥ 3.5 g/dL	1			
2: < 3.5 g/dL	1.22 (0.30–4.88)	0.783		
Total bilirubin				
1: < 1.0 mg/dL	1			
2: ≥ 1.0 mg/dL	1.36 (0.36–5.06)	0.649		
Prothrombin activity				
1: ≥ 70%	1			
2: < 70%	2.04 (0.25–16.39)	0.505		
AST				
1: < 40 IU/L	1			
2: ≥ 40 IU/L	4.99 (0.62–39.93)	0.130		
AFP				
1: < 100 μg/L	1			
2: ≥ 100 μg/L	1.01 (0.13–8.02)	0.998		
DCP				
1: < 30 AU/L	1			
2: ≥ 30 AU/L	3.73 (1.00–13.89)	0.050		
Tumor diameter				
1: < 20 mm	1			
2: ≥ 20 mm	1.62 (0.43–6.03)	0.473		
Tumor on subcapsular portion				
1: Yes	1			
2: No	2.44 (0.50–11.11)	0.272		
Tumor on subphrenic portion				
1: No	1			
2: Yes	1.60 (0.43–5.96)	0.484		
Type of RFA needle				
1: LeVeen Needle Electrode[a] (Boston Scientific Japan)	1			
2: Cool-tip[b] (Covidien)	0.46 (0.06–3.75)	0.470		
3: Model 1500 series[a] (RITA Medical Systems)	1.36 (0.17–11.05)	0.774		
Type of enhancement pattern				
1: Types 1, 2, and 3	1		1	
2: Type 4	29.52 (7.28–119.82)	< 0.001	27.68 (6.82–112.33)	< 0.001

Note—AFP = α-fetoprotein, AST = aspartate aminotransferase, DCP = des-γ-carboxy prothrombin.
[a]Multitined expandable electrode.
[b]Internally cooled electrode.

HCV-related HCC generally have smaller tumors than those with HBV-related HCC. Thus, more patients with HCV-related HCC were treated by RFA. Another limitation is that diagnosis of HCC was essentially based on image analysis, and heterogeneous enhancement resembling the type 4 enhancement pattern is recognized in other hepatic tumors (e.g., cholangiocellular carcinoma and fibrolamellar HCC). However, these other tumors that show the type 4 enhancement pattern are rare in patients with chronic hepatitis or liver cirrhosis compared with HCC: Cholangiocellular carcinoma comprises 4.4% of primary liver cancers [22] and fibrolamellar HCC represents only 0.68% of liver tumors in Japan. Thus, detection of a heterogeneous enhancement pattern on dynamic CT images should be considered first to represent HCC with a highly malignant potential. Moreover, regarding HCC nodules that have a type 4 enhancement pattern, MRI (T1- and T2-weighted images, contrast-enhanced MRI, and comparison of diffusion-weighted images obtained with different b values) is considered to contribute to improved tumor characterization. Adoption of these advanced techniques is expected to increase moving forward.

In our opinion, in patients with a type 4 enhancement pattern on dynamic CT images who have adequate liver reserve to allow any treatment, including surgical resection, we believe that the information about recurrence in this population could be used as an index to prioritize surgical resection. If surgical resection cannot be performed, we recommend up-front embolic therapies (e.g., TACE, radioembolization) rather than RFA monotherapy alone.

In conclusion, the current study showed a strong relationship between the type 4 enhancement pattern and HCC recurrence characterized by 10 or more nodules, portal vein invasion, or both after RFA treatment. The management of HCC with a type 4 enhancement pattern should include a thorough therapeutic approach including surgical resection.

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Original Article

Cancer preventive effect of pegylated interferon α-2b plus ribavirin in a real-life clinical setting in Japan: PERFECT interim analysis

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Aim: This study was conducted to clarify the incidence of hepatocellular carcinoma (HCC) and the factors contributing to its occurrence by following chronic hepatitis C patients who received pegylated interferon (PEG-IFN) α-2b plus ribavirin (RBV) combination therapy.

Methods: Patients who received PEG-IFN α-2b and RBV combination therapy with no history of HCC or HCC within 3 months after the start of treatment were observed for the onset of HCC at 67 centers.

Results: Sustained virological response (SVR) was observed in 999 (53.5%) of 1865 patients eligible for analysis. During the observation period (median duration: 4 years and 3 months), HCC developed in 59 patients (3.1%). A significant difference was observed in the 5-year cumulative incidence of HCC between SVR and non-SVR patients (1.1% vs. 7.1%). Factors contributing to HCC selected in multivariate analysis were therapeutic efficacy, sex, age, alanine aminotransferase (ALT) level at 24 weeks after the end of treatment, and platelet count. Non-SVR patients with ALT improvement after the end of treatment had a significantly lower 5-year cumulative incidence of HCC than those without (3.4% vs. 11.0%). HCC developed in 10 patients who achieved SVR, and multivariate analysis indicated that ALT level at 24 weeks after the end of treatment was the only significant factor contributing to HCC.

Conclusion: Several known risk factors for HCC contributed to HCC in patients who received PEG-IFN α-2b and RBV combination therapy, and ALT abnormality after the end of treatment contributes to the onset of HCC in both non-SVR and SVR patients.

Key words: alanine aminotransferase, chronic hepatitis C virus, hepatocellullar carcinoma, pegylated inteferon, ribavirin

Abbreviations: AFP, alpha fetoprotein; ALT, alanine aminotransferase; BR, biochemical response; CHC, chronic hepatitis C; HCC, hepatocellular carcinoma; IFN, interferon; LVR, late virological response; NR, no response; NVR, non-virological response; PEG-IFN, pegylated interferon; ; RBV, ribavirin; SVR, sustained virological response; TR, transient response.

INTRODUCTION

THE INCREASE IN the incidence of hepatocellular carcinoma (HCC) in Japan peaked in 2004 and is now in a declining trend.[1] The HCC mortality rate, however, is still particularly high among developed countries,[2] and even now nearly 35 000 people die

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