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ORIGINAL ARTICLE—LIVER, PANCREAS, AND BILIARY TRACT

Percutaneous radiofrequency ablation therapy for hepatocellular carcinoma: a proposed new grading system for the ablative margin and prediction of local tumor progression and its validation

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Abstract
Background In the present study we classified the radicality of percutaneous radiofrequency thermal ablation (RFA) therapy according to the extent of the ablated margin. We measured the local recurrence rate for each radicality grade to evaluate the significance of the grading system in assessing the therapeutic effectiveness of RFA and predicting local tumor progression.
Methods This retrospective study involved 269 patients with solitary hypervascular hepatocellular carcinoma who had undergone RFA. The mean ± SD observation period after RFA, number of treatment sessions, and tumor diameter were 25.7 ± 19.9 months, 1.2 ± 0.5, and 2.1 ± 0.7 cm, respectively. Patients were evaluated using dynamic computed tomography. We classified the radicality of RFA treatment into four grades (R grades: A, B, C, and D) according to the extent of the ablated tumor margin, calculated the post-RFA cumulative local recurrence rate for each R grade, and analyzed the factors (patient characteristics, biochemical data, contiguous vessels, and tumor marker) contributing to local recurrence.
Results The cumulative local recurrence rates at 3 years were 6.7, 17.6, 55.8, and 82.2% for Grades A, B, C, and D, respectively. Using univariate analysis, R grade, tumor size (>2 cm), and des-γ-carboxy prothrombin (DCP) (>200 mAU/mL) were shown to be significant factors contributing to local recurrence. However, using multivariate analysis, only the R grade was found to be a significant independent factor.
Conclusions The proposed R grading method is a valid and useful method for assessing treatment efficacy, and for predicting local tumor progression after RFA.

Keywords Hepatocellular carcinoma · Radiofrequency thermal ablation · Treatment outcome · Grading · Local tumor progression

Introduction

Hepatocellular carcinoma (HCC) is a problem worldwide [1–5]. Unlike most solid cancers, the future incidence and mortality rates for HCC are projected to increase substantially in many countries over the next 20 years, mostly as a result of infection with the hepatitis C virus [6].

HCC frequently recurs after treatment, leading to high mortality rates. Current options for the treatment of HCC include surgical resection, transcatheter arterial embolization (TAE), percutaneous ethanol injection therapy (PEIT), and percutaneous radiofrequency thermal ablation (RFA) therapy. Recently, systemic treatments with molecular-targeted drugs, such as sorafenib, have been recommended for advanced-stage HCC [6]. Surgical resection plays only a limited role in the treatment of HCC, because the inclusion criteria are usually very limited. TAE is often performed in patients with multiple hypervascular nodules. However, complete necrosis of the tumor tissue is rarely achieved [7]. PEIT continues to play an important role in the treatment of small HCCs. However, its efficacy depends on tumor size, and a higher rate of local tumor progression has been reported compared with other procedures [8, 9].

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RFA therapy, an alternative technique to PEIT that was introduced in Japan in 1999, has been widely used as a curative treatment for HCC [1–5]. An area of <3 cm in diameter can be ablated with a single application of RFA. This technique has proven to be a safe and effective modality for the treatment of small HCCs in patients who are considered unsuitable for surgical intervention because of insufficient hepatic reserve [1–5]. Moreover, for local tumor control, RFA therapy has proven to be superior to PEIT and percutaneous microwave thermocoagulation therapy (PMCT), both of which have been used previously [8–11].

Many studies have indicated that the incidence of local tumor progression after treatment with RFA has ranged from 2 to 53% [11–17]. Complete response to the initial RFA treatment has been reported to contribute to the long-term survival of HCC patients [18, 19]. The majority of recurrent lesions emerge from the ablated area within 5 mm of the tumor border, which is the area most likely to contain viable tumor cells [16]. Consequently, an adequate ablative margin and an accurate method to assess the treatment efficacy of RFA for HCC are required.

We have routinely classified patients treated with RFA into four groups based on the extent of the ablative margin; this is a novel classification system, which we have referred to as Radicality Grading (R grades: A, B, C, and D). To our knowledge, no other investigators have used this or a similar classification system to grade the extent of the ablative margin. The objective of the present study was to examine the usefulness of the R grading as a predictor of local tumor progression.

Patients and methods

Patients and HCC diagnosis

We performed RFA therapy in 315 treatment-naive patients diagnosed with solitary HCC at the Gastroenterology Department, Osaka Red Cross Hospital, between January 2004 and October 2010. Prior to the performance of RFA, written informed consent was obtained from all patients. The ethics committee of our department approved the protocol for RFA therapy. The present study comprised a retrospective analysis of patient records, and all treatments were conducted in an open-label manner.

HCC was diagnosed using abdominal ultrasound and dynamic computed tomography (CT) scans (hyperattenuation during the arterial phase in all or some part of the tumor, and hypoattenuation in the portal-venous phase). Arterial and portal phase dynamic CT images were obtained at approximately 30 and 120 s, respectively, after injecting contrast material. Of the 315 patients, 21 who were diagnosed with hypovascular HCC (hypoattenuation in the arterial phase) and 25 who were lost to follow-up were excluded. Thus, 269 patients diagnosed with solitary hypervascular HCC were included in this analysis. For all patients, abdominal angiography was performed before RFA. We confirmed solitary and hypervascular HCC with no vascular invasion and no satellite nodules using CT during hepatic arteriography (CTHA) and arterial-portography (CTAP).

Assessment of treatment efficacy

To assess treatment efficacy, we performed dynamic 16-column multi-detector CT (MDCT) using 3-mm slice scans within 1 week after RFA. In assessing the ablated margin, for each patient, using the image in the portal-venous phase, we analyzed not only the maximum frame of the CT scan but also all of the frames that showed tumor. Within 1 week after RFA, the increase of inflammatory arterial blood flow brought about by performing RFA could not be ignored, and this is the reason that we used the image in the portal-venous phase. When using the image in the portal-venous phase, it was considered that the timing of evaluation did not affect the results. The patients were then classified into four groups as follows: Grade A (absolutely curative), a $\geq$5 mm ablative margin around the entire tumor; Grade B (relatively curative), an ablative margin was present around the tumor, but the diameter was <5 mm in some places; Grade C (relatively non-curative), only an incomplete ablative margin was formed although no residual tumor was apparent; Grade D (absolutely non-curative), the tumor was not completely ablated (Fig. 1). We used a >5 mm ablative margin because Nakazawa et al. [16] reported that an ablative margin of 5 mm or greater was the most important factor for the local control of HCC. Using this method to assess treatment efficacy, we calculated the local tumor progression rate for all 269 patients. In other words, we used the R grading method and examined its usefulness (R Judgment). We defined local tumor progression as the presence of a hypervascular nodule adjacent to the ablated area after RFA using dynamic CT scan. A recurrence that was distant from the ablated area in the same segment was not included in the assessment of local tumor progression. And local tumor progression was determined by three radiologists experienced in liver imaging. This approach was essentially based on the standardized terminology and reporting criteria published by the Society of International Radiology Technology Assessment Committee; International Working Group on Image-Guided Tumor Ablation [20]. Regarding tumors of <5 mm located at the periphery of the liver, if the tumor was ablated just below the liver capsule we considered it an ablative margin of >5 mm. This

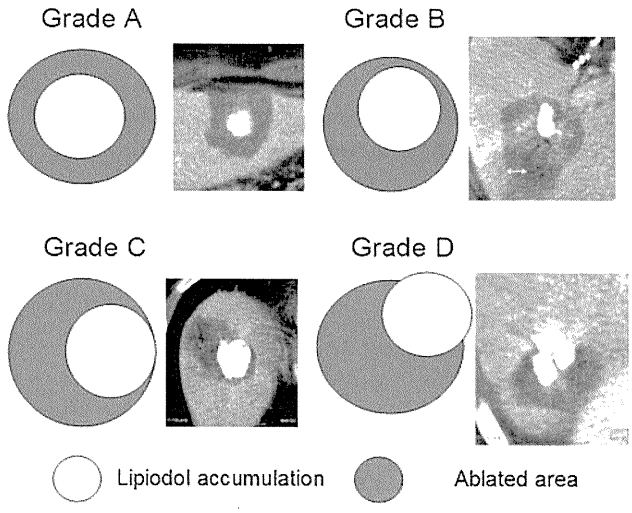

Fig. 1 Diagrammatic representation of the proposed radicality (R) grading method. Grade A (absolutely curative): an ablative margin ≥5 mm is achieved around the entire tumor; Grade B (relatively curative): an ablative margin extends around the entire tumor but the diameter is <5 mm in some places; Grade C (relatively non-curative): a complete ablative margin is not formed although no residual tumor is apparent; Grade D (absolutely non-curative): the tumor has not been entirely ablated

decision, the R Judgment, was made by the three radiologists experienced in liver imaging mentioned above. If the decisions of the three radiologists differed (for example, if two radiologists judged Grade A and the other radiologist judged Grade B), a decision was made by majority rule.

In our department, during abdominal angiography, we routinely perform arterial infusion of iodized oil (Lipiodol Ultra-Fluid; Schering Japan, Osaka, Japan) alone (1–2 mL). Lipiodol was injected to intensify the radiologic visibility of the target tumor. For patients in whom the tumor location was determined because of the dense accumulation of Lipiodol, we assessed treatment efficacy using dynamic CT scans. However, in patients for whom it was difficult to determine the exact location of the tumor because of insufficient Lipiodol accumulation, and for those with Lipiodol accumulation in only part of the tumor, such as nodule-in-nodule HCC, we measured the ablative margin using CTHA with a CTAP image as the reference image. Follow-up consisted of monthly blood tests and monitoring of tumor markers, including des-γ-carboxy prothrombin (DCP), which was measured by a chemiluminescent enzyme immunoassay (Lumipulse PIVKAII Eisai; Eisai, Tokyo, Japan). Dynamic CT scans were obtained every 3–4 months after RFA.

In addition to the R grade, a total of 20 factors, including patient characteristics, clinical biochemical data, contiguous vessels, and tumor markers, were retrospectively examined, using univariate and multivariate analyses, for their contribution to local tumor progression.

RFA procedure

We routinely used a cool-tip needle (Radionics, Burlington, MA, USA) while performing RFA. Using the intercostal or subcostal approach, a 17-gauge, 2- or 3-cm cooled-tip electrode was inserted under real-time ultrasound guidance. The initial treatment was planned with one ablation for tumors of <2 cm in diameter and two or more ablations with the overlapping technique for tumors of ≥2 cm in diameter. We defined a session as a single intervention episode that consisted of one or more ablations performed on a single tumor, and a treatment as the completed effort to ablate the tumor. This approach was in accordance with the working party report on image-guided tumor ablation [21].

After insertion of the electrode into the tumor, we started ablation at 60 W for the 3-cm exposed tip and 40 W for the 2-cm exposed tip. The power was increased to 120 W at a rate of 10 W/min. The duration of a single ablation was 12 min for the 3-cm electrode and 6 min for the 2-cm electrode. After RFA exposure, the pump was stopped and the temperature of the needle tip was measured. When the temperature reached >60°C, additional ablation was not performed. When tumor ablation was complete, thermal ablation was performed along the needle track. All patients were carefully observed for treatment-related complications. All procedures were performed under ultrasound guidance by one of five operators who had at least 3 years of experience of performing RFA. We used the artificial ascites technique to prevent collateral thermal injury when the anticipated RFA zone was in contact with a critical organ, such as the hepatic flexure of the colon. We also used this technique to improve visibility when the index tumor was located in the hepatic dome area.

Complete ablation of HCC was defined as hypoattenuation of the lesion including the surrounding liver parenchyma. Therefore, we routinely performed additional RFA treatment until we had confirmed that the ablative margin surrounded the entire circumference of the tumor (R grade: Grade A or B), provided that patient consent had been given. If we were not able to acquire consent from the patient, or if the patient was judged to be at high risk if given additional treatment, no further RFA treatment was given.

Statistical analysis

Data were analyzed using univariate and multivariate analyses. The cumulative local tumor progression rate was

calculated using the Kaplan–Meier method, and tested using the log-rank test. The Cox proportional hazard model was used for multivariate analyses of factors that were considered significant in univariate analysis. These statistical methods were used to estimate the interval from RFA treatment to local tumor progression. Data were analyzed using SPSS software, version 9.0 (SPSS, Chicago, IL, USA) for Microsoft Windows. Data are expressed as means ± standard deviation (SD). Values of $P < 0.05$ were considered to be statistically significant.

Results

Clinical characteristics

The clinical characteristics of the patients with HCC are shown in Table 1. No patient had major complications after RFA. The mean ± SD tumor diameter, observation period, and number of treatment sessions were 2.1 ± 0.7 cm, 25.7 ± 19.9 months, and 1.2 ± 0.5, respectively. We confirmed 84 cases of local tumor progression (31.2%) and the mean observation period until local tumor progression occurred after RFA was 20.0 months. Using the proposed R grading system, 49 patients were classified as Grade A (18.2%), 113 as Grade B (42.0%), 74 as Grade C (27.5%), and 33 as Grade D (12.3%).

Reasons for not attempting to perform additional RFA in patients with Grade C and D

It was considered that patients with Grade C and D (total 107 patients) should receive additional RFA because a sufficient ablative margin had not been obtained. Despite this decision, we did not attempt to perform additional RFA in some of these patients; details of the reasons why and the number of patients are as follows: (1) patients in whom additional RFA was decided against by the doctors because of sites at which it was extremely difficult to perform additional RFA, such as sites directly under the hepatic dome or the heart (39 patients), (2) patients in whom additional RFA was considered to be difficult to perform because of poor visibility under ultrasonography owing to extreme obesity and impossibility of breath-hold when performing RFA (15 patients), (3) patients in whom high rates of complications were expected, such as when HCC at the site of a hepatic hilar lesion was treated by RFA (23 patients), (4) patients in whom additional RFA was difficult to perform because ascites appeared after the first session of RFA owing to poor hepatic function before RFA (20 patients), (5) and patients whose informed consent could not be obtained for additional RFA for reasons such as a physical burden (10 patients).

Table 1 Clinical characteristics of patients with hepatocellular carcinoma

Characteristics	Number of patients or mean ± SD
Gender	
Male/female	165/104
Age (years)	69.4 ± 8.8
Tumor size (cm)	2.1 ± 0.7
Observation period (months)	25.7 ± 19.9
Number of RFA sessions	1.2 ± 0.5
Cause of liver disease	
Hepatitis C/hepatitis B/nonB, nonC	213/20/36
Child–Pugh classification	
Chronic hepatitis/Child–Pugh A/B/C	61/167/37/4
The R factor	
Grade A/B/C/D	49/113/74/33
Contiguous vessels	
Yes/no	117/152
Local tumor progression	
Yes/no	84/185
BMI (kg/m^2)	
>25/≤25	78/191
DM	
Yes/no	90/179
Post-RFA antiviral therapy	
Yes/no	26/243
BCAA medication	
Yes/no	45/224
Biochemical analysis	
AST (IU/L)	57.2 ± 30.9
ALT (IU/L)	50.3 ± 43.2
ALP (IU/L)	362.1 ± 216.3
γGTP (IU/L)	74.7 ± 73.4
Alb (g/dL)	3.80 ± 0.51
T-Bil (mg/dL)	0.95 ± 0.51
PT (%)	86.9 ± 15.9
Platelets (10^4/mm^3)	11.0 ± 4.73
AFP (ng/mL)	184.8 ± 966.1
DCP (mAU/mL)	352.7 ± 2787

SD standard deviation, *BMI* body mass index, *DM* diabetes mellitus, *RFA* radiofrequency thermal ablation, *R* radicality, *BCAA* branched chain amino acid, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *ALP* alkaline phosphatase, *γGTP* γ-glutamyl transpeptidase, *Alb* albumin, *T-Bil* total bilirubin, *PT* prothrombin time, *AFP* alpha-fetoprotein, *DCP* des-γ-carboxy prothrombin

Quantitative analysis of the ablative margin and local tumor progression

The cumulative local tumor progression rate in all patients at 1, 2, and 3 years was 12.8, 23.6, and 36.6%, respectively (Fig. 2). In terms of extent of the ablation margin, among

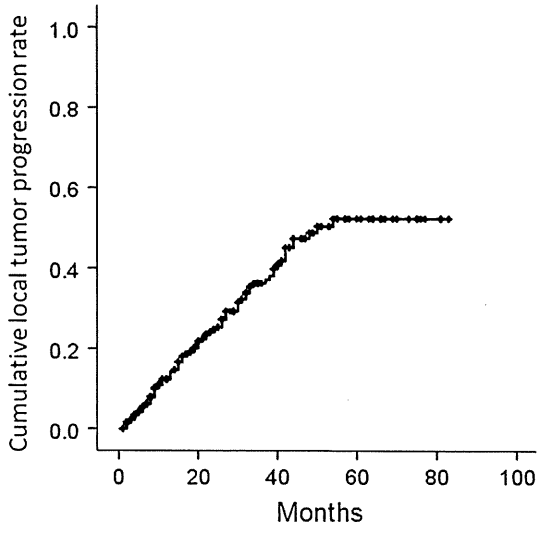

Fig. 2 Cumulative local tumor progression rate in all patients

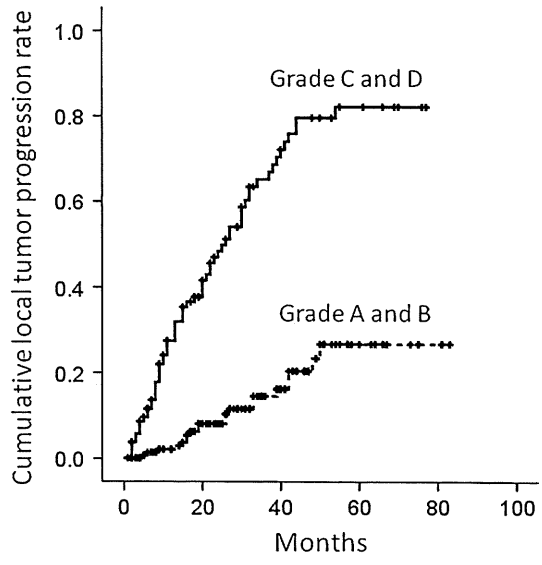

Fig. 3 Cumulative local tumor progression rate in patients with a sufficient or insufficient ablative margin. The local tumor progression rate was significantly lower in patients with a sufficient ablative margin (corresponding to R grade A and B) than in those with an insufficient ablative margin (corresponding to R grade C and D) ($P < 0.001$)

the 162 patients with complete circumferential ablation (corresponding to R grades A and B), the cumulative rates of local tumor progression at 1, 2, and 3 years, were 1.4, 8.2, and 13.8%, respectively. In the 107 patients with incomplete circumferential ablation (corresponding to R grades C and D), the cumulative rates of local tumor progression at 1, 2, and 3 years were 32.2, 49.1, and 63.4%, respectively. Accordingly, the local tumor progression rate was significantly lower in patients with complete circumferential ablation versus those with incomplete circumferential ablation ($P < 0.001$) (Fig. 3).

Analysis by the R grading

We also determined the rates of tumor progression for each of the four grades in the R grading system. The cumulative rates of local tumor progression at 1, 2, and 3 years were as follows: 2.6, 2.6, and 6.7%, respectively, for Grade A; 2.4, 10.2, and 17.6%, respectively, for Grade B; 19.5, 44.0, and 55.8% for Grade C; and 46.2, 53.4, and 82.2% for Grade D. These differences between individual grades reached statistical significance, indicating that a more complete and a larger ablation margin was associated with a lower rate of recurrence (overall significance, $P < 0.001$) (Fig. 4).

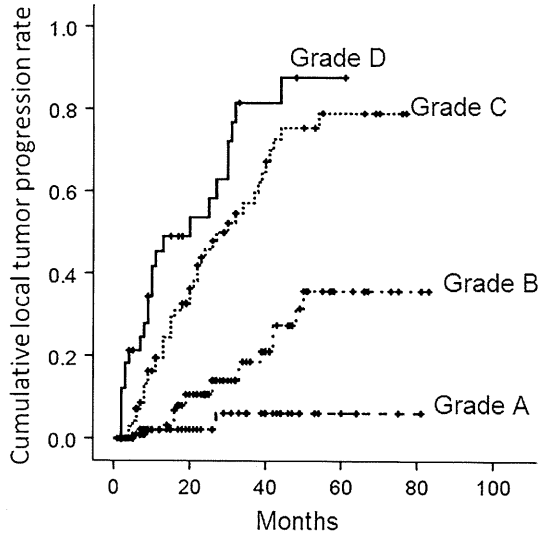

Fig. 4 Cumulative rates of local tumor progression according to R grading. The rate of local progression differed significantly among the four R grades (overall significance, $P < 0.001$)

Analysis including all factors other than the R grading

Using univariate analysis, the R grade ($P < 0.001$), tumor size >2 cm ($P = 0.014$), and des-γ-carboxy prothrombin (DCP >200 mAU/mL) ($P = 0.007$) were found to be significant factors for predicting local tumor progression (Table 2). In addition, although the difference was not significant ($P = 0.051$), the local tumor progression rate tended to be higher in patients aged over 65 years (Table 2). In the multivariate analyses involving the three factors that were found to be significant in the univariate analysis, the hazard ratios (HRs) for tumor size and DCP values for Grades B, C, and D are detailed in Table 3. Only the R grade was found to be a significant independent factor linked to local tumor progression.

Table 2 Univariate analysis of local tumor progression in patients with hepatocellular carcinoma after treatment with RFA

Variables	*n*	*P* value[a]
Age (>65 years), yes/no	186/83	0.051
Gender (male), yes/no	165/104	0.355
Tumor size (>2 cm), yes/no	149/120	0.014
Child–Pugh classification		
Chronic hepatitis/C-P A/C-P B or C-P C	61/167/41	0.561
Cause of liver disease		
Hepatitis B/hepatitis C/nonB nonC	20/213/36	0.263
AST (>40 IU/L), yes/no	189/89	0.935
ALT (>40 IU/L), yes/no	140/129	0.384
ALP (>340 IU/L), yes/no	106/163	0.686
γGTP (>80 IU/L), yes/no	78/191	0.573
Alb (>3.5 g/dL), yes/no	190/79	0.821
T-Bil (>1 mg/dL), yes/no	82/187	0.377
PT (>70%), yes/no	230/39	0.626
Platelets (>10^4/mm^3), yes/no	147/122	0.334
AFP (>100 ng/mL), yes/no	48/221	0.203
DCP (>200 mAU/L), yes/no	42/227	0.007
Post-RFA antiviral therapy, yes/no	26/243	0.221
BMI (>25 kg/m^2), yes/no	78/191	0.657
DM, yes/no	90/179	0.157
BCAA medication, yes/no	45/224	0.113
Contiguous vessels, yes/no	117/152	0.099
R grade, A/B/C/D	49/113/74/33	<0.001

C-P Child–Pugh, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *ALP* alkaline phosphatase, *γGTP* γ-glutamyl transpeptidase, *Alb* albumin, *T-Bil* total bilirubin, *PT* prothrombin time, *AFP* alpha-fetoprotein, *DCP* des-γ-carboxy prothrombin, *RFA* radiofrequency thermal ablation, *BMI* body mass index, *DM* diabetes mellitus, *BCAA* branched chain amino acid, *R* radicality

[a] Log-rank test

Table 3 Multivariate analysis of local tumor progression in patients with hepatocellular carcinoma after treatment with RFA

Variable	Hazard ratio	95% CI	*P* value[a]
Tumor size			
>2 cm	1.000		
≤2 cm	0.754	0.477–1.190	0.255
DCP			
>200	1.000		
≤200	0.718	0.408–1.264	0.251
The R grade			
Grade A	1.000		
Grade B	4.023	0.930–17.406	0.048
Grade C	17.432	4.207–72.226	<0.001
Grade D	26.879	6.218–116.200	<0.001

CI confidence interval, *DCP* des-γ-carboxy prothrombin, *R* radicality

[a] Cox proportional hazard model

Discussion

RFA has several advantages as compared with resection, such as lower invasiveness and liver volume loss, and superior cost-effectiveness [15]. As a result, its use in Japan has been rapidly increasing since its introduction in 1999 and since its inclusion in insurance cover in 2004 [11, 15]. However, it is believed that the local tumor progression rate after RFA is higher relative to that of resection [22, 23]. Therefore, in addition to attaining good local control of HCC, radiologists have been looking for an accurate method to assess RFA treatment efficacy that is strongly correlated with the local tumor progression rate. In our study, the cumulative local tumor progression rates in all patients at 1, 2, and 3 years were 12.8, 23.6, and 36.6%, respectively. These rates were relatively higher than those reported in previous studies [11, 13–17, 24, 25]. One possible reason for this is that our study involved 41 patients (15.2%) with a tumor >3 cm in diameter. Local tumor progression occurred in most of these patients, and in patients that were considered to have insufficient ablative margins (such as Grades C and D); however, additional

RFA was not performed in these patients, because informed consents were not obtained or because these patients were judged to be at high risk if given additional treatment.

Using univariate analysis, the R grade, tumor size (>2 cm), and DCP (>200 mAU/mL) were found to be significant predictive factors for local tumor progression. Kim et al. [13] reported that risk factors for local tumor progression included large tumor size and an insufficient ablative margin. It can be difficult to acquire an ablative margin around the entire circumference of large tumors. In these patients, it might be valuable to use image-supporting methods such as real-time virtual sonography (RVS) and enhanced ultrasonography to detect non-ablated regions when performing additional RFA [11, 26, 27].

In the present study, 42 patients (15.6%) had a DCP value of more than 200 mAU/mL. Kobayashi et al. [28] have reported that high DCP levels reflect the aggressiveness and progression of HCC tumors, and that the DCP level is a predictor of microvascular invasion. These findings seemed to correlate with our results using univariate analysis.

Although age was not found to be a significant factor for predicting local progression ($P = 0.051$) in the present study, the >65-year age group tended to have a higher local tumor progression rate. Using the R Judgment for this age group, 33 patients were classified as Grade A, 75 as Grade B, 48 as Grade C, and 30 as Grade D, and 78 patients did not have an ablative margin around the entire circumference of the tumor. In particular, 30 patients classified as Grade D were expected to require additional treatment. However, in the majority of these patients additional treatment was not performed due to the physical burden of advanced age, decreased liver function, and concerns related to the high incidence of complications due to comorbidities. It was assumed that these factors were linked to the higher local tumor progression rate in patients aged >65 years (local tumor progression occurred in 22 patients (73.3%) out of the 30 patients judged as Grade D).

It has been suggested that the presence of blood vessels contiguous to HCC is related to local tumor progression after RFA, because blood flow reduces the thermal effects of RFA [16]. However, in our study, the presence of contiguous vessels was not a significant factor ($P = 0.099$), possibly because most of the contiguous vessels in the 117 patients with contiguous vessels were hepatic veins rather than portal veins. We performed RFA to tumors adjacent to a hepatic vein, thus destroying the vein. However, hepatic vein injury caused by an RFA electrode does not usually cause serious complications. In fact, Kim et al. [14] reported that aggressive ablation of the portion of the tumor close to a hepatic vein might be useful to prevent local tumor progression.

In our study, antiviral therapy, such as interferon treatment, after RFA was not also found to be a significant factor ($P = 0.221$). This result suggests that antiviral therapy after RFA does not contribute to the suppression of the local tumor progression after RFA, although Ikeda et al. [29] reported that the administration of interferon for two or more years decreased the recurrence rate of early-stage HCC after radical ablation.

We routinely performed arterial infusion of Lipiodol alone, because we believed that Lipiodol accumulation was useful in confirming the tumor border. However, in 96 patients (35.7%) in our study, it was considered difficult to determine the exact location of the tumor because of insufficient Lipiodol accumulation. Exactly how we can measure the ablative margin in such patients will be a challenge that will be met in a future study.

We found a significant difference in the local tumor progression rate more than 1 year after RFA between Grade A and Grade B. In Grade B patients, local tumor progression was observed in 18 patients (15.9%), and in 16 patients, local tumor progression was observed from a site that was <5 mm from the ablative margin of RFA. And in the 18 Grade B patients who showed local tumor progression, the tumor recurred more than 1 year after RFA in 15 patients, in all of whom the tumor recurred <5 mm from the site of the ablative margin. One possible reason that a significant difference in local tumor progression rate was found more than 1 year after RFA between Grade A and Grade B is that, in most Grade B patients who showed local tumor progression, small satellite nodules were already present at a site <5 mm from the tumor border when RFA was performed.

In our study, of the 49 cases judged as Grade A, two had local tumor progression. In these two patients, the intervalsuntil local tumor progression were 5 months and 2.2 years, respectively. When assessing treatment efficacy after RFA at the site of local tumor progression, the ablative margins were found to be 8 and 9 mm in diameter in these two patients. In some HCC patients who underwent surgery, it has been reported that small satellite nodules were found in the lesion within 0.5–1 cm of the main tumor [30]. In the future, further study is needed to determine whether setting the ablative margin at 5 mm is sufficient for adequate assessment.

In our study, in the multivariate analysis, only the R grade was found to be a significant factor for assessing local progression after RFA treatment for HCC. Cases that acquired an ablative margin around the entire circumference, and those that did not were significantly stratified. Using the R grading, all groups (Grades A–D) were significantly stratified. These findings suggest that the proposed R Judgment approach is a valid method for assessing the efficacy of RFA treatment for HCC. Nakazawa et al.

[16] reported that an ablative margin of ≥5 mm was the most important factor in the local control of HCC, while Kim et al. [14] found that an insufficient ablative margin (<3 mm) was the only factor to be significantly associated with local tumor progression. In general agreement with the findings of our study, it has also been reported that, in addition to an insufficient ablative margin, tumor size and age were significant risk factors for local tumor progression, and that patients at high risk of local tumor progression should be closely monitored [24].

In the present study, we used a cohort of patients that was sufficiently large for comprehensive statistical analyses, and we compared the four R grades of our classification system. In addition, we verified the validity of the R Judgment as a method for predicting RFA treatment efficacy and assessing local tumor progression in HCC.

In conclusion, the R Judgment we have proposed is a useful method for predicting local tumor progression after RFA.

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

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ORIGINAL ARTICLE—LIVER, PANCREAS, AND BILIARY TRACT

Decrease in alpha-fetoprotein levels predicts reduced incidence of hepatocellular carcinoma in patients with hepatitis C virus infection receiving interferon therapy: a single center study

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Abstract
Background Increasing evidence suggests the efficacy of interferon therapy for hepatitis C in reducing the risk of hepatocellular carcinoma (HCC). The aim of this study was to identify predictive markers for the risk of HCC incidence in chronic hepatitis C patients receiving interferon therapy.
Methods A total of 382 patients were treated with standard interferon or pegylated interferon in combination with ribavirin for chronic hepatitis C in a single center and evaluated for variables predictive of HCC incidence.
Results Incidence rates of HCC after interferon therapy were 6.6% at 5 years and 13.4% at 8 years. Non-sustained virological response (non-SVR) to antiviral therapy was an independent predictor for incidence of HCC in the total study population. Among 197 non-SVR patients, independent predictive factors were an average alpha-fetoprotein (AFP) integration value $\geq$10 ng/mL and male gender. Even in patients whose AFP levels before interferon therapy were $\geq$10 ng/mL, reduction of average AFP integration value to <10 ng/mL by treatment was strongly associated with a reduced incidence of HCC. This was significant compared to patients with average AFP integration values of $\geq$10 ng/mL ($P = 0.009$).
Conclusions Achieving sustained virological response (SVR) by interferon therapy reduces the incidence of HCC in hepatitis C patients treated with interferon. Among non-SVR patients, a decrease in the AFP integration value by interferon therapy closely correlates with reduced risk of HCC incidence after treatment.

Keywords Alpha-fetoprotein · Hepatocellular carcinoma · Hepatitis C · Interferon

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Introduction

Hepatitis C virus (HCV) infection is a predominant cause of liver cirrhosis and hepatocellular carcinoma (HCC) in many countries, including Japan, the United States, and countries of Western Europe [1–5]. The annual incidence of HCC in patients with HCV-related cirrhosis ranged from 1 to 8% [6–9]. Even in the absence of liver cirrhosis, patients with chronic hepatitis caused by HCV infection are at a high risk of developing HCC. Indeed, a large-scale Japanese cohort study showed that the annual incidence of HCC is 0.5% among patients with stage F0 or F1 fibrosis and 2.0, 5.3, and 7.9% among those with F2, F3, and F4 fibrosis, respectively [9]. Periodic surveillance is recommended to detect HCC as early as possible in patients with HCV-related chronic liver disease; however, this may not be cost-effective. For patients with chronic hepatitis C, more effective detection and prevention of HCC is being sought by two important routes: (1) the attempt to discover noninvasive predictive markers and (2) development of treatment strategies to reduce the risk of HCC. There have been several attempts to discover non-invasive markers capable of predicting the risk of HCC incidence in patients with chronic hepatitis C [6, 10]. For example, a cohort

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derived from the Hepatitis C Antiviral Long-term Treatment Against Cirrhosis (HALT-C) Trial identified older age, African American race, lower platelet count, higher alkaline phosphatase, and esophageal varices as risk factors for HCC [11].

There have also been a number of studies to evaluate the effect of anti-viral treatment of chronic hepatitis C on the incidence of HCC [12–19]. The results were summarized in a meta-analysis, which concluded that the effect of interferon on risk of HCC is mainly apparent in patients achieving a sustained virological response (SVR) to interferon therapy [13]. In addition, a number of studies have suggested the incidence of HCC is reduced in treated patients compared to historical controls [12, 15, 16, 19]. However, the recent HALT-C randomized control trial revealed that long-term pegylated interferon therapy does not reduce the incidence of HCC among patients with advanced hepatitis C who do not achieve SVRs. Reduction in the risk of HCC by maintenance therapy was shown only in patients with cirrhosis [14, 17]. These controversial results suggest that interferon therapy reduces the risk of HCC only in a group of patients with HCV-related chronic liver disease. Thus, it is important to evaluate the risk of HCC development in hepatitis C patients receiving interferon therapy and it will be clinically useful to discover markers distinguishing high- and low-risk groups.

Serum alpha-fetoprotein (AFP) has been widely used as a diagnostic marker of HCC [20–22]. However, elevation of serum AFP levels is often found in non-neoplastic liver diseases without evidence of HCC, including acute liver injury and chronic viral hepatitis [23–27], especially among patients with advanced chronic hepatitis C [28]. An increase of AFP after liver damage is interpreted as a sign of dedifferentiated hepatic regeneration [27]. There have been some reports that AFP is a significant predictor of HCC in patients with chronic hepatitis C [4, 5, 29]. In addition, it has recently been shown that AFP levels decrease in response to interferon administration in patients with chronic hepatitis C [30, 31], and that long-term interferon therapy for aged patients with chronic HCV infection is effective in decreasing serum AFP levels and preventing hepatocarcinogenesis [32, 33]. However, little is known about the relationship between changes in serum AFP level over time during interferon therapy and the development of HCC.

The aim of this large single center study was to identify predictive markers for the risk of HCC development in patients receiving interferon therapy for chronic hepatitis C. For this purpose, patients treated with standard or pegylated interferon, in combination with ribavirin, for chronic hepatitis C were enrolled and subjected to scheduled periodic surveillance for HCC and a number of potential predictive markers, including AFP and alanine aminotransferase (ALT) integration values, at a single center.

Materials and methods

Patients

Between January 2002 and April 2010, 528 patients with chronic hepatitis C received combination therapy with standard interferon and ribavirin ($n = 84$) or pegylated interferon and ribavirin ($n = 444$) at Osaka Red Cross Hospital. Eligibility criteria for treatment were positivity for serum HCV RNA and histological evidence of chronic hepatitis C ($n = 427/444$; 80.9%), or positivity for serum HCV RNA, liver enzyme levels greater than the normal upper limit, and an ultrasound image demonstrating chronic liver damage ($n = 101/444$; 19.1%). Exclusion criteria for treatment were as follows: neutrophil count <750 cells/μL, platelet count <50,000 cells/μL, hemoglobin level ≤9.0 g/dL, and renal insufficiency (serum creatinine levels >2 mg/dL).

Of 528 patients who received interferon therapy for chronic hepatitis C, 146 were excluded from this study for the following reasons: follow-up <24 weeks after the termination of the interferon therapy ($n = 122$), previously treated for HCC ($n = 22$), or occurrence of HCC during or within 24 weeks after treatment ($n = 2$). Therefore, 382 patients were enrolled for the study and were retrospectively analyzed.

To detect early-stage HCC, ultrasonography, dynamic contrast enhanced computed tomography (CT), dynamic contrast enhanced magnetic resonance imaging (MRI), and/or measurement of tumor markers (including AFP) were performed for all patients at least every 6 months. HCC was diagnosed radiologically as liver tumors displaying arterial hypervascularity and venous or delayed phase washout by dynamic contrast enhanced CT or MRI.

The study protocol was approved by the Ethics Committee at Osaka Red Cross Hospital and performed in compliance with the Helsinki Declaration.

Treatment protocol and definition of responses to treatment

The basic treatment protocol for patients with chronic hepatitis C consisted of 6 mega units of interferon-α-2b 3 times a week or 1.5 μg/kg of pegylated interferon α-2b once a week, combined with ribavirin at an oral dosage of 600–1000 mg/day. Duration of the treatment was 48–72 weeks for those with HCV genotype 1 and serum HCV RNA titer of >5 log IU/mL, and 24 weeks for all other patients.

Patients who were negative for serum HCV RNA for >6 months after completion of interferon therapy were defined as showing an SVR. Patients whose serum ALT levels decreased to the normal range and remained normal for >6 months after the termination of interferon therapy were defined as showing a sustained biochemical response (SBR).

Patients who did not achieve SVR received ursodeoxycholic acid and/or glycyrrhizin containing preparation (Stronger Neo-Minophagen C), when serum ALT levels were higher than the upper limit of normal.

Virological assays

HCV genotype was determined by polymerase chain reaction (PCR) amplification of the core region of the HCV genome using genotype-specific PCR primers [34]. Serum HCV RNA load was evaluated once a month during and 24 weeks after treatment using a PCR assay (Cobas Amplicor HCV Monitor, Roche Molecular Systems, Pleasanton, CA, USA).

Measurement of AFP and calculation of average integration value

AFP was measured in serum samples obtained from each patient at intervals of 1–3 months. The median number of examinations was 15 (range 1–70) in each patient. Serum AFP levels were determined by enzyme-linked immunosorbent assay, which was performed using a commercially available kit (ELISA-AFP, International Reagents, Kobe, Japan). Integration values of AFP and ALT were calculated as described in previous reports [35]. For example, the integration value of AFP was calculated as follows, $(y_0 + y_1) \times x_1/2 + (y_1 + y_2) \times x_2/2 + (y_2 + y_3) \times x_3/2 + (y_3 + y_4) \times x_4/2 + (y_4 + y_5) \times x_5/2 + (y_5 + y_6) \times x_6/2$, i.e., the area of each trapezoid representing an AFP value was measured the sum of the resulting values used to calculate the integration value (Fig. 1). The average integration value was obtained by dividing the integration value by the observation period from initiation of the treatment.

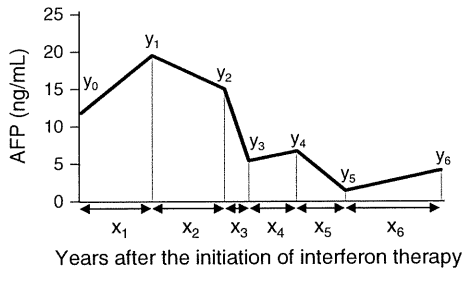

Fig. 1 Example plot of data used for calculation of average integration value of alpha-fetoprotein (AFP)

Statistical analysis

The Kaplan–Meier method was used to estimate the rates of development of HCC in patients after interferon therapy. Log-rank tests were used to evaluate the effects of predictive factors on incidence of HCC. Significance was defined as $P < 0.05$. Multivariate Cox regression analysis using the stepwise method was used to evaluate the association between HCC incidence and patient characteristics, and to estimate hazard ratio (HR) with a 95% confidence interval (CI). A P value of 0.1 was used for variable selection and was regarded as statistically significant. SAS version 9.2 (SAS Institute Inc., Cary, NC, USA) was used for statistical analysis.

Results

Characteristics of patients and incidence of HCC

This study included 382 patients treated for chronic hepatitis C with standard interferon or pegylated interferon in combination with ribavirin. Baseline clinical and virological characteristics of patients included in the study are summarized in Table 1. The median age of the patients at the outset of therapy was 59.0 years (range 18–81 years) and the median follow-up period was 4.1 years (range 0.1–8.4 years). The majority of patients were infected with HCV genotype 1b ($n = 229$; 60%), and median serum HCV RNA load was 6.1 log IU/mL (range 2.3–7.3 log IU/mL). Baseline (before interferon therapy) median serum AFP level was 6.9 ng/mL (range 1.6–478.3 ng/mL).

During follow-up, 23 patients (4.9%) developed HCC. The cumulative incidences of HCC, which was estimated using the Kaplan–Meier method, were 3.1, 6.6, and 13.4% at 3, 5, and 8 years, respectively (Fig. 2).

Predictive factors for incidence of HCC in all patients

Predictive factors for incidence of HCC in all 382 patients were analyzed using log-rank tests (Table 2). Univariate analysis showed that age ≥70 years ($P = 0.040$), non-SVR ($P < 0.0001$), non-SBR ($P = 0.027$), average ALT integration value ≥40 IU/L ($P = 0.001$), baseline AFP ≥10 ng/mL ($P = 0.005$), average AFP integration value ≥10 ng/mL ($P < 0.0001$), and baseline platelet count <150,000 platelets/μL ($P = 0.001$) were all significantly associated with the incidence of HCC. After multivariate analysis, the only variable remaining in the model was non-SVR (HR 8.413, 95% CI 1.068–66.300, $P = 0.043$).

Table 1 Characteristics of 382 patients with hepatitis C treated with interferon therapy in this study

Age (years)	59.0 (18–81)
[a]Males/females	192/190
Observation period (years)	4.1 (0.1–8.4)
[a]IFN + RBV/PEG-IFN + RBV	69/313
HCV genotype 1/2/unclassified	229/57/96
HCV RNA (log IU/mL)	6.1 (2.3–7.3)
White blood cell count (/μL)	4950 (2050–9970)
Hemoglobin (g/dL)	14.0 (10.3–18.8)
Platelet (10^4/μL)	15.0 (5.3–36.4)
AST (IU/L)	56 (17–244)
ALT (IU/L)	67 (16–416)
Bilirubin (mg/dL)	0.8 (0.3–2.4)
AFP (ng/mL)	6.9 (1.6–478.3)

Qualitative variables ([a]) are shown in number, and quantitative variables expressed as median (range)

IFN interferon, *RBV* ribavirin, *PEG-IFN* pegylated interferon, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *AFP* alpha-fetoprotein

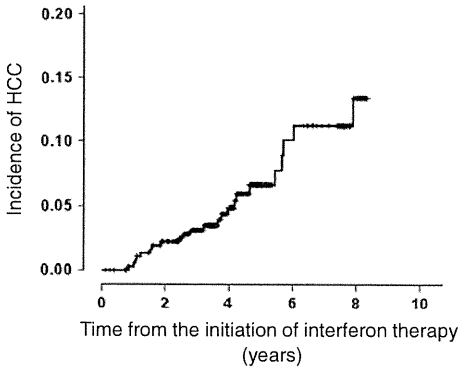

Fig. 2 Incidence of hepatocellular carcinoma (HCC) in 382 patients with hepatitis C who received interferon therapy, estimated using the Kaplan–Meier method

Further, although patients with average AFP integration values ≥10 ng/mL also appeared to have an increased risk of HCC, the difference did not reach statistical significance in the multivariate analysis ($P = 0.050$) (Table 3).

Predictive factors for incidence of HCC in non-SVR patients

Because non-SVR was the only predictive factor across the entire study cohort, to clarify predictive factors for incidence of HCC within this group, the same variables were further analyzed in non-SVR patients alone. By univariate analysis, average AFP integration value ≥10 ng/mL ($P = 0.019$) and baseline platelet count <150,000 ($P = 0.0022$) (Table 2) were again identified as significant predictive factors for incidence of HCC. In addition, male gender was significantly associated with incidence of HCC in non-SVR patients ($P = 0.022$). Multivariate analysis, however, indicated that only two variables were independently associated with incidence of HCC in non-SVR patients: average AFP integration value ≥10 ng/mL (HR 4.039, 95% CI 1.570–10.392, $P = 0.004$), and male gender

Table 2 Univariate analysis of predictive factors for incidence of hepatocellular carcinoma in all 382 and 197 non-SVR patients

Factors	All ($n = 382$)			Non-SVR ($n = 197$)		
	No.	Incidence of HCC ($n = 23$)		No.	Incidence of HCC ($n = 22$)	
		No. (%)	P value[a]		No. (%)	P value[a]
Age (years)						
<70	359	19 (5)	0.040	182	18 (10)	0.089
≥70	23	4 (17)		15	4 (27)	
Sex						
Female	190	8 (4)	0.125	111	8 (7)	0.022
Male	192	15 (8)		86	14 (16)	
HCV genotype						
1	229	12 (5)	0.452	137	12 (9)	0.796
Non-1	57	1 (2)		10	1 (10)	
Virological response						
SVR	185	1 (1)	<0.0001			
Non-SVR	197	22 (11)				
Biochemical response						
SBR	282	12 (4)	0.027	102	11 (11)	0.857
Non-SBR	86	11 (13)		81	11 (14)	
ALT before IFN therapy						
<40	79	2 (3)	0.274	39	2 (5)	0.319
≥40	301	21 (7)		158	20 (13)	
ALT integration value						
<40	238	6 (3)	0.001	79	5 (6)	0.153
≥40	142	17 (12)		118	17 (14)	
AFP before IFN therapy						
<10	230	7 (3)	0.005	102	7 (7)	0.124
≥10	116	14 (12)		75	13 (17)	
AFP integration value						
<10	258	8 (3)	<0.0001	115	8 (6)	0.019
≥10	63	12 (19)		53	11 (21)	
Platelet before IFN therapy						
<150,000	187	20 (11)	0.001	121	19 (16)	0.022
≥150,000	194	3 (2)		76	3 (4)	

[a] Log-rank test

SVR sustained virological response, *SBR* sustained biochemical response, *ALT* alanine aminotransferase, *IFN* interferon, *AFP* alpha-fetoprotein

Table 3 Multivariate analysis of the predictive factors for incidence of hepatocellular carcinoma in all 382 patients

Factors	Hazard ratio	95% CI	*P* value
Virological response			
SVR	1		
Non-SVR	8.413	1.068–66.300	0.043
AFP integration value			
<10	1		
≥10	2.580	0.999–6.659	0.050

SVR sustained virological response, *IFN* interferon, *AFP* alpha-fetoprotein

Table 4 Multivariate analysis of predictive factors for incidence of hepatocellular carcinoma in 197 non-SVR patients

Factors	Hazard ratio	95% CI	*P* value
AFP integration value			
<10	1		
≥10	4.039	1.570–10.392	0.004
Sex			
Female	1		
Male	3.636	1.383–9.563	0.009

AFP alpha-fetoprotein

(HR 3.636, 95% CI 1.383–9.563, $P = 0.009$) (Table 4). There was no significant difference in other variables including those identified as predictive factors in the entire study population (i.e., age, non-SBR, ALT integration value, AFP before interferon therapy) (Table 2).

AFP integration value as a predictive factor for HCC

Further analysis focused on the AFP integration value as this was the strongest predictive factor for incidence of HCC in non-SVR patients. Of the 382 patients, both baseline and AFP integration values were available for 321. These were divided into four groups: (1) AFP "low–low," (2) AFP "low–high," (3) AFP "high–low," and (4) AFP "high–high," for baseline AFP-average AFP integration values, respectively, where "high" is ≥10 ng/mL and "low" is <10 ng/mL. As shown in Fig. 3a, of the 321 patients, 211 (65.7%) showed baseline AFP levels <10 ng/mL. Of these 211, 207 (98%), were in the AFP low–low group, and only four in the AFP low–high groups. Baseline characteristics, including age, gender, serum HCV-RNA, aspartate aminotransferase (AST), ALT, bilirubin, white blood cell, hemoglobin, platelet, observation periods, and number of times of AFP measurement, were not different between AFP high–low group and high–high group. However, AFP-low group, which is a combination of the low–high and low–low groups, showed significantly lower AST level ($P < 0.00001$), lower ALT level ($P < 0.00001$), higher platelet count ($P < 0.00001$), shorter observation period ($P = 0.01448$), and fewer number of times of AFP examination ($P = 0.00035$), compared to both AFP high–high and AFP high–low group. Six patients (2.8%) with baseline AFP levels <10 ng/mL developed HCC in the follow-up period and none of these patients were among the four low–high group patients. Even in patients with high baseline AFP levels, incidence of HCC was only 3.9% among the AFP high–low group (2 of 51 patients). In contrast, 20.3% of patients in the AFP high–high group developed HCC during the follow-up period.

The incidence rate of HCC in three patient groups, "AFP-low" (a combination of the "low–high" and "low–low" groups),"high–low," and "high–high", was estimated using the Kaplan–Meier method and compared using log-rank tests (Fig. 3b). The rate of HCC incidence was significantly higher in the AFP high–high group compared to both the AFP high–low group and patients with low baseline AFP levels ($P = 0.009$ and 0.001, respectively). There was no significant difference between patients with low baseline AFP levels and the AFP high–low group. The 7-year incidence rate of HCC was 32.3% in the AFP high–high group, compared to only 6.6% in the AFP high–low group, and 8.1% in all patients with low pre-treatment levels.

Discussion

It is well recognized that the most effective strategy for the prevention of HCC development in patients with chronic hepatitis C is likely to be the complete elimination of the HCV infection accompanied by the resultant normalization of liver function [7, 12, 13, 15, 16, 19]. Indeed, we confirmed here that non-SVR is the most significant predictive factor for incidence of HCC in patients receiving interferon therapy for chronic hepatitis C. However, it should be noted that the risk of HCC, even in non-SVR patients, differs between individuals. In the current study, we identified AFP integration value and male gender as independent risk factors for incidence of HCC in non-SVR patients. The incidence of HCC was significantly reduced in individuals with average AFP integration values < 10 ng/mL after interferon therapy, which suggests that the decrease of AFP by interferon therapy lowers the risk of developing HCC. Indeed, even where patients had high baseline AFP levels, incidence of HCC was reduced when the AFP integration value decreased after interferon therapy. Thus, our current findings identify AFP integration value as a useful predictive marker of HCC development in non-SVR patients.

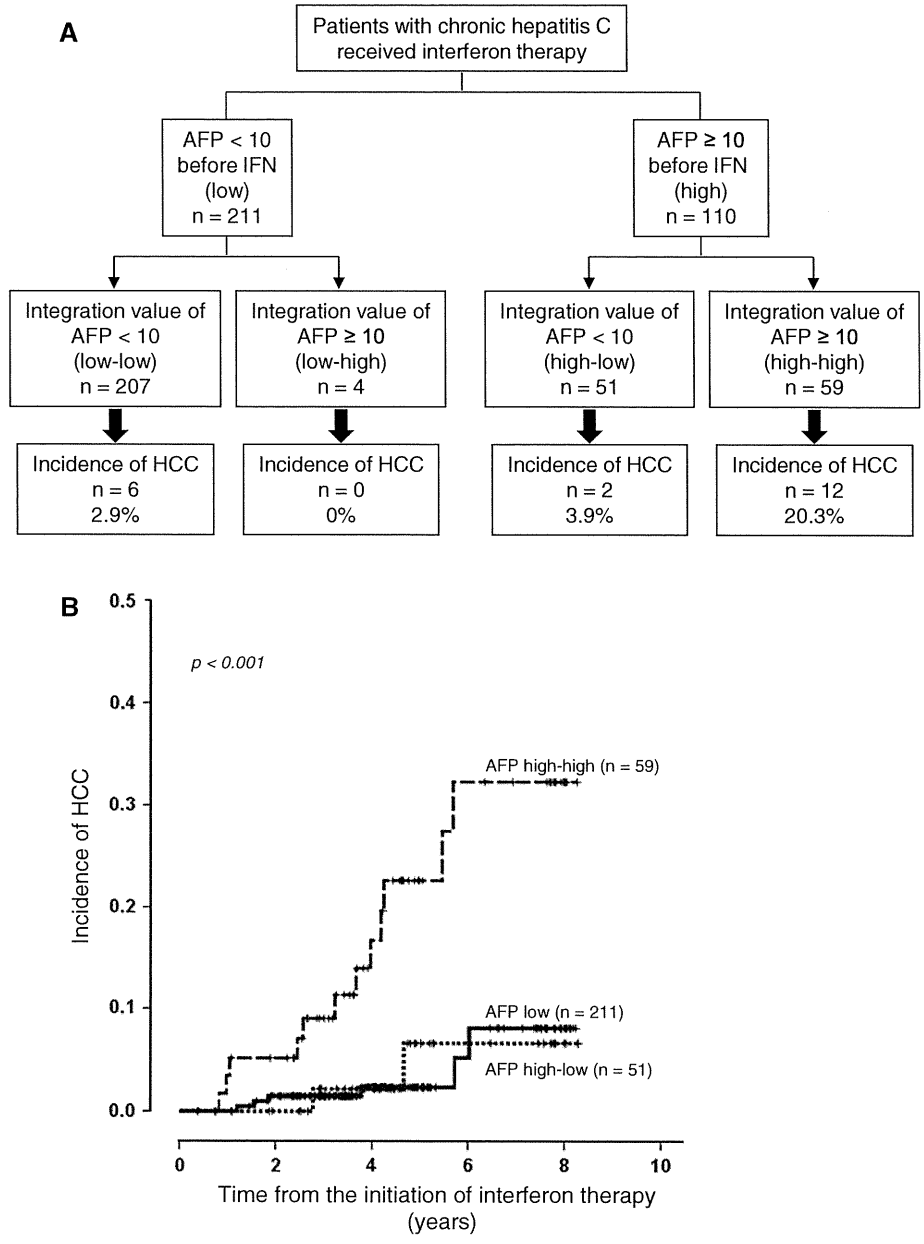

Fig. 3 AFP integration value as a predictive factor for HCC. **a** *Flow diagram* showing the number of patients (*n*) classified by baseline alpha-fetoprotein (AFP) levels before interferon (IFN) therapy and average AFP integration value, and the incidence of hepatocellular carcinoma (HCC) of each group. **b** Kaplan–Meier estimates of the incidence of HCC. *Solid line* AFP-low group (AFP levels before interferon therapy <10 ng/mL); *dotted line* AFP high–low group (baseline AFP levels ≥10 ng/mL, average AFP integration value <10 ng/mL); *dashed line* AFP high–high group (both baseline and average AFP integration values ≥10 ng/mL)

Data from several previous studies suggest that the continuous normalization of alanine aminotransferase (ALT) levels by interferon therapy can reduce the risk of HCC development [36–39]. In addition, one recent study suggested that the ALT integration value is a predictive factor for HCC [35]. In contrast to published data (22), our multivariate analysis did not identify the ALT integration value as a significant predictive factor for HCC incidence, although it was identified as significant by univariate analysis in all 382 patients. Since the previous study did not evaluate AFP levels as a factor for prediction of HCC [35], our results indicate that the AFP integration value is superior to that of ALT as a predictive factor for incidence of HCC. We do not know the reason for this result, but it is speculated that significance of AFP as a marker of hepatic regeneration resulted in the more accurate prediction of hepatocarcinogenesis by integration value of AFP than that of ALT.

As AFP is a diagnostic marker for the existence of HCC, high integration value of AFP in the present study might be a result of HCC development. However, we concluded that the high AFP integration values in patients who developed HCC were not caused by a result of existence of HCC, because of the following two reasons. First, the last AFP values before detection of HCC were not the highest level in the follow-up periods in 19 of 23 patients who developed

HCC, suggesting that the AFP was not produced by the developing HCC in these patients. Second, to exclude the influence of the remaining four patients whose last AFP levels were the highest in the follow-up periods, we analyzed the same statistical analysis by using average AFP integration values excluded the last two examinations of AFP before the detection of HCC. The results of the analysis also showed average integration value of AFP as a significant predictive factor for incidence of HCC.

Male gender was also identified as an independent risk factor for HCC in non-SVR patients in this study. Several reports have shown that men are at a higher risk of developing HCC than women [6, 10, 33, 40, 41]. The male gender also appears to be a risk factor for more severe disease and a greater risk of developing cirrhosis in chronic hepatitis C [42]. Although the association of male gender with the risk of HCC is as yet unexplained, hormonal or genetic factors may lead to increased risk for HCC and cirrhosis in men as previously discussed [10].

In conclusion, a decrease in the AFP integration value predicts reduced incidence of HCC in patients with hepatitis C receiving interferon therapy. Further prospective studies with a larger number of patients are required to validate the significance of these findings.

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

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ORIGINAL ARTICLE—LIVER, PANCREAS, AND BILIARY TRACT

Risk factors for recurrence after transarterial chemoembolization for early-stage hepatocellular carcinoma

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Abstract
Background Radiofrequency ablation (RFA) is a standard therapy for the treatment of hepatocellular carcinoma (HCC) with 3 or fewer tumors of up to 3 cm (early-stage HCC); when RFA is unsuccessful or unfeasible, transcatheter arterial chemoembolization (TACE) has often been performed. However, little information about the outcome of TACE for early-stage HCC has been reported and it is hard to decide whether to perform additional treatment following TACE in these difficult conditions. The aim of this study was to determine the risk factors for local or intrahepatic distant recurrence after TACE in early-stage HCC.
Methods Among 1,560 newly diagnosed HCC patients who were admitted to Okayama University Hospital, 43 patients with early-stage HCC who received only TACE in at least one nodule were enrolled in this study. We analyzed the risk factors for local and distant recurrence by the Cox proportional hazard model.
Results The local recurrence rates and intrahepatic distant recurrence rates at 3 months, 6 months, and 1 year were 18.6, 33.4, and 61.8%, and 2.8, 2.8, and 10.2%, respectively. Among 12 parameters examined as possible risk factors for recurrence, heterogeneous Lipiodol uptake (risk ratio 3.38; 95% confidence interval 1.14–10.60) and high serum des-gamma-carboxy prothrombin (DCP) (2.58; 1.03–7.14) were significantly correlated with local recurrence, and the presence of multiple tumors (10.64; 1.76–93.75) was significantly correlated with intrahepatic distant recurrence.
Conclusions Heterogeneous Lipiodol uptake, high serum DCP, and multiple tumors are risk factors for recurrence in patients with early-stage HCC who have undergone palliative TACE.

Keywords Hepatocellular carcinoma · Small HCC · TACE · Early-stage HCC

Introduction

Hepatocellular carcinoma (HCC) has become increasingly detected at an early stage with the growing use of surveillance systems. The guidelines established by the American Association for the Study of Liver Disease (AASLD) [1] and the European Association for the Study of the Liver (EASL) [2], and the Japanese "Evidence-Based Guidelines" recommend local treatment [3, 4], such as radiofrequency ablation (RFA) or operation, for HCCs with 3 or fewer tumors of up to 3 cm in patients with good liver functional reserve and performance status. Additionally, RFA combined with transcatheter arterial chemoembolization (TACE) has been reported to be an efficient and safe treatment that provides overall survival rates similar to those achieved with surgical resection [5–7]. If the HCC is a hypervascular tumor, HCCs with 3 tumors or fewer of up to 3 cm are often subjected to sequential TACE followed by RFA, percutaneous ethanol injection therapy (PEIT), or operation regardless of the size because TACE is expected to enhance the efficacy of local therapy by reducing arterial blood flow [8].

Occasionally, various factors such as poor liver functional reserve, difficult location for RFA treatment, and the presence

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