Table 2. Clinical data at diagnosis of extrahepatic metastasis

	Lung ($n = 92$)	Bone ($n = 60$)	Lymph node ($n = 49$)	Adrenal gland ($n = 23$)	P
Age (year)*†	65.6 ± 9.6	68.0 ± 7.9	67.5 ± 7.9	65.7 ± 9.3	0.47
Men, n (%)	72 (78.3%)	45 (75.0%)	37 (75.5%)	18 (78.3%)	0.96
Symptomatic, n (%)	10 (10.9%)	46 (76.7%)	3 (6.1%)	1 (4.3%)	< 0.001
Diagnostic modality, n (%)					
Plain X-ray	45 (48.9%)	2 (3.3%)	0 (0.0%)	0 (0.0%)	
CT/MRI	46 (50.0%)	29 (48.3%)	45 (91.8%)	22 (95.7%)	
Scintigraphy	1 (1.1%)	29 (48.3%)	1 (2.0%)	0 (0.0%)	
Ultrasound	0 (0.0%)	0 (0.0%)	3 (6.1%)	1 (4.3%)	
HBsAg/anti-HCVAb, n (%)					
+/−	19 (20.7%)	5 (8.3%)	3 (6.1%)	4 (17.4%)	0.054
−/+	63 (68.5%)	49 (81.7%)	41 (83.7%)	18 (78.3%)	0.133
+/+	4 (4.3%)	3 (5.0%)	3 (6.1%)	0 (0%)	0.70
−/−	6 (6.5%)	3 (5.0%)	2 (4.1%)	1 (4.3%)	0.93
Intrahepatic lesion, n (%)	82 (89.1%)	53 (88.3%)	39 (79.6%)	20 (87.0%)	0.43
Massive type	9 (9.8%)	1 (1.7%)	3 (6.1%)	3 (13.0%)	0.18
Vascular invasion	23 (25.0%)	9 (15.0%)	10 (20.4%)	5 (21.7%)	0.53
AFP > 100 ng/ml, n (%)	70 (76.1%)	33 (55.0%)	28 (57.1%)	13 (56.5%)	0.041
DCP > 100 mAU/ml‡, n (%)	60 (65.2%)	33 (57.9%)	20 (40.8%)	12 (52.2%)	0.046
AFP-L3 > 15%§, n (%)	57 (75.0%)	29 (61.7%)	25 (67.6%)	12 (66.7%)	0.47
Coexisting extrahepatic lesion					
Lung		17 (28.3%)	16 (32.7%)	6 (26.1%)	
Bone	19 (20.7%)	–	5 (10.2%)	5 (21.7%)	
Lymph Node	17 (18.5%)	6 (10.0%)	–	3 (13.0%)	
Adrenal Gland	7 (7.6%)	4 (6.7%)	3 (6.1%)	–	
Others	11 (12.0%)	3 (5.0%)	3 (6.1%)	1 (4.3%)	

*At diagnosis of extrahepatic metastasis.

†Mean + SD.

‡Missing in 3.

§Missing in 46, including overlaps.

AFP, α-fetoprotein; AFP-L3, lens culinaris agglutinin-reactive fraction of AFP; CT, computed tomography; DCP, des-γ-carboxy prothrombin; HBsAg, hepatitis B surface antigen; HCVAb, hepatitis C virus antibody; MRI, magnetic resonance imaging; SD, standard deviation.

carcinoma (29). HCC cells presumably reach the lungs through hepatic vein and reside in the capillary network. The vertebrae were the most frequent site of osseous metastasis (37.5%), to which vertebral venous plexus is reportedly responsible (32, 33). Vertebral metastasis bears clinical importance because it may cause paraplegia. Metastasis to the adrenal gland is theoretically through systemic circulation and thus chances of metastasis to right and left glands are equal (34). However, in the current study, as in previous reports, adrenal metastasis was much more frequent to the right gland than to the left (35, 36).

Opportunities for the diagnosis of extrahepatic metastases could be classified into three categories. The first category was chance detection by abdominal CT or chest X-ray that were routinely taken on each admission for the treatment of intrahepatic recurrence or other causes. Those examinations may not have been performed as meticulously at terminal stages, resulting in possible underestimation of overall incidence of extrahepatic metastasis. The second category was the detection by systemic scrutiny for elevated tumour biomarkers in spite of well-controlled intrahepatic lesions. In the current study, 9.1% cases of extrahepatic metastasis were diagnosed in the absence of viable intrahepatic lesions. The last category was the detection owing to specific symptoms such as local pain or dyspnoea. About 80% cases of osseous metastasis were detected based on subjective symptoms.

Response to treatment is undoubtedly a strong predictor for prognosis of HCC patients as well as other malignancies (37, 38). The complete response to treatment strongly reduces the risk for extrahepatic metastasis. However, the effect size was reduced in the multivariate analysis, although the variable retained significance in the final model after stepwise variable selection. This may be owing to the strong correlation between treatment response and tumour-related factors such as tumour size, number of tumour nodules and presence of vascular invasion.

The choice of treatment modalities may affect the risk of extrahepatic metastasis (39–41). Indeed, it was

Table 3. Predictors for extrahepatic metastasis: univariate analysis

Variables*	Relative risk (95% CI)	*P*
Age > 65 years	0.99 (0.97–1.01)	0.29
Men	1.12 (0.76–1.66)	0.57
HBsAg, positive	3.92 (1.30–11.82)	0.015
Anti-HCVAb, positive	2.91 (1.07–7.92)	0.036
Albumin (g/dl)		
< 2.8	1	
2.8–3.5	2.31 (0.57–9.35)	0.24
> 3.5	1.97 (0.49–7.95)	0.34
Bilirubin (mg/dl)		
≤ 1	1	
1.1–2.0	1.12 (0.74–1.71)	0.58
> 2	0.57 (0.14–2.30)	0.43
Platelet count > 10×10^4/μl	1.32 (0.92–1.90)	0.13
AST > 80 IU/l	1.12 (0.77–1.62)	0.55
ALT > 80 IU/l	1.29 (0.90–1.86)	0.17
Child–Pugh classification		
A	1	
B/C	0.90 (0.60–1.33)	0.59
Tumour diameter (cm)		
≤ 2.0	1	
2.1–5.0	2.04 (1.30–3.18)	0.002
> 5.0	4.11 (2.24–7.53)	< 0.001
Number of nodules		
Single	1	
2–3	1.63 (1.09–2.45)	0.019
> 3	3.20 (2.02–5.09)	< 0.001
Vascular tumour invasion	7.80 (3.14–19.4)	< 0.001
AFP (ng/ml)		
≤ 100	1	
101–400	1.74 (1.07–2.82)	0.026
> 400	4.14 (2.63–6.52)	< 0.001
DCP (mAU/ml)		
≤ 100	1	
101–400	2.77 (1.72–4.45)	< 0.001
> 400	2.63 (1.51–4.60)	< 0.001
AFP-L3 (%)		
≤ 15	1	
15.1–40	2.49 (1.05–5.92)	0.039
> 40	5.59 (3.21–9.72)	< 0.001
Complete response to treatment	0.307 (0.204–0.460)	< 0.001

*Data at initial treatment.

AFP, α-fetoprotein; AFP-L3, lens culinaris agglutinin-reactive fraction of AFP; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DCP, des-γ-carboxy prothrombin; HBsAg, hepatitis B surface antigen; HCVAb, hepatitis C virus antibody.

Table 4. Predictors for extrahepatic metastasis: multivariate analysis

Variables*	Relative risk (95% CI)	*P*
HBsAg, positive	2.58 (1.40–4.75)	0.002
Anti-HCVAb, positive	2.32 (1.24–4.34)	0.008
Diameter (cm)		
≤ 2.0	1	
2.1–5.0	1.76 (1.11–2.77)	0.015
> 5.0	2.46 (1.27–4.75)	0.008
Number of nodules		
1	1	
2–3	1.51 (1.00–2.29)	0.047
> 3	1.75 (1.00–3.08)	0.05
Vascular tumour invasion	3.20 (1.05–9.83)	0.04
AFP > 100 ng/ml	1.61 (0.87–2.95)	0.12
DCP > 100 mAU/ml	1.52 (0.93–2.49)	0.095
Complete response to treatment	0.600 (0.345–1.04)	0.071

*Data at initial treatment.

AFP, α-fetoprotein; DCP, des-γ-carboxy prothrombin; HBsAg, hepatitis B surface antigen; HCVAb, hepatitis C virus antibody.

extremely rare that the first recurrence occurred as an extrahepatic metastasis when curative ablation had been performed. However, because patients with HCC usually receive multimodality treatment during clinical course, it is difficult to determine which treatment is associated with extrahepatic metastasis. In the current study, the majority of patients had received TACE before extrahepatic metastasis was diagnosed. However, the choice of treatment modalities was highly dependent on tumour-related factors such as tumour size, number of tumour nodules and vascular invasion. Those treated with TACE had larger tumour and more tumour nodules than those treated with medical ablation, which makes analysis concerning treatment modality rather difficult.

The predictors for extrahepatic metastasis the current study revealed to be significant, such as the size and number of HCC nodules, the presence of vascular tumour invasion, or seropositivity of tumour biomarkers, are similar to the factors shown to be associated with prognosis in general in previous studies (42–44). Because we used in analysis the data obtained at the time of initial treatment, the relative importance of each factor may have changed through the course of disease. In particular, at least one of the three tumour biomarkers, AFP, DCP or AFP-L3, was positive in 92.7% of cases at the diagnosis of extrahepatic metastasis, in contrast to the positivity of 42.0% at the initial treatment. This may reflect the degree of malignancy enhanced during the time course of disease. Viral markers, HBsAg and anti-HCVAb, were associated with the risk of extrahepatic metastasis probably because they are also risk factors of intrahepatic HCC recurrence.

In contrast to the relatively rare incidence of extrahepatic metastasis, intrahepatic recurrence is quite frequent with HCC. Whereas some cases of intrahepatic recurrence are attributable to metachronous *de novo* carcinogenesis, the risk of intrahepatic

metastasis via the portal vein has been emphasized for HCC nodules > 2.0 cm in diameter. This is in marked contrast to the fact that recurrence of HCC after liver transplantation is rare if HCC meets the Milan criteria, i.e. a solitary nodule not > 5.0 cm in diameter or less than four nodules each not > 3.0 cm. The present study has shown that the commonest route of extrahepatic metastasis is via the hepatic vein. Metastasis through the hepatic vein seems to occur at later stages than does metastasis through the portal vein. Because most patients in the current study were treated for intrahepatic nodules more than once, we could not analyse the size of tumour critical to extrahepatic metastasis. However, the large seropositivity of tumour markers at extrahepatic metastasis suggests an advanced degree of malignancy.

In conclusion, this large-scale study has shown that the incidence of extrahepatic metastasis of HCC was approximately 13% in 5 years after medical treatment. The extent of hepatic HCC lesions, tumour biomarkers and the presence of viral hepatitis were revealed to be the significant predictors of extrahepatic metastasis. Elevation of tumour biomarkers in spite of well-controlled hepatic lesions may indicate extrahepatic metastasis, frequent location of which included lung, bone, lymph node and adrenal gland. Symptoms such as dyspnoea or bone pain may be caused by extrahepatic metastasis of HCC.

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Neoplastic Seeding After Radiofrequency Ablation for Hepatocellular Carcinoma

Jun Imamura, M.D., Ph.D., Ryosuke Tateishi, M.D., Ph.D., Shuichiro Shiina, M.D., Ph.D., Eriko Goto, M.D., Takahisa Sato, M.D., Takamasa Ohki, M.D., Ph.D., Ryota Masuzaki, M.D., Ph.D., Tadashi Goto, M.D., Ph.D., Hideo Yoshida, M.D., Ph.D., Fumihiko Kanai, M.D., Ph.D., Keisuke Hamamura, M.D., Ph.D., Shuntaro Obi, M.D., Ph.D., Haruhiko Yoshida, M.D., Ph.D., and Masao Omata, M.D., Ph.D.
Department of Gastroenterology, The University of Tokyo Hospital, Tokyo, Japan

BACKGROUND: Neoplastic seeding reportedly occurs in up to 12.5% of patients treated with radiofrequency ablation (RFA) for hepatocellular carcinoma (HCC). The aim of this study is to assess the incidence, risk factors, and prognosis of neoplastic seeding after RFA among a large number of patients with a long-term follow-up.

METHOD: From February 1999 to December 2004, 1,031 patients underwent a total of 1,845 treatments with RFA for a total of 3,837 HCC nodules. The following variables were assessed to elucidate the risk factors of neoplastic seeding: age, sex, positivity for viral markers, tumor size, number of tumor nodules, number of RFA sessions, tumor location, percutaneous biopsy prior to RFA, alpha-fetoprotein (AFP), des-gamma-carboxy prothrombin (DCP) and *lens culinaris* agglutinin-reactive fraction of AFP (AFP-L3) levels, and the degree of tumor differentiation.

RESULTS: Neoplastic seeding was detected in 33 patients (3.2% per patient) at intervals of 4.8–63.8 (median, 15.2) months after RFA. On multivariate logistic regression analysis, only the poor differentiation degree was associated with the risk of neoplastic seeding ($P = 0.012$). Of tumor factors, tumor size, and AFP, DCP, and AFP-L3 levels were significantly associated with the poor differentiation degree. The cumulative survival rates 1 and 2 yr after the detection of neoplastic seeding were 86% and 47%, respectively.

CONCLUSION: Poor differentiation degree was the risk factor of neoplastic seeding after RFA for HCC. The surrogate markers for poor differentiation degree were larger tumor size and elevated tumor marker levels. Indication for RFA should be carefully considered for HCC patients under these conditions.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is a common malignancy worldwide, showing increasing incidence in the United States and elsewhere (1, 2). Current options for the treatment of this cancer consist of surgical resection, transcatheter arterial chemoembolization (TACE), and percutaneous ablation therapy. Although surgical resection is usually considered as the first-choice treatment, few patients affected by HCC are the ideal candidates for surgical resection because of impaired background liver function as a result of chronic hepatitis B or C (3). TACE is feasible even with impaired liver function reservoir, but complete elimination of whole lesions is difficult to attain with TACE only. Orthotopic liver transplantation (OLT) is a strategy that can treat both cancer and liver dysfunction, and indeed has shown excellent survival in patients at an early stage of the cancer (*e.g.*, single nodule of $\leq$5 cm in diameter or less than three nodules of $\leq$3 cm in diameter) (4). However, with increasing demand for donor tissue but a limited supply, the waiting time now exceeds 1 yr in Europe and the United States (5, 6).

Radiofrequency ablation (RFA) was introduced as an alternative locoregional therapy to ethanol injection, which can achieve high local cure without deteriorating background liver function (7–10). RFA has been shown to be superior to ethanol injection in terms of local cure, and it can achieve better overall survival (11–14). However, various complications associated with RFA have been reported, although infrequently, as the number of treated patients has been increased (10, 15, 16). Among them, neoplastic seeding is one of the most unfavorable complications that can be critical especially for those who are waiting for liver transplantation (17).

Thus, we conducted this study to elucidate the incidence of neoplastic seeding after RFA, assess its characteristics, and evaluate the risk factors as experienced in a single high-volume center.

PATIENTS AND METHODS

Patients

Between February 1999 and December 2004, 1,031 patients with HCC were treated with RFA at the authors' department. All of these patients were consecutively included in this study. Inclusion criteria for RFA were as follows: total bilirubin concentration lower than 3 mg/dL, platelet count no less than $50 \times 10^3/mm^3$, and prothrombin activity no less than 50% (approximately equal to 1.5 international normalized ratio [INR]). Ascites should be controlled beforehand by diuretics. Patients with portal vein tumor thrombosis or extrahepatic metastasis were excluded. We also excluded patients who had a history of bilioenteric anastomosis or sphincterotomy, which are considered as a high risk for hepatic abscess formation. In general, we performed RFA on patients with three or fewer lesions, all of which were 3 cm or smaller in diameter. However, we performed ablation also on patients who did not meet these conditions when complete ablation could be anticipated in all tumors without deteriorating liver function (18). Written informed consent was obtained from each enrolled patient, and the protocol was approved by the institutional review board.

Technical Terms

We defined a session as a single intervention episode that consists of one or more ablations performed on one or more tumors, and a treatment as the completed effort to ablate one or more tumors that consists of one or more sessions according to the working party report on the image-guided tumor ablation (19). To assess the depth of tumor location as a possible risk factor for neoplastic seeding, we categorized the location into the following two groups: *direct subcapsular insertion* when the tumor was located just under the surface of the liver and the ablation needle was directly inserted to the tumor, and *deep* when otherwise. When a tumor was located just under the liver surface but the needle was approached from the opposite direction through nontumorous tissue, the location was defined as deep. Subcapsular location of tumors, regardless of the route of needle insertion, was evaluated in a distinct analysis.

Diagnosis of HCC

HCC was diagnosed based on typical findings on ultrasonography and computed tomography (CT) (hyperattenuation in the arterial phase and hypoattenuation in the portal-venous phase) (20). The diagnosis of HCC was also confirmed histopathologically with ultrasound-guided biopsy in the majority of patients. Until 2004, we performed tumor biopsy before almost every RFA treatment. Afterward we restricted biopsy to cases where definite diagnosis could not be made on dynamic CT. Specimens for histological evaluation were obtained by ultrasound-guided core needle biopsy using a 20-gauge needle (Bard Monopty, C.R. Bard Inc., Covington, GA). Histopathological grading of tumor differentiation was done according to the criteria of Edmondson *et al.* (21).

Radiofrequency Ablation

A 17-gauge cooled-tip electrode with a 2- or 3-cm exposed tip was inserted under real-time ultrasound guidance. The electrode was connected to a 500 kHz RF Generator (Radionics, Burlington, MA) (22, 23). A tip temperature of 10–20°C was maintained by a peristaltic pump infusing chilled saline solution. After insertion of the electrode into the lesion, 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 140 W at a rate of 20 W/min. When a rapid increase in impedance was observed during thermal ablation, we minimized the output for 15 s and restarted the emission at a lower output. The duration of a single ablation was 12 min for the 3-cm electrode and 6 min for the 2-cm electrode. After RF exposure, the pump was stopped and the temperature of the needle tip was measured. When the temperature was below 65 °C, additional ablation was performed. When the target nodule was larger than 2 cm in diameter, we performed multiple ablations. When the total ablation time in a treatment took more than 60 min, we divided a treatment into two or more sessions in consideration (10). After 1 to 2 sessions of RFA, dynamic CT was performed 1 to 3 days after the last session with a slice thickness of 5 mm to evaluate treatment efficacy. The interval between the initiation of contrast material infusion and CT image recording was 30 s and 120 s for single detector-row spiral CT (Highspeed Advantage; GE Medical Systems, Milwaukee, WI) and 25 s, 40 s, and 120 s for multidetector-row CT (LightSpeed QX/I; GE Medical Systems). The images were presented after axial reconstruction with a slice thickness of 5 mm. Complete ablation was defined on the CT findings as nonenhancement in the entire lesion with a safety margin in the surrounding liver parenchyma. Patients received additional sessions of ablation until complete ablation was confirmed in each nodule.

The follow-up consisted of bimonthly blood tests and monitoring of tumor markers at the outpatient clinic, and ultrasonography and dynamic CT scan were performed every 4 months. The observation up to December 31, 2006 was used in this analysis.

Neoplastic Seeding

The diagnosis of neoplastic seeding was made by imaging modalities, which was usually performed as surveillance for intrahepatic recurrence. A newly detected tumor attached to the peritoneum or the pleura was considered as neoplastic seeding. The incidence of neoplastic seeding was assessed on the basis of the number of patients. Survival after the diagnosis of tumor seeding was assessed according to the Kaplan-Meier method.

Statistical Analysis

Risk factors for neoplastic seeding were analyzed on treatment basis. To elucidate the risk factors of neoplastic seeding, the following variables were assessed: age, sex, positivity for hepatitis B surface antigen (HBsAg), positivity for anti-hepatitis C antibody (anti-HCVAb), tumor size,

number of tumor nodules, number of RFA sessions, number of insertions of the RFA needle, tumor location, percutaneous biopsy prior to RFA, the level of alpha-fetoprotein (AFP) and des-gamma-carboxy prothrombin (DCP) and *lens culinaris* agglutinin-reactive fraction of AFP (AFP-L3), and the degree of tumor differentiation. Continuous variables were compared between those with and without neoplastic seeding by Student's *t*-test. χ^2 test or Fisher's exact test was applied to compare nominal valuables between the groups. Factors showing P value of less than 0.1 as a predictor were further analyzed with a multivariate logistic regression model using stepwise selection of variables based on Akaike information criterion (AIC) (24). To find surrogate markers for differentiation of tumor, which requires percutaneous biopsy, we applied multivariate logistic regression analysis with poor differentiation (Edmondson grade 3 or greater) as the dependent variable and the following factors as independent variables: size and number of tumor nodules and AFP, DCP, and AFP-L3 values. The differences with a P value of less than 0.05 were considered statistically significant. All statistical analyses were performed with S-plus 2000 (Insightful Co., Seattle, WA).

RESULTS

As 459 of 1,031 patients received two or more treatments during the study period because of tumor recurrence, the total number of treatments was 1,845, consisting of 3,585 sessions of RFA to 3,837 nodules. The baseline characteristics of patients were summarized in Table 1. When one patient received more than one treatment, the data on the initial treatment were adopted. The mean age of the patients was 67.3 yr (range 42.3–91.5). The patients were male dominant (68.0%) and the majority was HCV positive (80.3%). The median tumor size was 2.5 (range 0.8–9.7) cm.

During the follow-up period (median 35.3 months; range 0.6–95.8 months), neoplastic seeding was diagnosed in 33 patients (3.2% per patient, or 1.8% per treatment), with an interval time of 4.8–63.8 (median 15.2) months after RFA. The number of seeding nodule was 1 in 22 cases, 2 or 3 in 2 cases, and 4 or more in 9 cases. Twenty-one cases of seeding occurred on the line of previous RFA needle insertion, and 12 cases occurred distantly. Seeding was located on the peritoneum in 25 patients, on the pleura in 7 patients, and in the abdominal wall in 1 patient. In the 25 patients with seeding on the peritoneum, the seeding was located adjacent to the surface of the liver except one patient who showed seeding in the pelvic cavity.

We analyzed risk factors for neoplastic seeding not on patient basis but on treatment basis because most variables differed on each treatment. Univariate analysis showed that the following factors were associated with neoplastic seeding: younger age ($P = 0.02$), HBsAg positivity ($P = 0.003$), the absence of anti-HCVAb ($P = 0.046$), and poorly differentiated tumor ($P = 0.003$), whereas sex, tumor size, tumor number, number of sessions, number of insertions of RFA needle, tumor location, and biopsy prior RFA showed no significant association (Table 2). Multivariate analysis with stepwise variable selection revealed that the best model for the prediction of neoplastic seeding included poorly differentiated tumor (odds ratio [OR], 3.18; 95% confidence interval [CI] 1.3–7.8) and AFP-L3 value higher than 15% (OR 1.77; 95% CI 0.723–4.35) (Table 3). The logistic regression analysis to find surrogate marker for poor differentiation showed that larger tumor and higher value of tumor markers were significantly associated with the poor differentiation (Table 4).

Of the 33 patients with neoplastic seeding, 32 patients were treated for the tumor seeding: resection in 16, RFA in 12, ethanol injection in 2, radiation in 5, and chemotherapy in 3 (6 patients received a combination therapy of resection, RFA, radiation, or chemotherapy). By the end of the follow-up, 21 patients with neoplastic seeding died. The causes of death were cancer progression in 18, liver failure in 1, and malignancy unrelated to liver in 2 patients. Among them, 6 patients died from the growth of seeding nodules. Detailed causes of death were peritonitis carcinomatosa in 3, tumor rupture in 1, and cachexia because of HCC progression in 2 patients. In the remaining 15 patients with neoplastic seeding, seeding nodules were under control (curatively resected

Table 1. Baseline Characteristics of the Patients (N = 1,031)

Variables (%)	
Mean age (yr)*	67.3 ± 8.1
Male gender	701 (68.0%)
Etiology	
HBs-Ag positive only	103 (10.0%)
HCV-Ab positive only	810 (78.6%)
Both positive	18 (1.7%)
Both negative	100 (9.7%)
Alcoholic consumption >80 g/day	162 (15.7%)
Child-Pugh score	
Class A	700 (67.9%)
Class B	316 (30.6%)
Class C	15 (1.5%)
Tumor size (cm) †	2.5 (1.9–3.2)
Tumor number	
Single	514 (49.9%)
2–3	385 (37.3%)
>3	132 (12.8%)
Number of sessions	
Single	399 (38.7%)
2	335 (32.5%)
>2	297 (28.8%)
Tumor location	
Direct subcapsular insertion	163 (15.8%)
Deep	868 (84.2%)
Tumor marker	
AFP>100 ng/mL	234 (22.7%)
DCP>100 mAU/mL	152 (14.7%)
AFP-L3 >15%	231 (22.4%)

*Values are expressed as mean ± standard deviations.
† Values are expressed as median, first, and third quartile.

Table 2. Characteristics of Patients With/Without Neoplastic Seeding

Variable	Seeding Was Identified (N = 33)	Seeding Was Not Identified (N = 1,812)	*P* Value
Age, yr	65.0 ± 9.5	68.2 ± 7.9	0.02
Male gender	26 (78.8%)	1,256 (69.3%)	0.39
HBs-Ag positive only	8 (24.2%)	165 (9.1%)	0.003
HCV-Ab positive only	22 (66.7%)	1,459 (80.5%)	0.046
Both positive	0 (0%)	30 (1.7%)	0.46
Both negative	3 (9.1%)	158 (8.7%)	0.94
Tumor size, cm	2.5 ± 1.0	2.4 ± 1.1	0.81
Number of tumors	2.1 ± 1.4	2.1 ± 1.4	0.96
Number of sessions	1.9 ± 1.1	1.9 ± 1.1	0.73
Number of insertions	5.3 ± 2.8	4.4 ± 2.2	0.29
Direct subcapsular insertion	8 (24.2%)	328 (18.1%)	0.23
Subcapsular location	21 (63.4%)	1,087 (60.0%)	0.72
Biopsy performed	22 (66.7%)	1,091 (60.2%)	0.28
Poorly differentiated tumor*	8 (36.4%)	143 (13.1%)	0.003
AFP >100 ng/mL	7 (21.2%)	424 (23.4%)	0.77
DCP >100 mAU/mL	7 (21.2%)	266 (14.7%)	0.29
AFP-L3 >15%	11 (33.3%)	374 (20.6%)	0.08

*Among 1,113 treatments (on 774 patients) in which biopsy was performed.

or did not affect survival) throughout the follow-up period. The cumulative survival rates of the 33 patients after the diagnosis of neoplastic seeding at 1 and 2 yr were 81% and 45%, respectively (Fig. 1).

DISCUSSION

RFA has been proposed as a promising alternative to conventional ethanol injection and shown to be more effective in terms of local efficacy (11, 12, 14). The safety of RFA, however, was questioned following the reported occurrence of neoplastic seeding in 12.5% of patients with HCC (4 in 32 patients) (17). Llovet *et al.* concluded that RFA with a cooled-tip needle should not be considered as a curative treatment for HCC or an adjuvant therapy before liver transplantation. However, this extremely high incidence of neoplastic seeding was contradicted by several investigators, who reported lower incidence from 0% to 0.9% (15, 25, 26). Livraghi *et al.* reported that seeding was identified in 12 patients (0.9%) among a total of 1,314 treated cases during the median follow-up period of 37 months (26). The incidence of 33 events in 1,031 patients (3.2%) in this study was rather high as compared with the latter reports. The difference may be because of more advanced tumor stage (21% patients had nodules larger than 3 cm in diameter) in this study, where we often employed strategy of multiple electrode insertion to achieve complete response (10). Alternatively, the rate of complications may have been underestimated in multicenter survey with questionnaire. In contrast, all complications analyzed in this study had been recorded in the database immediately after their identification (27).

Table 3. Multivariate Logistic Regression

Variable	Odds Ratio (95% CI)	*P* Value
Poorly differentiated tumor	3.18 (1.3–7.8)	0.012
AFP-L3 >15%	1.77 (0.723–4.35)	0.21

Table 4. Factors Correlated With Poorly Differentiated HCC

Variable	Odds Ratio (95% CI)	*P* Value
Tumor size		0.018
2.1–5.0 cm	1.57 (1.08–2.28)	
>5.0 cm	2.37 (1.10–5.08)	
Number of tumors >3	1.30 (0.84–2.00)	0.25
AFP >100 ng/ml	2.54 (1.77–3.65)	<0.001
DCP > 100 mAU/ml	1.76 (1.16–2.66)	0.01
aAFP-L3 >15%	2.96 (2.05–4.26)	<0.001

Among the 1,113 cases on which biopsy were performed, 151 cases had poorly differentiated HCC.

According to the previous reports, subcapsular tumor location, poor degree of differentiation, high baseline AFP levels, and tumor biopsy prior to RFA were associated with neoplastic seeding (17, 26). Also in this study, poor differentiation degree was significantly associated with neoplastic seeding in multivariate analysis. It is possible that poorly differentiated HCC grows more rapidly, and thus the seeding could be identified earlier. Another possibility is that cancer cells may be prone to migrate through needle tract into the peritoneal cavity as poorly differentiated HCC lacks cohesiveness (21).

Llovet *et al.* reported that subcapsular location of tumor was also a risk factor for neoplastic seeding (17). Intratumoral pressure increased by heat during RFA may facilitate dissemination of viable cancer cells into the peritoneal cavity, especially when the tumor is located subcapsular (28). Thus, we have adopted gradual elevation of radiofrequency power to avoid rapid increase in intratumoral pressure (10).

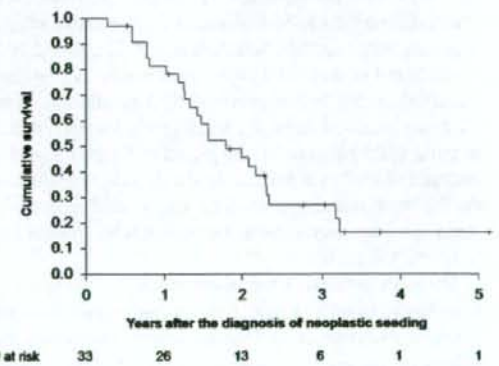

Figure 1. Cumulative survival of patients with neoplastic seeding. Cumulative survival rates of 33 patients at 1, 2, and 3 yr after the diagnosis of neoplastic seeding were 81.3%, 45.4%, and 26.9%, respectively.

This may explain why the location of tumor did not affect the incidence of neoplastic seeding in this study.

The same authors also reported that tumor biopsy prior to RFA was a risk factor of neoplastic seeding after RFA (26). A possible explanation of neoplastic seeding related to tumor biopsy is that viable cancer cells are extruded into the peritoneal cavity during RFA through the tract perforated by the biopsy needle. Another possibility is that cancer cells attached to the biopsy needle drop during needle withdrawal (29, 30). In this study, there also was a tendency of higher incidence of neoplastic seeding in patients who had received biopsy. It would be safer to avoid tumor biopsy when the diagnosis of HCC can be confirmed by dynamic CT or magnetic resonance imaging (20).

Poor differentiation degree was the only risk factor of neoplastic seeding found in this study. To find surrogate markers for differentiation of tumor, we applied univariate logistic regression analysis. Of the tumor factors, tumor size, AFP, AFP-L3, and DCP showed a significant association with poor differentiation degree. The application of RFA should be conservative for patients with large tumors (*e.g.*, >5 cm) or elevated tumor marker levels especially in candidates for surgical resection or liver transplantation.

Although the presence of neoplastic seeding may indicate aggressive tumor character, the survival rate was not extremely low in the patients with neoplastic seeding (the cumulative survival rates at 1 and 2 yr were 81% and 45%, respectively). In approximately 80% of patients with neoplastic seeding in this study, seeding nodules themselves did not affect directly the patients' survival. Taking into consideration the relatively low incidence of neoplastic seeding, 3.2% per patient, or 1.8% per treatment, the risk of neoplastic seeding after RFA would be considered acceptable in general.

In conclusion, poor differentiation degree was the risk factor of neoplastic seeding after RFA for HCC. Larger tumor size and elevated tumor marker levels surrogate poor differentiation. The indication for RFA should be carefully considered for HCC patients under these conditions.

STUDY HIGHLIGHTS

What Is Current Knowledge

- Neoplastic seeding is one of the most unfavorable complications after radiofrequency ablation (RFA).
- Subcapsular tumor location, poor degree of differentiation, high baseline alpha-fetoprotein (AFP) levels, and tumor biopsy prior to RFA were reported to be associated with seeding.

What Is New Here

- Seeding occurred in 33 (3.2%) of 1,031 patients treated with RFA in this study.
- Only poor differentiation degree was the risk factor of seeding after RFA.

Reprint requests and correspondence: Ryosuke Tateishi, M.D., Ph.D., Department of Gastroenterology, The University of Tokyo Hospital, 7-3-1, Hongo, Bunkyo-ku, Tokyo 113–8655, Japan.
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CONFLICT OF INTEREST

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Treatment strategy for hepatocellular carcinoma: expanding the indications for radiofrequency ablation

Ryosuke Tateishi[1], Shuichiro Shiina[1], Takamasa Ohki[1], Takahisa Sato[1], Ryota Masuzaki[1], Jun Imamura[1], Eriko Goto[1], Tadashi Goto[1], Hideo Yoshida[1], Shuntaro Obi[2], Shinpei Sato[3], Fumihiko Kanai[1], Haruhiko Yoshida[1] and Masao Omata[1]

[1]Department of Gastroenterology, The University of Tokyo Hospital, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan
[2]Department of Hepatology, Kyoundo Hospital, Tokyo, Japan
[3]Division of Gastroenterology, Department of Internal Medicine, Teikyo University, Chiba Medical Center, Chiba, Japan

Background. Radiofrequency ablation (RFA) for hepatocellular carcinoma (HCC) is ordinarily indicated for those with three or fewer nodules, none of which exceeds 3 cm in diameter. This study investigated whether an apparent threshold exists in the diameter and number of nodules in terms of the prognosis of patients with HCC. ***Methods.*** We enrolled 663 naïve patients with HCC who were treated with RFA at our hospital between 1999 and 2005. We analyzed the patients' prognosis using multivariate Cox proportional regression with the diameter and number of nodules as covariates and Child–Pugh class as a stratification factor. The diameter and number were categorized as ≤2.0, 2.1–3.0, 3.1–4.0, 4.1–5.0, and >5 cm and 1, 2–3, 4–5, and >5, respectively. ***Results.*** The adjusted hazard ratio of patients whose largest nodule was ≤2.0, 2.1–3.0, 3.1–4.0, 4.1–5.0, and >5 cm was 1, 1.51, 2.56, 2.25, and 2.71, respectively. The adjusted hazard ratio of patients with one, two or three, four or five, and more than five nodules was 1, 1.35, 1.70, and 2.12, respectively. Therefore, patients with three or fewer nodules, none of which exceeds 5 cm in diameter, have a 5-year survival of 40%. ***Conclusions.*** The prognosis of the patients worsened gradually as the diameter and number of nodules increased. No apparent threshold in the diameter or number of HCC nodules was detected. RFA can be applied beyond the conventional indications.

Key words: hepatocellular carcinoma, radiofrequency ablation, survival analysis

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Reprint requests to: R. Tateishi

Introduction

Hepatocellular carcinoma (HCC), an extremely common malignancy, is increasing in incidence worldwide.[1–4] Current options for the treatment of this cancer consist of surgical resection, orthotopic liver transplantation, transcatheter arterial chemoembolization (TACE), and percutaneous tumor ablation. Although surgical resection is usually considered the first-choice treatment,[5,6] it is often contraindicated by underlying chronic liver diseases resulting from hepatitis B or C virus infection.[7,8] Liver transplantation is an ideal strategy that can treat both cancer and liver dysfunction and results in excellent survival in patients at an early stage of the cancer (e.g., a single nodule ≤5 cm in diameter or fewer than three nodules ≤3 cm in diameter).[9,10] However, in countries such as Japan where cadaveric donor organs are scarce, the application of liver transplantation is quite limited.

Percutaneous tumor ablation methods, such as ethanol injection and microwave coagulation, are important nonsurgical treatments that can achieve high local cure rates without reducing background liver function.[11–14] Radiofrequency ablation (RFA) is a recently introduced technique that is rapidly gaining worldwide use because of its greater efficacy for local cure compared to ethanol injection.[15–18]

RFA is usually indicated for patients with three or fewer nodules, none of which exceeds 3 cm in diameter. However, these conventional criteria originated from the experience with ethanol injection.[11,19] Whether an apparent threshold in the size and number of tumor nodules exists for the effectiveness of RFA is unclear. Therefore, we conducted this retrospective cohort study to evaluate the prognosis of patients who underwent RFA according to the size and number of HCC nodules.

Patients and methods

Patients

This study enrolled 663 consecutive patients who underwent RFA as the initial treatment for HCC between 1999 and 2005 at the Department of Gastroenterology, the University of Tokyo Hospital. Inclusion criteria for RFA were as follows: total bilirubin concentration lower than 3 mg/dl, platelet count no less than $50 \times 10^3/mm^3$, and prothrombin activity no less than 50%. Patients with portal vein tumor thrombosis, refractory ascites, or extrahepatic metastasis were excluded. We did not restrict the indications for RFA according to the size and number of nodules.[20,21]

The study protocol was approved by our institutional review board, and informed consent was obtained from all patients.

Diagnosis of HCC

Hepatocellular carcinoma was diagnosed using dynamic computed tomography (CT), considering hyperattenuation in the arterial phase with washout in the late phase as defining HCC.[22] Most nodules were also confirmed histopathologically with an ultrasound-guided biopsy.

TACE before RFA

When four or more hypervascular nodules were detected on dynamic CT or the largest nodule exceeded 3 cm in diameter, we usually performed TACE before RFA. Under local anesthesia, a catheter was inserted into the hepatic artery via the femoral artery. After hypervascular tumors were identified by arteriography, the feeding arteries were selectively embolized with gelatin sponge particles after an emulsion of epirubicin hydrochloride (Pharmorubicin; Pfizer Japan, Tokyo, Japan) and iodized oil (Lipiodol Ultra-Fluid; Schering Japan, Osaka, Japan) was injected under X-ray monitoring.

RFA procedure

All patients underwent dynamic CT with a slice thickness of 5 mm within 1 month before ablation for comparison. After one or two sessions of RFA, dynamic CT was performed to evaluate the treatment efficacy. The interval between initiating the contrast infusion and CT recording was 30 and 120 s for single-detector-row spiral CT (Highspeed Advantage; GE Medical Systems, Milwaukee, WI, USA) and 25, 40, and 120 s for multi-detector-row CT (LightSpeed QX/I; GE Medical Systems). The images were presented after axial reconstruction with a slice thickness of 5 mm. On treatment evaluation, we compared the CT findings of the early and late phases before ablation and those of the late phase after ablation. We did so because the CT findings of the early phase immediately after ablation are not suitable for treatment evaluation because of arterial enhancement of the surrounding liver parenchyma caused by the presence of vascular abnormalities related to the treatment itself, which may only reflect inflammatory changes or a microscopic arterioportal shunt.[23] A lesion was judged as ablated completely when the nonenhanced area in the late phase of CT after ablation covered the entire lesion in both the early and late phases of CT before RFA with a safety margin in the surrounding liver parenchyma. We confirmed complete ablation in all slices on which a target nodule was visualized. Patients underwent additional sessions of ablation until complete ablation was confirmed in each nodule.

Follow-up protocol

The follow-up consisted of blood tests and monitoring of tumor markers as an outpatient; ultrasonography and dynamic CT were performed every 4 months. Tumor recurrence was defined using the same criteria applied to the initial HCC. When HCC recurrence was identified, RFA was performed if the same criteria as for primary HCC were again satisfied.

For those with no indications for RFA because of multiple recurrent nodules, we performed TACE if the liver function was Child–Pugh class A or B. Patients with localized portal invasion of the tumor were treated with radiotherapy.[24] Patients with tumor invasion to the first branch or main tract of the portal vein were treated with intraarterial 5-fluorouracil and systemic interferon-α combination therapy if indicated.[25] Those with extrahepatic metastasis of the tumor received systemic chemotherapy if they had well-preserved liver function and performance status. Living related donor liver transplantation was considered in cases of less advanced HCC with severely decompensated liver function.

Statistical analysis

The data are expressed as the median and 25th and 75th percentiles unless otherwise indicated. Survival analysis was performed on a patient basis. Survival time was defined as the interval between the day of the first treatment (TACE or RFA) and death or the last visit to the outpatient clinic until December 31, 2006. Cumulative survival was estimated using the Kaplan–Meier method.

We assessed the risk factors for survival using multivariate Cox proportional hazard regression with the Child–Pugh classification as a stratification factor. For

the analysis, the diameter and number of nodules were categorized as ≤2.0, 2.1–3.0, 3.1–4.0, 4.1–5.0, and >5 cm and one, two or three, four or five, and more than five, respectively. Estimated 5-year survival rates categorized by tumor size and number were assessed according to the results of the Cox regression using the survival of patients who had a single HCC nodule equal to or smaller than 2 cm in diameter as a reference.

Differences with $P < 0.05$ were considered statistically significant. All statistical analyses were performed with S-plus 2000 (Mathsoft, Seattle, WA, USA).

Results

Patient profiles

The enrolled patients consisted of 425 men and 238 women with a median age of 68 years (Table 1). The median tumor diameter was 2.4 cm, ranging from 0.9 to 9.7 cm. The number of nodules was one in 371 (56.0%) patients, two or three in 236 (35.6%) patients, and more than three in 56 (8.4%) patients. The distribution of the size and number of nodules is shown in Table 2. Of the patients, 439 (66.2%) met the conventional criteria (i.e., three or fewer nodules, none of which exceeded 3 cm in diameter). Up to the end of the follow-up, 189 patients died. The cumulative survival rate at 1, 2, 3, 4, and 5 years was 96.3%, 88.4%, 81.3%, 70.0%, and 59.6%, respectively.

Table 1. Baseline characteristics of the patients ($n = 663$)

Variable	*n* (%)
Age[a] (years)	68 (63–73)
Male	425 (64.1)
Viral infection	
HBsAg, positive	72 (10.9)
Anti-HCVAb, positive	524 (79.0)
Both positive	11 (1.7)
Both negative	78 (11.8)
Child–Pugh classification	
Class A	469 (70.7)
Class B	186 (28.1)
Class C	8 (1.2)
Tumor size (cm)	
≤2.0	216 (32.6)
2.1–3.0	263 (39.7)
3.1–4.0	118 (17.8)
4.1–5.0	35 (5.3)
>5	31 (4.7)
Number of nodules	
1	371 (56.0)
2–3	236 (35.6)
>3	56 (8.4)

HBsAg, hepatitis B surface antigen; anti-HCVAb, antihepatitis C virus antibody
[a]Expressed as the median (25th–75th percentiles)

Relative risk of tumor size and number assessed using Cox proportional regression

Multivariate analysis using the Cox proportional hazard model revealed that the hazard ratio increased gradually with the size and number of tumor nodules (Fig. 1A,B). The estimated 5-year survival was assessed using the combined hazard ratio using the survival of patients who had a single HCC nodule equal to or smaller than 2 cm in diameter as a reference. The 5-year survival rate was 75% in reference patients and more than 40% when patients had a single nodule; two or three nodules, none of which exceeded 5 cm; four or five nodules, none of which exceeded 3 cm; or multiple nodules 2 cm or smaller (Table 3).

Discussion

An indication for treatment of a neoplastic disease should be decided according to the disease severity, invasiveness of the treatment, and expected prognosis. If a wide difference in survival exists after a treatment between two stages, the condition that separates these two might be an indication for the treatment. In this study, the hazard ratio assessed using a multivariate analysis increased gradually with the size and number of tumor nodules and no apparent threshold was observed. Therefore, the conventional criteria (i.e., three or fewer nodules, none of which exceeds 3 cm in diameter) is not definitive in terms of survival.

Table 2. Number of patients categorized by the size and number of tumor nodules

	Number of tumor nodules			
Tumor size (cm)	1	2–3	4–5	>5
≤2.0	132	73	10	1
2.1–3.0	148	86	23	6
3.1–4.0	58	53	6	1
4.1–5.0	18	15	2	0
>5.0	15	9	3	4

Table 3. Estimated 5-year survival based on the size and number of tumor nodules

	Number of tumor nodules			
Tumor size (cm)	1 (%)	2–3 (%)	4–5 (%)	>5 (%)
≤2.0	75	68	61	54
2.1–3.0	65	55	47	39
3.1–4.0	48	37	28	21
4.1–5.0	52	42	33	25
>5.0	46	35	26	19

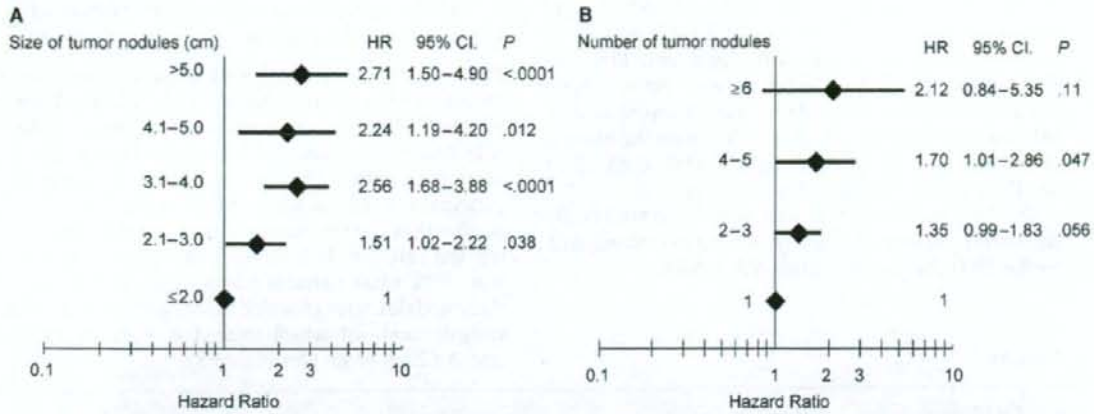

Fig. 1A–B. **A** Results of the multivariate Cox proportional hazard regression analysis. The hazard ratios of the patients increased with tumor size. The *diamonds* indicate the hazard ratios and the *horizontal lines* denote the 95% confidence intervals. **B** Results of the multivariate Cox proportional hazard regression analysis. The hazard ratios of the patients increased with the number of tumor nodules. *Diamonds* indicate the hazard ratios and the *horizontal lines* denote the 95% confidence intervals

Table 4. Treatment options classified by their invasiveness and curative potential

Treatment option	Invasiveness	Probability of cure
First-line treatment	Maximal	Highest
Second-line treatment	Intermediate	Intermediate
Third-line treatment	Minimal	Lowest

The first-line treatment option for most solid tumors is surgical resection. In general, resection is considered the most invasive treatment and is indicated only if the expected survival exceeds that of a second-line treatment that is less invasive than resection (Table 4). In the treatment strategy for HCC, RFA is considered the second-line treatment for unresectable HCC due to tumor multiplicity or impaired liver function when liver transplantation is not indicated.[26] Therefore, expanding the indications for RFA to resectable patients needs randomized controlled trials comparing the survival of patients who can undergo both resection and RFA.[27,28] At present, whether to choose resection or ablation for those who have three or fewer HCC nodules, none of which exceeds 3 cm in diameter, remains controversial.

For unresectable patients, the indications for RFA should be assessed in comparison with the third-line treatment, TACE. Although the probability of local cure of HCC with RFA depends on tumor size,[21,29] RFA is far more reliable for destroying the target nodule than TACE, for which the treatment efficacy also depends on tumor size.[30,31] For nodules larger than 3 cm in diameter, patients with HCC 5 cm or smaller were treated by RFA in combination with TACE for local cure within two sessions (data not shown). Therefore, increasing the indication to tumors 5 cm in diameter is technically feasible and acceptable. Indeed, a recent report suggested that TACE + RFA combination therapy improves the survival of patients with one to three HCC nodules, at least one of which exceeded 3 cm, as compared to TACE or RFA alone.[32]

The presence of more than three hypervascular HCC nodules strongly indicates disseminated malignant cells throughout the liver. The application of RFA, which is a locoregional treatment, is thought to have limited efficacy in such patients. However, patients with multiple HCC nodules often have one or two main nodules and small minor nodules. Ablating the major nodules may reduce the total tumor burden considerably and prolong survival.

The prognosis of patients with HCC depends strongly on the background liver function, as well as tumor stage.[33–35] Therefore, the improvement in survival with RFA may be minimal in patients at advanced tumor stages with severe liver dysfunction. One should be cautious when applying RFA to these patients.

In conclusion, patients' prognosis decreased as the diameter and number of nodules increased. However, we found no apparent threshold in the diameter or number of HCC nodules. RFA can be applied beyond the conventional indications after considering liver function.

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特集　腫瘍栓のすべて

Ⅲ. 切除以外の治療

2. インターフェロンの併用動注療法(2)*

小尾俊太郎**

〔要旨〕われわれは門脈腫瘍栓を伴った肝細胞癌374例に，インターフェロン(IFN)併用5-FU動注化学療法を行った．治療効果予測因子，予後予測因子を解析した．全体の生存率は0.5年50%，1年29%，2年13%，3年8%であった．治療効果は奏効率44%，完全寛解率14%であった．予後因子は奏効，転移なし，腹水なし，PIVKA-II(DCP)<1,635 mAU/ml，門脈腫瘍栓Vp_3が条件であった．奏効予測因子は，腹水なしとPLT<12.4×10⁴/μlであることが判明した．

はじめに

近年，画像診断の進歩と肝癌高危険群の囲い込みが浸透してきた結果，肝細胞癌の早期診断が可能となり，また治療の進歩も相まって肝細胞癌患者の予後は著しく改善した．しかしながら，90%以上の肝細胞癌はウイルス肝炎を背景としているため再発を繰り返し，やがて16～65%の症例は門脈腫瘍栓をきたし，これらの予後は約6ヵ月と著しく不良である．門脈腫瘍塞栓をきたすと腫瘍細胞が門脈血流を介して肝内転移を引き起こしたり，門脈血流低下により肝不全を惹起するとともに，門脈圧が亢進して腹水貯留や食道静脈瘤破裂を引き起こす．それゆえ門脈腫瘍塞栓の存在は病状を悪化させて，さらなる肝癌治療を困難にする．

門脈腫瘍栓に対する治療として，切除や放射線治療，化学療法があげられる．しかし，切除は肝機能が維持されている症例に限られる．また，放射線治療は病変が限局していないと困難であり肝内に広がった癌は適応にならない．われわれ内科にいる大部分の門脈腫瘍栓症例は，肝機能不良で肝内全体に広がった病変を合併している．そこで化学療法が必要であった．しかし，過去の検討から全身化学療法では奏効が得られにくいことがわかっており，遠隔転移がない門脈腫瘍栓の症例に動注化学療法が検討された．Andoら[1]のlow dose FPを追試したが，われわれの症例は肝機能が低かったことや前治療がかなり行われていたこともあり，副作用で治療の遂行ができなかった．特にcisplatinによる倦怠感や嘔気が強かった．また肝炎の悪化も疑われた[2,3]．Urabeら[4]は，methotrexate＋5-FU＋cisplatin＋インターフェロン(IFN)の併用療法を行った．血液毒性が強く，

キーワード：肝細胞癌，門脈腫瘍栓，動注化学療法，インターフェロン

* Combination therapy of intra-arterial 5-FU and systemic interferon

** S. Obi(部長)：杏雲堂病院肝臓科(〒101-0062　東京都千代田区神田駿河台1-8)．

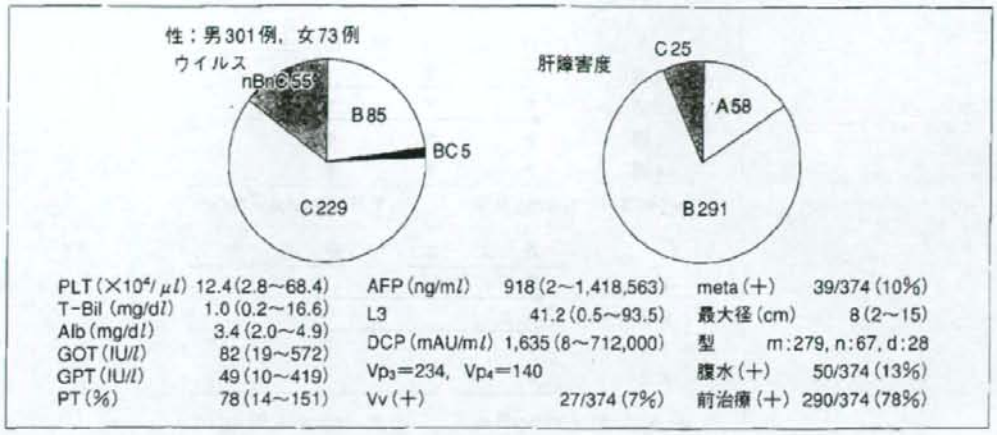

図1. 対　象

切除塞栓の適応外となったVp_{3-4}肝細胞癌．2000年9月～2007年9月にIFN併用5-FU動注化学療法を施行した374例

すでに汎血球減少のある肝硬変合併症例には施行しがたかった．Sakonら[5]のIFN＋5-FUのレジメンはもっとも副作用が少なく，肝硬変を合併した症例でも治療遂行が可能であった．

IFN＋5-FUの併用療法は，1989年にWadlerら[6]によって進行大腸癌において報告された．1993年にPattら[7]によって，IFN＋5-FU(全身投与)併用療法の有効性が肝細胞癌で確認された．これらの報告をもとにわれわれは門脈腫瘍浸潤(Vp_{3-4})進行肝細胞癌に対してIFN併用5-FU動注化学療法を行い，その有用性を報告[8]した．

I. 対　　象

2000年9月～2007年9月にVp_{3-4}の門脈腫瘍栓を伴った肝細胞癌374例を対象に，IFN併用5-FU動注化学療法を行った．治療効果予測因子，予後予測因子を解析した．男性301例，女性73例，背景肝は61%がC型肝炎由来，23%がB型肝炎由来であった．肝障害度は16%がA，78%がB，6%がCであった．各項目の中央値はPLT 12.4×10⁴/μl，T-Bil 1.0 mg/dl，Alb 3.4 mg/dl，GOT 82 IU/l，GPT 49 IU/l，プロトロンビン時間78%，AFP 918 ng/ml，AFP-L3 41.2%，PIVKA-II(DCP) 1,635 mAU/ml，Vp_3 63%，Vp_4 37%，Vvあり7%，遠隔転移あり10%，最大径8 cm，塊状型75%，結節型18%，びまん型7%，腹水あり13%，前治療あり78%であった(図1)．

II. 方　　法

プロトコールを図2に示す．Sakonら[5]の報告に従い，4週間を1クールとして最初の2週間はIFNと5-FUの併用，後半の2週間はIFNのみとした．5-FUは500 mg/日を5日間動注，IFNはnatural-alpha(OIF)を週3回皮下注した．Pegylated(Peg)-IFNが本邦でも発売されたのをきっかけにnatural-alphaからPeg-IFNに切り替えた．Peg-IFNはnatural-alphaと同等の効果が得られた[9,10]．効果判定は各クール終了時にEastern Cooperative Oncology Group(ECOG)クライテリアに準じて行い，progression以外は動注を繰り返した．統計解析はKaplan-Meier法にて算出した．また，予後予測因子はCox proportional hazard regression modelで算出した．効果予測因子はlogistic regression analysisで算出した．

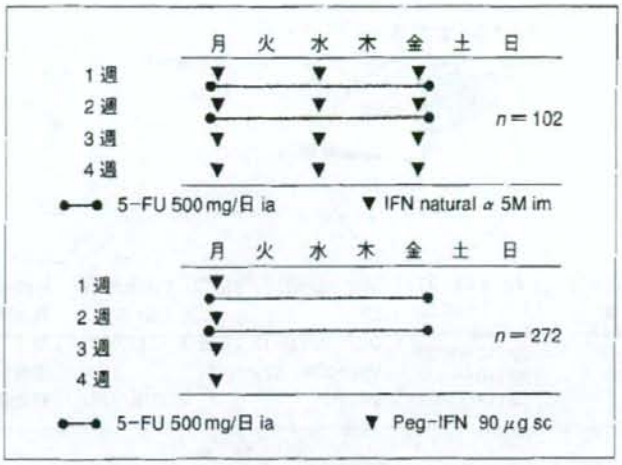

図2. プロトコール
ia：動注，im：筋注，sc：皮下注

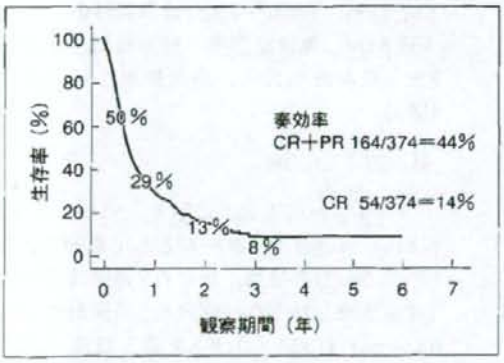

図3. 効果（n＝374）〔2007年10月1日現在〕
ECOGクライテリア．CR 54例，PR 110例，SD 47例，PD 163例

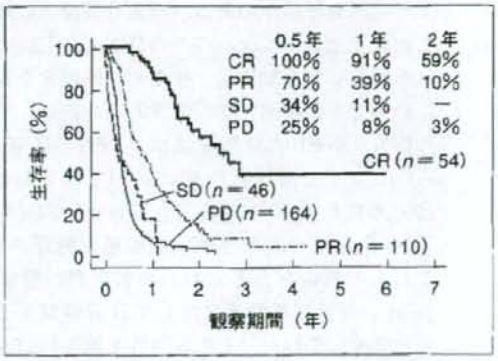

図4. 治療効果別生存率（n＝374）〔2007年10月1日現在〕

III. 結　　果

IFN併用5-FU動注化学療法を施行した374例，全体の生存率は0.5年50%，1年29%，2年13%，3年8%であった（図3）．治療効果は，complete response（CR）54例（14%），partial response（PR）110例（29%），stable disease（SD）47例（13%），progression disease（PD）163例（44%）であった．奏効率は44%，完全寛解率は14%にのぼった．奏効はそのまま生存に寄与した．効果別生存曲線を図4に示す．CRは1年生存率91%，2年生存率59%ともっとも良好であった．PRは1年生存率39%，2年生存率は10%であった．これに対してPDは1年生存率がわずかに8%と不良であった．

予後予測因子を21項目のパラメーターを用いて検討した（表1）．単変量解析の結果，年齢，Vp，転移，腹水，T-Bil，Alb，GOT，プロトロンビ

表1. 予後因子の解析(2007年10月1日現在)

a. 予後因子単変量解析

	Exp	95% CI	p
性別(男)	0.997	0.750～1.325	0.9811
年齢＜65歳	1.263	1.006～1.586	0.0442
前治療なし	1.265	0.968～1.651	0.0846
HCV以外	1.204	0.952～1.524	0.1215
Vp_3	0.553	0.436～0.702	＜0.0001
Vv_0	0.782	0.510～1.198	0.2586
転移なし	0.580	0.407～0.826	0.0025
腹水なし	0.358	0.259～0.484	＜0.0001
PLT＜$12.4\times10^4/\mu l$	0.885	0.706～1.110	0.2918
T-Bil＜1.0mg/dl	0.614	0.488～0.776	＜0.0001
Alb＜3.4mg/dl	1.477	1.177～1.854	0.0008
GOT＜82IU/l	0.617	0.491～0.775	＜0.0001
GPT＜49IU/l	1.002	0.788～1.257	0.9882
PT＜78%	1.314	1.047～1.648	0.0183
AFP＜918ng/ml	0.709	0.565～0.890	0.0030
L3＜41.2%	1.112	0.886～1.395	0.5430
DCP＜1,635mAU/ml	0.639	0.509～0.802	0.0001
腫瘍径＜8cm	0.747	0.594～0.890	0.0030
massive以外	1.126	0.874～1.451	0.3568
IFN natural α	0.885	0.691～1.134	0.3333
効果なし	4.107	3.177～5.309	＜0.0001

b. 予後因子多変量解析

	Exp	95% CI	p
効果なし	4.154	3.153～5.472	＜0.0001
転移なし	0.510	0.340～0.736	0.0003
腹水なし	0.556	0.395～0.783	0.0008
DCP＜1,635mAU/ml	0.696	0.549～0.883	0.0028
Vp_3	0.740	0.570～0.960	0.0236

ン時間，AFP，PIVKA-II，腫瘍径，奏効が予後因子(表1，網かけ)となった．これらに対して多変量解析を行うとVp，転移，腹水，PIVKA-II，奏効の5項目が予後因子と判明した．奏効はもっとも強力な予後規定因子であった．そこで奏効(治療効果)予測因子を20項目のパラメーターを用いて解析した(表2)．単変量解析の結果，前治療，Vp，腹水，PLT，T-Bil，GOT，PIVKA-IIが有意因子(表2，網かけ)として残った．これらに対して多変量解析を行った結果，腹水とPLTが奏効の予測因子であることが判明した．

IV. 結　論

予後因子は奏効が得られること，転移がないこと，腹水がないこと，PIVKA-II＜1,635mAU/ml(中央値)，門脈腫瘍塞栓がVp_3にとどまっていることが条件であった．奏効予測因子としては，腹水がないこととPLT＜$12.4\times10^4/\mu l$(中央値)であることが判明した．

これらをまとめると，$Vp_{3\text{-}4}$の門脈腫瘍塞栓を

表2. 効果予測因子の解析(2007年10月1日現在)

a. 効果予測因子単変量解析

	Exp	95% CI	p
性別(女)	0.760	0.455～1.270	0.2950
年齢＞65歳	1.223	0.812～1.843	0.3357
前治療あり	2.172	1.290～3.659	0.0035
HCV	1.486	0.973～2.271	0.0669
Vp_4	0.458	0.296～0.709	0.0005
Vvあり	1.205	0.550～2.641	0.6407
転移あり	0.609	0.303～1.227	0.1651
腹水あり	0.357	0.180～0.709	0.0032
PLT＞12.4×$10^4/\mu l$	0.619	0.400～0.934	0.0222
T-Bil＞1.0mg/dl	0.551	0.364～0.835	0.0050
Alb＞3.4mg/dl	1.233	0.819～1.856	0.3164
GOT＞82IU/l	0.486	0.321～0.736	0.0007
GPT＞49IU/l	0.897	0.596～1.350	0.6009
PT＞78%	1.425	0.945～2.147	1.4250
AFP＞918ng/ml	0.676	0.448～1.019	0.0611
L3＞41.2%	1.112	0.624～1.416	0.7662
DCP＞1,635mAU/ml	0.592	0.392～0.894	0.0126
腫瘍径＞8cm	0.721	0.478～1.088	0.1192
massive	1.038	0.649～1.661	0.8749
Peg-IFN	0.933	0.590～1.474	0.7659

b. 効果予測因子多変量解析

	Exp	95% CI	p
腹水あり	0.424	0.206～0.871	0.0195
PLT＞12.4×$10^4/\mu l$	0.584	0.368～0.928	0.0226

伴った肝細胞癌に対するIFN併用5-FU動注化学療法のよい適応基準は,「切除適応のない門脈腫瘍浸潤で遠隔転移や腹水を認めない症例かつPLT＜12.4×$10^4/\mu l$でVp_3止まりの症例」がIFN併用5-FU動注化学療法のよい適応である. この適応基準を満たす症例は97例(26%)であったが, この群の奏効率は62%であった. CR 21例(22%), PR 39例(40%)にのぼった. 適応基準外の症例における奏効率は38%であった. また適応基準を満たした群の生存率は6ヵ月66%, 1年40%であったのに対し, 適応基準外の症例はわずかに6ヵ月43%, 1年25%であった.

おわりに—今後の展望

奏効予測因子は, PLT＜12.4×$10^4/\mu l$であった. Ukaら[11]も効果予測因子を解析し, HCV抗体陽性とperformance status(PS)をあげている. HCV抗体が予測因子となった背景はおそらく血小板低下であろう. なぜPLTが低いほうが効くのか不明である. Poonら[12]は血清中のvascular endothelial growth factorレベルが, PLTと相関することを報告している. ここにPLTと奏効の相関を解く鍵があると思われる.