Table 4 Efficacy of transcatheter arterial chemotherapy using platinum analogue for advanced HCC in 152 patients unresponsive to TACE-epirubicin, according to type of therapy

	CR (%)	PR (%)	SD (%)	PD (%)
Total ($n = 152$)	6 (4%)	28 (18%)	35 (23%)	83 (55%)
Type of therapy				
HAI ($n = 73$)	1 (1%)	9 (12%)	16 (22%)	47 (65%)
CL ($n = 20$)	1 (5%)	3 (15%)	7 (35%)	9 (45%)
TACE ($n = 59$)	4 (7%)	16 (27%)	12 (20%)	27 (46%)

CL, chemolipiodalization; CR, complete remission; HAI, hepatic arterial injection; HCC, hepatocellular carcinoma; PD, progressive disease; PR, partial response; SD, stable disease; TACE, transcatheter arterial chemoembolization.

(1%) patients showed CR, 9 of 73 (12%) patients showed PR, 16 of 73 (22%) patients showed SD, and 47 of 73 (65%) patients showed PD; in CL group: 1 of 20 (5%) patients showed CR, 3 of 20 (15%) patients showed PR, 7 of 20 (35%) patients showed SD, and 9 of 20 (45%) patients showed PD; in TACE group: 4 of 59 (7%) patients showed CR, 16 of 59 (27%) patients showed PR, 12 of 59 (20%) patients showed SD, and 27 of 59 (46%) patients showed PD (Table 4).

Factor influencing curative effect (PR or CR)

We then investigated the factors associated with curative effect (PR or CR) after treatment using platinum analogue. Univariate analysis identified the following 11 factors that influenced the rate of curative effect (PR or CR): serum DCP (< 100 IU/L/≥ 100 IU/L, $P = 0.001$), serum AFP (< 200 μg/L/≥ 200 μg/L, $P = 0.005$), ICG-R15 (< 30%/≥ 30%, $P = 0.005$), tumor size (< 20 mm/≥ 20 mm, $P = 0.011$), portal vein invasion (yes/no, $P = 0.014$), total bilirubin (< 1.5 mg/dL/≥ 1.5 mg/dL, $P = 0.018$), treatment method (HAI/CL/TACE, $P = 0.021$), type of platinum analogue (carboplatin/cisplatin, $P = 0.021$), intrahepatic multiplicity that extended to both lobes (yes/no, $P = 0.028$), age (< 60/≥ 60, $P = 0.057$), and serum AST (< 50 IU/L/dL/≥ 50 IU/L, $P = 0.057$). These parameters were entered into multivariate logistic regression analysis. The curative effect (PR or CR) was significantly higher for elderly patients (aged ≥ 60, risk ratio: 7.75; 95% CI: 1.80–33.40), small size HCC (< 20 mm, risk ratio: 4.88; 95% CI: 1.62–14.71), TACE-platinum analogue treatment (yes, risk ratio: 3.91; 95% CI: 1.34–11.38), lower serum total bilirubin level (< 1.5 mg/dL, risk ratio: 3.44; 95% CI: 1.22–9.71), and Tumor multiplicity, extended to both lobes (no, risk ratio: 2.30 (1.03–7.09) (Table 5).

Table 5 Factors associated with curative effects in patients who underwent transcatheter arterial platinum analogue therapy for advanced HCC unresponsive to TACE-epirubicin

Factors	Category	Risk Ratio (95% confidence interval)	*P*
Age (year)	1: < 60	1	
	2: ≥ 60	7.75 (1.80–33.40)	0.006
Tumor size (mm)	1: ≥ 20	1	
	2: < 20	4.88 (1.62–14.71)	0.005
Tumor therapy	1: HAI	1	
	2: CL	2.47 (0.52–11.69)	0.256
	3: TACE	3.91 (1.34–11.38)	0.012
Bilirubin (mg/dL)	1: ≥ 1.5	1	
	2: < 1.5	3.44 (1.22–9.71)	0.020
Multiple HCC, extended to both lobes (yes/no)	1: yes	1	
	2: no	2.30 (1.03–7.09)	0.044

CL, chemolipiodalization; CR, complete remission; HAI, hepatic arterial injection; HCC, hepatocellular carcinoma; PR, partial response; TACE, transcatheter arterial chemoembolization.

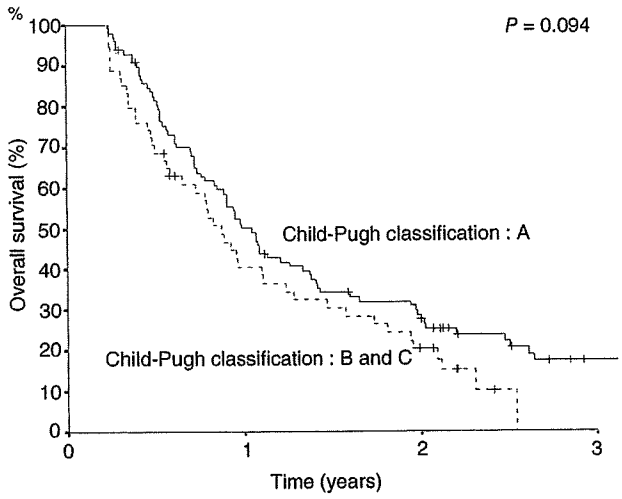

Figure 1 Cumulative survival rates after the first use of platinum-analogue for advanced HCC unresponsive to TACE-epirubicin, according to Child-Pugh classification.

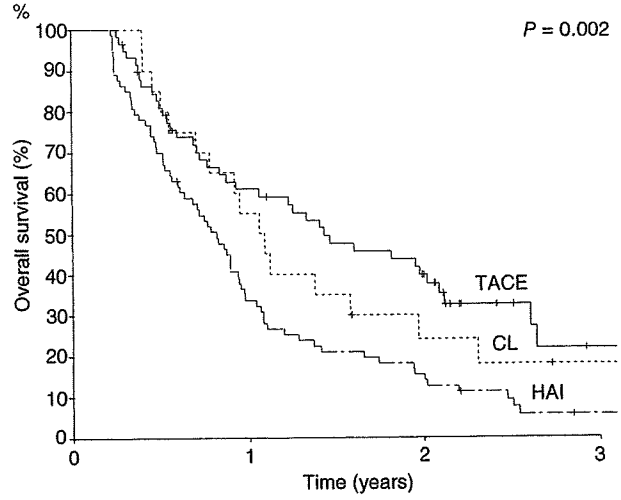

Figure 2 Cumulative survival rates after the first use of platinum-analogue for advanced HCC unresponsive to TACE-epirubicin, according to type of therapy.

Cumulative survival rate according to Child-Pugh classification

During the observation period, 125 of 152 (82.2%) patients died. The cumulative survival rates after the first use of platinum analogue therapy for advanced HCC unresponsive to TACE-epirubicin according to Child-Pugh classification were 50.1% at the end of the first year, 28.7% at the second year, and 17.2% at the third year for patients with Child-Pugh class A, and 40.5% at the first year, 20.3% at the second year, 0% at the third year for patients with Child-Pugh class B and C. The cumulative survival rates were slightly higher in patients with Child-Pugh class A than in those with Child-Pugh class B and C ($P = 0.094$), but no statistical significance was not there (Fig. 1).

Cumulative survival rate according to type of therapy

The cumulative survival rates after the first use of platinum analogue therapy for advanced HCC unresponsive to TACE-epirubicin according to type of therapy were 33.6% at the end of the first year, 15.4% at the second year, and 5.6% at the third year for patients with HAI group, 55.0% at the first year, 24.0% at the second year, 18.0% at the third year for patients with CL group, and 60.8% at the first year, 40.0% at the second year, 21.7% at the third year for patients with TACE group.

The cumulative survival rate was significantly different in these three type of therapy ($P = 0.002$) (Fig. 2).

Cumulative survival rate according to treatment effect

The cumulative survival rates after the first use of platinum analogue therapy for advanced HCC unresponsive to TACE-epirubicin were 81.8% at the end of the first year, 53.9% at the second year, and 33.1% at the third year for patients with PR or CR, and 36.6% at the first year, 17.5% at the second year, 7.4% at the third year for patients with PD or SD. The cumulative survival rates were significantly higher in patients with PR or CR than in those with SD or PD by transcatheter arterial chemotherapy using platinum analogue ($P < 0.001$) (Fig. 3). The 50% survival period was extended almost 1.4 year in patients with PR or CR by transcatheter arterial chemotherapy using platinum analogue.

Factor affecting survival rate

We then investigated the factors associated with survival rate after the first transcatheter arterial chemotherapy using platinum analogue for advanced HCC unresponsive to TACE-epirubicin. Univariate analysis identified the following 13 factors that influenced the survival rate: portal vein invasion (yes/no, $P < 0.001$), type of platinum analogue (carboplatin/cisplatin, $P = 0.001$), tumor size (< 20 mm/≥ 20 mm, $P = 0.001$), serum DCP (< 100 IU/L/≥ 100 IU/L, $P = 0.001$), age (< 60/≥ 60, $P = 0.001$), serum AFP (< 200 μg/L/≥ 200 μg/L, $P = 0.006$), treatment method (HAI/CL/TACE, $P = 0.008$), intrahepatic multiplicity that extended to both lobes

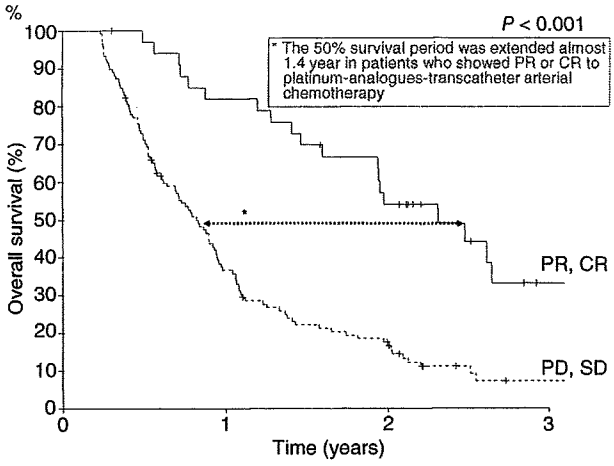

Figure 3 Overall survival rates after the first use of platinum-analogue for advanced HCC unresponsive to TACE-epirubicin, according to treatment effect.

(yes/no, $P = 0.012$), serum AST (< 50 IU/L/dL/ ≥ 50 IU/L, $P = 0.014$), prothrombin activity (< 80%/ ≥ 80%, $P = 0.020$), HBs-Ag (positive/negative, $P = 0.048$), anti HCV antibody (positive/negative, $P = 0.063$), and total bilirubin (< 1.5 mg/dL/≥ 1.5 mg/dL, $P = 0.068$). These parameters were entered into multivariate Cox proportional hazard analysis. The curative survival rate was significantly higher for small size HCC (< 20 mm, hazard ratio: 2.60; 95% CI: 1.30–5.19), no evidence of portal vein invasion (hazard ration: 2.08; 95% CI: 1.37–3.16), TACE treatment (yes, hazard ratio: 1.93; 95% CI: 1.23–3.02), HBs antigen negative (yes, hazard ratio: 1.82; 95% CI: 1.13–2.93), and low AST level (< 50 IU/L, hazard ratio: 1.67; 95% CI: 1.06–2.61) (Table 6).

Toxic effects

The most common side effects observed after treatment with a platinum analogue were fever and vomiting. Low-grade fever of 37–38°C lasting for a few days occurred in 78 (51.3%) patients, and fever of ≥ 38°C occurred in the other 51 (33.6%) patients. Nausea was reported in 125 (82.2%) patients, vomiting was noted at the time of treatment in 49 (32.2%) patients, dull pain in the upper abdomen was reported at the time of infusion by 31 patients (20.4%), a rise in serum aminotransferases was seen in 80 (52.6%) patients: 36 showed a rise up to twice the values before treatment, and 44 showed a rise of 1.5 to 1.9 times the baseline values. Within one week of treatment, 42 (27.6%) patients showed a transient rise in total bilirubin level to twice the pretreatment value. No adverse effects due to embolization in critical organs such as the lung, the heart, or brain were noted.

Causes of death

During the observation period, 125 (82.2%) patients died. The cause of death was HCC in 106 (84.8%) patients, liver failure in 14 (11.2%) patients and other causes in 5 (4.0%) patients.

Table 6 Factors associated with overall survival rate in patients with underwent transcatheter arterial platinum analogue therapy for advanced HCC unresponsive to TACE-epirubicin (Multivariate Cox proportional hazard analysis)

Factors	Category	Hazard Ratio (95% confidence interval)	*P*
Tumor size (mm)	1: ≥ 20	1	
	2: < 20	2.60 (1.30–5.19)	0.007
Portal vein invasion (yes/no)	1: yes	1	
	2: no	2.08 (1.37–3.16)	0.001
Tumor therapy	1: HAI	1	
	2: CL	1.80 (1.00–3.24)	0.050
	3: TACE	1.93 (1.23–3.02)	0.004
HBs antigen	1: positive	1	
	2: negative	1.82 (1.13–2.93)	0.013
AST (IU/L)	1: ≥ 50	1	
	2: < 50	1.67 (1.06–2.61)	0.026

CL, chemolipiodalization; HAI, hepatic arterial injection; HCC, hepatocellular carcinoma; TACE, transcatheter arterial chemoembolization.

DISCUSSION

ALTHOUGH TACE IS one of the most potent methods of treatment for unresectable HCC, various types of resistances to therapy can occur during the repetition of embolization. However, to our knowledge, there is no report that assessed the efficacy of platinum analogue for TACE-resistant HCC patients. Since various chemotherapeutic agents have occasionally produced objective tumor regression in palliative management of advanced liver cancer, we used platinum analogues for embolization-resistant HCC.

In our study, the 50% survival period was extended almost 1.4 year in patients who showed PR or CR in response to transcatheter arterial chemotherapy using platinum analogue for TACE-resistant HCC. We consider this outcome encouraging in TACE-resistant HCC, because these types of tumors are usually unexpected respond to any treatment. Multivariate analysis indicated that it is important to deliver the platinum analogue via TACE in order to achieve a satisfactory curative effect. A previous study reported the efficacy of cisplatin when injected with Lipiodol for preoperative TACE therapy (termed "sandwich therapy") in patients with HCC who received TACE as the first treatment.[14]

In univariate analysis, the cumulative survival rates were slightly higher in patients with Child-Pugh class A than in those with Child-Pugh class B and C, but in multivariate analysis, the factor of liver function was not significantly related to survival rate. In the result of multivariate analysis, tumor related factors more affected on the cumulative survival rates than liver function in this study.

The type of therapy, in univariate analysis, the cumulative survival rates were significantly different among the therapies. Multivariate analysis disclosed that the type of therapy significantly affected on cumulative survival rate after the first use of platinum analogue therapy for advanced HCC unresponsive to TACE-epirubicin.

These results indicated that it is important to deliver the platinum analogue via TACE in order to obtain a more long term survival, as well as curative effect.

Our results showed that the survival rate of HBV-positive HCC patients was significantly lower than that of HCV-positive patients with advanced HCC. HBV-related HCC or non-viral hepatitis-related HCC are often diagnosed at a more advanced stage than HCV-related HCC, and patients with such advanced-stage HCC related to HBV or non-viral etiology showed poor prognosis compared to those with HCV-related HCC.[21] This may explain the lower survival rate in our patients with HBV-related HCC.

In this study, we used two types of platinum analogues (cisplatin and carboplatin), and the results of univariate analysis, the curative effect (PR and CR) and overall survival rate were significantly better for cisplatin than carboplatin use. It is reported that cisplatin is more effective as an anti-tumor agent compared with carboplatin,[22,23] although there are no studies that compared the efficacy of the two agents in HCC. Our study was limited because it was retrospective in nature, but our results indicate that the chemotherapeutic effects of platinum analogues against HCC are more favorable for cisplatin than carboplatin, similar to other solid tumors. Further studies are required to investigate the underlying mechanism for the difference in efficacy of cisplatin than carboplatin.

A number of molecular-based chemotherapeutic agents are expected to become available in the future, such as Sorafenib,[24] and the primary therapy of advanced stage HCC may change with the introduction of these drugs. However, the results of our study suggested the advantage of using cisplatin in patients with TACE-resistant HCC. Although further studies are required to confirm our findings, the combination of various types of molecular targeting drugs and TACE may improve the treatment outcome in advanced-stage HCC.

In conclusion, the present study reports the efficacy of platinum analogues in patients with advanced HCC unresponsive to TACE-epirubicin. Most such patients have poor prognosis mainly because of lack of effective therapy. However, our results show that the 50% survival period of patients who respond to platinum analogues-transcatheter arterial chemotherapy was extended to almost 1.4 years. Accordingly, we recommend this form of chemotherapy for patients with advanced HCC unresponsive to TACE-epirubicin.

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Original Article

High Serum Des-gamma-carboxy Prothrombin Level Predicts Poor Prognosis After Radiofrequency Ablation of Hepatocellular Carcinoma

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BACKGROUND: Currently, surgical resection is considered the first-line treatment for early stage hepatocellular carcinoma (HCC). Radiofrequency ablation (RFA) has been an alternative choice for unresectable HCC. However, RFA is expected to have similar therapeutic efficacy for early stage HCC with fewer invasions. **METHODS:** The authors retrospectively analyzed 199 patients who underwent surgery and 209 patients who underwent RFA for HCC with a maximum diameter of ≤3 cm and tumors numbering ≤3. All patients were complicated with Child-Pugh A cirrhosis. **RESULTS:** The 3- and 5-year survival rates of the resection (90.3%, 79.0%, respectively) and RFA groups were similar (87.4%, 74.8). The 1- and 3-year tumor recurrence-free survival rates of the resection group (83.1%, 51.0%, respectively) were higher than in the RFA group (82.7%, 41.8%; $P=.011$). Multivariate analysis identified prothrombin time ≥80% (hazard ratio [HR], 2.72; 95% confidence interval [CI], 1.56-4.74; $P < .001$) as an independent prognostic factor for survival in the resection group. Des-gamma-carboxy prothrombin (DCP) <100 arbitrary units (AU)/L (HR, 5.49; CI, 2.23-13.5; $P < .001$) and platelet count $\geq 1.0 \times 10^5$ (HR, 2.70; CI, 1.24-5.88; $P=.012$) were significant markers in the RFA group. Among patients with DCP ≥100 AU/L, treatment procedure (HR, 1.26; CI, 1.04-1.53; $P=.020$) was a significant prognostic factor for survival. **CONCLUSIONS:** High DCP levels reflect the biologic aggressiveness and progression of HCC tumors. In the aforementioned cases, we recommend surgical resection rather than RFA for such patients. **Cancer 2009;115:571-80. © 2008 American Cancer Society.**

KEY WORDS: hepatocellular carcinoma, DCP, radiofrequency, prognostic factor.

Hepatocellular carcinoma (HCC) is the sixth most common malignancy and third most deadly carcinoma in the world.[1] In Japan, HCC is ranked third among males and fifth among females as the leading causes of cancer death.[2] Most patients with HCC are infected with either hepatitis B virus (HBV) or hepatitis C virus (HCV), and have complications stemming from underlying chronic liver disease. The importance of liver condition in the treatment of HCC should be clearly discerned.[3]

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A maximum tumor diameter of ≤3 cm and tumors numbering ≤3 are good candidates for liver transplantation in patients with Child-Pugh class B and C.[4,5] However, patients with Child-Pugh class A conditions should be treated curatively.[5,6] Hepatectomy is currently recommended for patients with single asymptomatic HCC and extremely well-preserved liver function, who have neither clinically substantial portal hypertension nor abnormal bilirubin levels.[6] However, resection is suitable for only 20% to 35% of patients with HCC because of poor hepatic reserve.[7,8] Radiofrequency ablation (RFA) was introduced as a minimally invasive therapy for such cirrhotic patients.[9-13] RFA was the initial choice for unresectable HCC; however, 2 recent randomized controlled trials concluded that there were no substantial statistical survival differences between resection and RFA.[9,10] Although the results of these studies have not yet reached a worldwide consensus, some authors recommend RFA as a first-line therapy for such early stage HCC.[11-13]

Tumor staging and the decision between possible treatment options are conducted predominantly based on tumor size, number, vascular invasion, and extrahepatic metastasis evaluated by imaging analysis such as ultrasonography or dynamic computed tomography (CT). However, the malignant nature of the tumor as well as other characteristics are not generally considered.[14,15] Alpha-fetoprotein (AFP) and des-gamma-carboxy prothrombin (DCP) are HCC-specific tumor markers. High levels of serum tumor markers often indicate HCC development in the liver. On the basis of histopathological analysis, serum AFP and DCP levels are also correlated with tumor differentiation, microscopic portal invasion, or intrahepatic metastasis.[16,17]

This present study is an attempt to evoke discussion on treatment strategies for small HCC measuring ≤3 cm by comparing the long-term outcome of patients treated with either hepatectomy or RFA as the first-line treatment for HCC. AFP and DCP were also accounted as indicators in the decision-making and treatment procedure.

MATERIALS AND METHODS

Patients

A total of 1057 patients were admitted to the Department of Hepatology, Toranomon Hospital between 1995 and 2006 for the treatment of initially developed HCC. The major background liver disease was HCV (767 patients, 72.6%), followed by HBV (196 patients, 18.5%), HCV + HBV (8 patients, 0.8%), alcoholic liver diseases (habitual drinking of ethanol at >80 g/day, 48 patients, 4.5%), primary biliary cirrhosis (4 patients, 0.4%), autoimmune hepatitis (2 patients, 0.2%), and cryptogenic liver disease (42 patients, 4.0%). Treatment of HCC included surgical resection in 281 patients, local ablation therapy in 398 patients (RFA, 267 patients; microwave coagulation, 47 patients; ethanol injection, 84 patients), and transarterial chemoembolization in 378 patients. Among these patients, we included patients with Child-Pugh A cirrhosis and HCC measuring ≤3 cm in diameter and numbering ≤3 tumors who were treated radically by either surgical resection or RFA. Table 1 summarizes the profile of the 199 patients who received resection and 209 patients who received RFA. HBV-related liver diseases were more common among patients who underwent resection, who were younger (62 vs 67 years; $P < .001$) than patients with RFA. The maximum tumor diameter was larger in the resection group than in the RFA group (20 vs 18 mm; $P < .001$). With regard to laboratory tests, serum albumin level, platelet count, and prothrombin time (%) were higher among patients in the resection group, whereas serum aspartate aminotransferase (AST) levels were higher among patients in the RFA group. None of the patients in either group had tumor invasion of the major portal branch or extrahepatic metastasis. Our institution does not require informed consent for retrospective analysis.

Diagnosis of HCC

Diagnosis of HCC was predominantly based on image analysis. If a hepatic nodular lesion was found on screening ultrasonography, the patient underwent dynamic CT and/or dynamic magnetic resonance imaging (MRI). Furthermore, when a liver nodule showed hyperattenuation in the arterial phase of dynamic study and washout in portal or delayed phase, or showed typical hypervascular staining on digital subtraction angiography, the nodule was diagnosed as HCC. According to the American Association for the Study of Liver Disease guidelines, we obtained at least 2 dynamic imaging images before treatment.[5] When the nodule did not appear in the abovementioned typical imaging features, a fine needle aspiration biopsy was carried out followed by histological examination and diagnosis.

Table 1. Clinical Background of 199 Patients Who Underwent Hepatic Resection and 209 Patients Who Underwent Radiofrequency Ablation of Liver Tumor

Factors	Resection Group (n = 199)	RFA Group (n = 209)	*P*
Age, y*	62 (29-80)	67 (38-87)	<.001
Sex, men:women	146:53	137:72	NS
HBV:HCV:HBV + HCV:others	60:121:3:15	22:176:1:10	<.001
Habitual alcohol intake, yes:no	29:170	9:200	
Diameter of HCC, mm*	20 (9-30)	18 (8-30)	<.001
No. of HCC, 1:2:3	168:22:9	169:29:11	
Tumor vascularity, present:absent	185:14	156:53	
Albumin, g/dL*	3.7 (2.8-4.7)	3.6 (2.6-4.4)	<.001
Bilirubin, mg/dL*	1.0 (0.3-2.4)	1.0 (0.2-2.4)	NS
AST, IU/L*	43 (13-386)	55 (17-208)	<.001
Platelets, $\times 10^4/mm^3$*	13.1 (4.0-27.2)	10.5 (2.7-25.3)	<.001
Prothrombin time, %*	92 (62-115)	88 (57-125)	.006
AFP, ng/mL*	22 (1-7960)	18 (2-1490)	NS
DCP, AU/L*	20 (<10-1650)	17 (<10-1370)	NS

RFA indicates radiofrequency ablation; NS, not significant; HBV, hepatitis B virus; HCV, hepatitis C virus; HCC, hepatocellular carcinoma; AST, aspartate aminotransferase; IU, international units; AFP, alpha-fetoprotein (AFP); DCP, des-gamma-carboxy prothrombin; AU, arbitrary units.
*Data are expressed as median (range).

Method of Treatment

Physicians and surgeons usually discuss together the preferred choice of therapy in individual patients. Hepatic resection was performed under intraoperative ultrasonographic monitoring and guidance. For small and superficial HCCs, arterial and portal vein clamping at hepatic hilum was not usually performed to maintain liver perfusion.

RFA was performed using 3 different devices: the radiofrequency interstitial tumor ablation system (RITA, RITA Medical Systems Inc., Mountain View, Calif), the cool-tip system (Tyco Healthcare Group LP, Burlington, Vt), and the radiofrequency tumor coagulation system (RTC system, Boston-Scientific Japan Co., Tokyo, Japan). In the first 2 systems, treatment procedures were performed according to the protocol advised by the manufacturer. However, treatment using the RTC system was performed by adopting the "stepwise hook extension technique."[18] The needle was inserted into the tumor percutaneously under ultrasonographic guidance. Because the HCC nodule could not be observed by ultrasonography in 6 cases, the needle was inserted under CT assistance. In the case of RFA, dynamic CT was performed 1 to 3 days after therapy, and the ablated area was evaluated. The goal of treatment was to obtain a necrotic area larger than the original tumor size, with a surrounding treatment margin of $\geq$5 mm in all directions. When this was not achieved or a residual tumor was found, additional ablation was considered. Of 206 total patients, total ablation session was required once in 149 (71.3%) patients, twice in 47 (22.5%) patients, and 3 times or more in 13 patients (6.2%).

Measurement of Serum AFP and DCP

Serum AFP level was measured by chemiluminescent enzyme immunoassay (CLEIA) using a commercial assay kit (Lumipulse Prestoll AFP, Fujirebio Inc., Tokyo, Japan). DCP level was measured by CLEIA (Lumipulse PIVKA II Eisai, Eisai, Tokyo, Japan).

Follow-up Protocol

Physicians examined the patients every 4 weeks after treatment, and liver function tests and tumor markers were also measured once every month. After completion of HCC eradication, recurrence was surveyed with contrast enhancement 3-phase CT every 3 months. Local tumor progression was defined as tumor recurrence adjacent to the resected or ablated area.

Statistical Analysis

Differences in background features and laboratory data between resection and RFA groups were analyzed by the chi-square test and Mann-Whitney *U* test. Survival and recurrence-free survival were analyzed using the Kaplan-Meier technique, and differences in curves were tested using the log-rank test. Independent risk factors associated with survival and recurrence-free survival were studied using stepwise Cox regression analysis.[19] Potential risk factors for survival and recurrence-free survival included the following 14 variables: age, sex, etiology of background liver disease, amount of alcohol intake, serum albumin, bilirubin, AST, platelet count, prothrombin time, AFP, DCP, diameter of the HCC, tumor multiplicity, and tumor vascularity evaluated by dynamic CT or dynamic MRI. A probability of less than .05 was considered significant. Data analysis was performed using SPSS statistical software version 10 (SPSS Inc., Chicago, Ill).

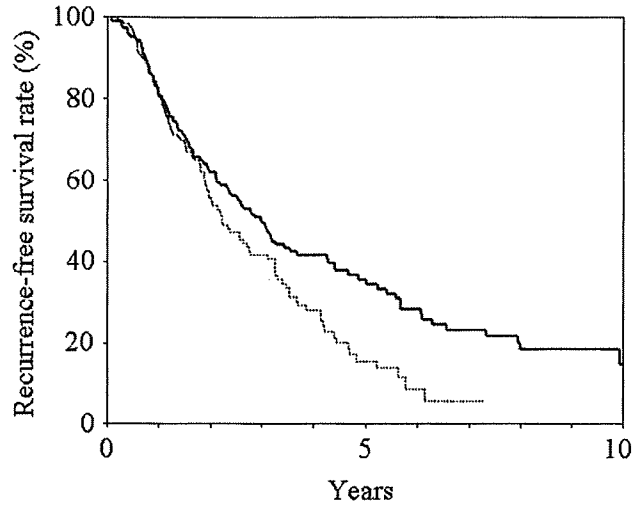

FIGURE 1. Cumulative recurrence free survival rates of the patients who underwent surgical resection (solid line) and radiofrequency ablation (RFA) (dotted line) are shown. The recurrence-free survival rate of the resection group was higher than of the RFA group ($P = .011$).

RESULTS

Survival and Recurrence-free Survival Rates

During the median follow-up of 3.3 years (range, 0.1-12.2 years), 112 (56.3%) of 199 patients in the resection group and 120 (57.4%) of 209 patients in the RFA group developed HCC recurrence. HCC recurrences mainly occurred in other sites in the liver. However, in the RFA group, local tumor progression, defined as HCC recurrence adjacent to the treated site, was seen in 18 (8.6%) of 209 patients, but noted in only 1 patient of the resected group. The cumulative local tumor progression rate in the RFA group was 2.7%, 11.3%, and 12.5% at 1, 3, and 5 years, respectively. The tumors were treated with surgical resection in 2 patients, additional tumor ablation in 8 patients, and transcatheter chemoembolization in the remaining 8 patients.

Exactly 64 patients of the resection group and 31 patients of the RFA group died during the follow-up. The cause of death among patients in the resection group was tumor progression in 51, hepatic failure in 10, gastrointestinal bleeding in 1, and other causes in 2. Uniformly, the cause of death in the RFA group was tumor progression in 16, hepatic failure in 13, gastrointestinal bleeding in 1, and other causes in 1. The cumulative survival rates for the resection group at 1, 3, 5, and 7 years were 96.9%, 90.3%, 79.0%, and 61.5%, whereas those for the RFA group were 99.0%, 87.4%, 74.8%, and 65.4%, respectively. The overall survival rates were not significantly different between the 2 groups.

The tumor recurrence-free survival rates for the resection group at 1, 3, 5, and 7 years were 83.1%, 51.0%, 36.8%, and 23.3%, and for the RFA group were 82.7%, 41.8%, 17.0%, and 5.8%, respectively (Fig. 1). The recurrence-free survival rate was higher in the resection group than in the RFA group ($P = .011$).

Factors Associated With Survival in Patients in the Resection Group

Among 199 patients treated with surgical resection, factors associated with survival were evaluated by both univariate and multivariate analysis (Table 2). Single tumor, serum albumin >3.8 g/dL, and prothrombin time >80% were significant by Kaplan-Meier analysis, whereas factors such as age, sex, etiology of background liver disease, amount of alcohol intake, bilirubin, AST, platelet count, AFP, DCP, diameter of the HCC, and tumor vascularity were not significantly related to patients' survival. In a multivariate analysis using the Cox proportional hazard model, prothrombin time >80 % (hazard ratio [HR], 2.72; 95% confidence interval [CI], 1.56-4.74; $P < .001$) was the independent prognostic factor for survival.

Table 2. Results of Univariate and Multivariate Analyses of Factors Associated With Survival of Patients Treated by Surgical Resection

Variable	No.	% 5-Year Survival Rate	Hazard Ratio (95% CI)	*P*
Univariate analysis				
No. of tumors				.012
Single	167	82.4	–	
Multiple	32	59.8	–	
Albumin, g/dL				.020
≥3.8	134	91.1	–	
<3.8	64	73.1	–	
Prothrombin time (%)				.003
≥80	168	83.0	–	
<80	29	60.1	–	
Multivariate analysis				
Prothrombin time, %, ≥80/<80			2.72 (1.56-4.74)	<.001

CI indicates confidence interval.

Table 3. Results of Univariate and Multivariate Analyses of Factors Associated With Survival in Patients Treated With Radiofrequency Ablation

Variable	No.	% 5-Year Survival Rate	Hazard Ratio (95% CI)	*P*
Univariate analysis				
Platelets, $\times 10^4/mm^3$				.006
≥10	111	84.1	–	
<10	98	65.5	–	
DCP, AU/mL				<.001
<100	187	77.3	–	
≥100	13	33.6	–	
Multivariate analysis				
DCP, AU/L, <100/≥100			5.49 (2.23-13.5)	<.001
Platelets, $\times 10^4/mm^3$, ≥10/<1			2.70 (1.24-5.88)	.012

CI indicates confidence interval; DCP, des-gamma-carboxy prothrombin; AU, arbitrary units.

Factors Associated With Survival in Patients in the RFA Group

We also evaluated the factors associated with the survival of 209 patients treated with RFA (Table 3). Platelet count $\geq 1.0 \times 10^5$ and DCP <100 arbitrary units (AU)/L were significant in univariate analysis, whereas 12 other variables were not associated with survival. Multivariate analysis identified DCP <100 AU/L (HR, 5.49; 95% CI, 2.23-13.5; $P < .001$) and platelet count $\geq 1.0 \times 10^5$ (HR, 2.70; 95% CI, 1.24-5.88; $P = .012$) as significant and independent determinants of survival.

Factors Associated With Recurrence-free Survival in Patients in the Resection Group

Next, we evaluated the factors associated with recurrence-free survival in patients treated with surgical resection (Table 4). Presence of a single tumor, serum albumin ≥3.8 g/dL, platelet count $\geq 1.0 \times 10^5$, and prothrombin time ≥80% were significant in the univariate analysis, whereas 10 other variables were not significant factors for recurrence-free survival. In multivariate analysis, single tumor (HR, 2.39; 95% CI, 1.51-3.80; $P < .001$), serum albumin ≥3.8 g/dL (HR, 1.54; 95% CI, 1.02-2.32;

Table 4. Results of Univariate and Multivariate Analyses of Factors Associated With Recurrence-free Survival Among Patients Treated With Resection

Variable	No.	% 3-Year Survival Rate	Hazard Ratio (95% CI)	P
Univariate analysis				
No. of tumors				<.001
Single	166	55.4	–	
Multiple	32	24.5	–	
Albumin, g/dL				.009
≥3.8	63	71.7	–	
<3.8	134	42.1	–	
Platelets, $\times 10^4/mm^3$				.025
≥10	137	60.3	–	
<10	60	33.0	–	
Prothrombin time, %				.009
≥80	167	55.7	–	
<80	29	29.0	–	
Multivariate analysis				
No. of tumors, single/multiple			2.39 (1.51-3.80)	<.001
Albumin, g/dL, ≥3.8/<3.8			1.54 (1.02-2.32)	.040
Platelets, $\times 10^4/mm^3$, ≥10/<10			1.47 (1.03-2.12)	.036

CI indicates confidence interval.

$P = .040$), and platelet count $\geq 1.0 \times 10^5$ (HR, 1.47; 95% CI, 1.03-2.12; $P = .036$) were independent prognostic factors for recurrence-free survival.

Factors Associated With Recurrence-free Survival in Patients in the RFA Group

Factors associated with recurrence-free survival were evaluated in patients treated by RFA. The 3-year recurrence-free survival rate was 44.7% in 185 patients with DCP <100AU/L, whereas it was 0.0% in 13 patients with DCP ≥100 AU/L. Univariate and multivariate analysis identified only DCP <100 AU/L (HR, 6.82; 95% CI, 3.49-13.3; $P < .001$) as a significant determinant of recurrence-free survival.

Survival and Recurrence-free Survival in Patients With DCP >100 AU/L

Figure 2 shows the cumulative survival rate, and Figure 3 shows the recurrence-free survival rate based on DCP levels. The survival rate and recurrence-free survival rate were associated with DCP in the RFA group, but they were not associated with DCP in the resection group. AFP >400 AU/L was associated with neither survival rate nor recurrence-free survival rate in either the resection or the RFA group. Therefore, 27 selected patients from the resection group and 13 from the RFA group whose DCP was ≥100 AU/L were examined to determine whether the overall survival rate was different between the resection and RFA groups. The backgrounds of the 2 groups based on treatment procedure are shown in Table 5. Treatment procedure (resection), age <65 years and serum albumin >3.8 g/dL were significant in the univariate analysis. Multivariate analysis revealed that treatment procedure (HR, 1.26; 95% CI, 1.04-1.53; $P = .020$) was a significant and independent determinant in the overall survival rate (Table 6).

DISCUSSION

Patients with HCC usually have a history of chronic liver disease, especially cirrhosis. Unfortunately, even when curative therapy is performed, tumor recurrence is frequent. For this reason, less invasive treatment procedures are needed to preserve liver function.

The Barcelona Clinic Liver Cancer (BCLC) guideline for the treatment of HCC recommends resection for patients with a single HCC and Child-Pugh A who have no other complications.[5] The suggested option for RFA includes patients with multiple tumors and associated

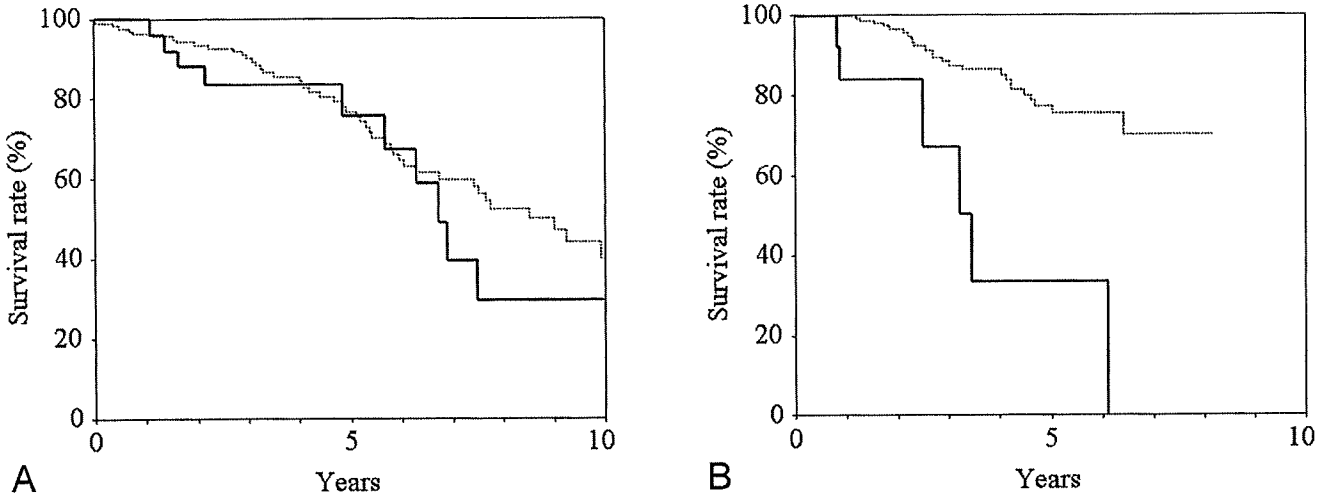

FIGURE 2. Cumulative overall survival rate of the patients who underwent surgical resection and radiofrequency ablation based on des-gamma-carboxy prothrombin (DCP) level is shown. Solid line indicates DCP level ≥100 AU/L; dotted line, DCP level <100 AU/L. (A) Cumulative survival rate of patients who underwent resection based on DCP level is shown. (B) Cumulative survival rate of patients who underwent radiofrequency ablation (RFA) based on DCP level is shown. Prognosis of patients who underwent RFA varied according to DCP level, whereas prognosis of patients who underwent resection was independent of DCP level.

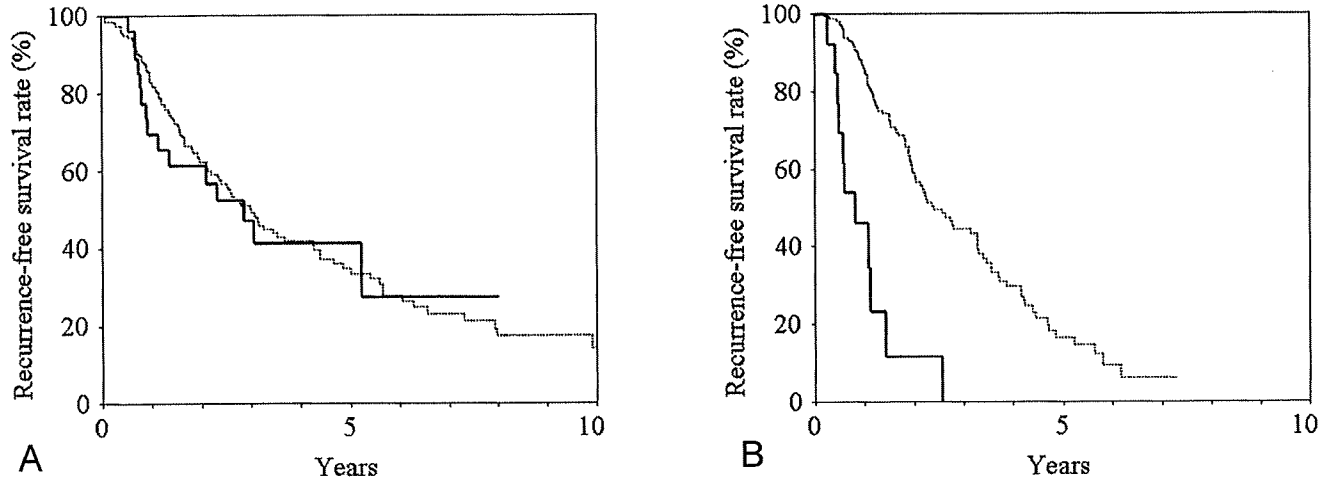

FIGURE 3. Cumulative recurrence-free survival (RFS) rate of the patients who underwent surgical resection and radiofrequency ablation based on des-gamma-carboxy prothrombin (DCP) level is shown. Solid line indicates DCP level ≥100 AU/L; dotted line, DCP level <100 AU/L. (A) Cumulative RFS rate of patients who underwent resection based on DCP level is shown. (B) Cumulative RFS rate of patients who underwent RFA based on DCP level is shown. Prognosis of patients who underwent RFA varied according to DCP level.

disease. However, in clinical practice, RFA is widely applied as a curative treatment for variable stages of HCC. Advances in imaging diagnosis have allowed identification of small HCC measuring <2 cm during the course of chronic liver disease.[3] The use of RFA seems to be an excellent option for the aforementioned tumors.

In the present study, we focused on the malignant potential of HCC and examined 2 representative tumor markers of HCC. AFP has been used as a tumor marker for HCC worldwide, and is considered by some as a predictor of survival or recurrence after RFA.[12] DCP is also useful as a prognostic factor in patients with HCC.[20-22]

In the present study, serum albumin levels and prothrombin time, which reflect liver function, were significantly associated with survival in patients who undergo resection similar to tumor multiplicity. Likewise, serum

Table 5. Clinical Background of 27 Patients Who Underwent Resection and 13 Patients Who Underwent Radiofrequency Ablation

Factors	Resection Group, n = 27	RFA Group, n = 13	*P*
Age, y*	60 (35-73)	67 (50-78)	.006
Sex (men:women)	23:4	10:3	NS
HBV:HCV:others	13:12:2	1:9:3	.015
Habitual alcohol intake, yes: no	3:24	2:11	NS
Diameter of HCC, mm*	22 (14-30)	22 (10-30)	NS
No. of HCC, single:multiple	26:1	9:4	.031
Tumor vascularity, present:absent	27:0	12:1	NS
Albumin, g/dL*	3.8 (3.3-4.3)	3.4 (2.6-4.1)	.003
Bilirubin, mg/dL*	0.9 (0.4-1.9)	0.9 (0.4-1.8)	NS
AST, IU/L*	38 (16-240)	49 (17-145)	NS
Platelets, $\times 10^4/mm^3$*	15.1 (6.0-24.5)	10.5 (4.5-24.6)	.025
Prothrombin time, %*	94 (79-112)	86 (73-110)	NS

*Data are expressed as median (range).

Table 6. Results of Univariate and Multivariate Analyses of Factors Associated With Survival Among Patients With Serum Des-gamma-carboxy Prothrombin Level ≥100

Variable	No.	% 5-Year Survival Rate	Hazard Ratio (95% CI)	*P*
Univariate analysis				
Age, y				.026
<65	25	87.7	—	
≥65	15	45.5	—	
Albumin, g/dL				.024
≥3.8	12	100	—	
<3.8	28	58.4	—	
Treatment procedure				.012
Resection	27	83.4	—	
RFA	13	33.6	—	
Multivariate analysis				
Treatment procedure				.020
Resection or RFA			1.26 (1.04-1.53)	

CI indicates confidence interval; RFA, radiofrequency ablation.

albumin level, platelet count, prothrombin time, and presence of multiple tumors were associated with recurrence-free survival. Alternatively, in RFA patients, in addition to platelet count, which indicates severity of portal hypertension, DCP levels were significant predictors of survival. Likewise, DCP levels were also significant predictors in recurrence-free survival. It is noteworthy that both survival and disease-free survival rates of patients who undergo RFA, but not resection, are correlated with DCP levels by multivariate analysis.

It is difficult to explain why DCP influenced survival and disease-free survival in the RFA group but not the resection group. We speculate that a high level of serum tumor marker reflects a high tumor malignant potential. Therefore, for a biologically aggressive tumor like HCC, resection is recommended over RFA because the radical nature of surgical resection may be superior to RFA.

According to previous reports, DCP is related to histological features of HCC.[21,22] Shirabe et al[21] examined

218 HCC patients who underwent surgical resection for HCC and concluded that serum DCP level is a predictor of microvascular invasion. They identified microvascular invasion in 44% of their patients with DCP ≥100 AU/L, but in only 16% of patients with DCP <100 AU/L. Shimada et al[22] examined explanted liver transplants and reported that serum DCP level is associated with vascular invasion and HCC recurrence. When we evaluated the relationship between clinicopathological features and serum DCP level in the resection group, microvascular invasion was found in 11 (44.0%) of 25 patients with DCP ≥100 AU/L, but in only 22 (13.6%) of 162 patients with DCP <100 AU/L, which was similar to the results in Shirabe et al.[21]

Unfortunately, in the RFA group, histological examination was performed only on nodules that showed atypical image findings. Moreover, it is sometimes difficult to judge microscopic vascular invasion in small specimens obtained by needle biopsy. However, we cannot deny the presence of microscopic vascular invasion in patients with high levels of tumor markers who have been treated with RFA. Furthermore, high levels of DCP are not only a marker of malignancy, but also indicate the biologic aggressiveness and progression of the HCC tumor. Hence, HCCs with high levels of DCP have greater chances of hypervascularity and early infiltration than do HCCs with lower levels of DCP.

In general, microscopic vascular invasion or intrahepatic metastasis is a poor prognostic factor for survival and recurrence-free survival even in patients who undergo surgical resection.[23-25] Why was survival and recurrence-free survival not different among the resection group in our study? One of the reasons is that we included patients with an HCC of a maximum diameter of ≤3 cm. In contrast, most previous studies included HCC as large as 5 cm in diameter.[23-25] The biological features of malignancy might be worse in such large tumors. We speculate that in HCC measuring ≤3 cm (median 2.0 cm), minimal microscopic vascular invasion or intrahepatic metastasis adjacent to the main tumor can be curatively resected by surgery, whereas these sometimes become incompletely necrotic even when a sufficient surrounding margin is obtained from treatment with RFA.

Analysis of factors associated with survival in patients with DCP of ≥100 AU/L showed that the type of treatment procedure (eg, hepatectomy) significantly influenced outcome. In contrast, no such relationship was found in patients with DCP of <100 AU/L. These results indicate that DCP is an important factor in selecting treatment procedure for patients with HCC measuring ≤3 cm and numbering ≤3 tumors.

In conclusion, DCP levels were significant predictors of both survival and recurrence-free survival in the RFA group. Hence, when the level of DCP is high, hepatic resection should be the treatment of choice even if the maximum tumor diameter is ≤3 cm and there are ≤3 tumors. If the level is low, RFA should be considered, because it is less invasive.

Because the current study was retrospective in nature, it has certain limitations and potential biases. The baseline characteristics of the 2 groups were quite different. Although we enrolled only Child-Pugh A patients, the resection group was younger and had better liver function. However, etiology of the liver disease was also different; the overall survival rates were not significantly based on etiology in either the resection or the RFA group. Therefore, we believe that the etiology of liver disease could be ignored in these patients. Our study did not uncover the reason for the high risk of mortality and tumor recurrence in patients in the RFA group with high levels of DCP. A cohort validation study is needed to confirm our results. In addition, clinicopathological and molecular analyses are also needed to define the biological significance of the biomarker.

Conflict of Interest Disclosures

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CLINICAL STUDIES

Predictive factors of advanced recurrence after curative resection of small hepatocellular carcinoma

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Keywords
advanced recurrence – α-foetoprotein – resection – small hepatocellular carcinoma

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Abstract

Background: The tumour recurrence rate after resection is still high even in patients with small hepatocellular carcinoma (HCC). The advanced patterns of recurrence occasionally occur after resection. In this study, we analysed the clinical and histological characteristics of small HCC and evaluated the predictive factors of advanced tumour recurrence. *Methods:* One hundred and sixty-five patients underwent resection of small HCC measuring 3 cm or less in greatest dimension. Patterns of tumour recurrences were classified into advanced recurrence and minor recurrence based on size, number, vascular invasion and extrahepatic metastasis of recurrent tumour. We created a simple index to closely evaluate the malignant potential of small HCC, named α-foetoprotein–size ratio index (ASRI). *Results:* Overall tumour recurrence was significantly associated with tumour multiplicity ($P < 0.001$) and ASRI ($P = 0.001$). Tumour multiplicity, ASRI and tumour differentiation were independent and significant predictive factors of advanced recurrences. The overall survival rates were lower in the advanced recurrence group than the minor recurrence or the no recurrence group. *Conclusions:* Patients with advanced recurrences have a poor prognosis, although they have undergone curative resection of small HCC. On the other hand, patients with minor recurrences have a relatively good prognosis. ASRI was a useful index to predict advanced recurrence after curative resection of small HCC. The therapeutic management to prevent advanced recurrences is needed.

Hepatocellular carcinoma (HCC) is one of the most common neoplasms in Africa and Asia, including Japan. Routine checkups are performed in patients with hepatitis or cirrhosis who constitute a significant high-risk group for HCC (1–3). Recently, technological advances in ultrasonography (US), computed tomography (CT) and magnetic resonance imaging have helped in the detection of small HCC during follow-up periods of chronic liver disease (4, 5). Moreover, resection of HCC has become safe in cirrhotic patients due to progress in surgical techniques, and perioperative management has contributed to very low operative mortality. However, the tumour recurrence rate after resection is still high even in patients with small HCCs (6–10). Recurrences in the remnant liver can occur based on two characteristics of HCC: intrahepatic metastasis from the primary tumour and de novo multicentric carcinogenicity (11–13).

Tumour status at the time of recurrence is important to improve prognosis because tumour recurrence rates after curative resection are high. The advanced patterns of recurrence occasionally occur as follows: widespread recurrence, a number of recurrent tumours, large recurrent tumour, involving vascular invasion and extrahepatic metastasis, despite curative resection (14–16). Because the therapeutic approach for recurrent tumours is limited, these cases have a poor prognosis. Therefore, it is important to pick up patients who are likely to have these advanced recurrence, and to develop effective adjuvant therapy. In the present study, we examined the clinical features of small HCC, and identified the factors associated with tumour recurrence, especially advanced recurrence and prognosis after curative resection of small HCCs using clinical data and results of histopathological examination. Furthermore, we created a simple index to closely evaluate the malignant potential of small HCC and evaluated the usefulness of this index as a predictor of recurrence of HCC after curative resection.

Patients and methods

Patients

Medical records of patients who were hospitalized at Toranomon Hospital from 1995 to 2005 were reviewed retrospectively. HCC was diagnosed by detailed imaging or histopathological examination. A total of 251 consecutive patients with tumours underwent resection as the initial therapy for HCC, and 165 of these patients were found to have HCC measuring $\leq$ 3 cm (greatest dimension) and were eligible for inclusion in this study. These 165 patients (127 men and 38 women; median age 61 years; range, 38–73 years) had chronic hepatitis or cirrhosis. Hepatitis B virus (HBV) surface antigen was positive in 33, anti-hepatitis C virus (HCV) was positive in 127, but neither of them was positive in eight. Table 1 lists the clinical characteristics of the 165 patients before hepatectomy. Of these, 125 patients (75.6%) were classified as grade A according to Child–Pugh classification. The median value for the indocyanine green retention rate at 15 min was 24%, and the median values for serum albumin, bilirubin, aspartic transaminase (AST), α-foetoprotein (AFP) concentration and platelet counts were 3.7 g/dl, 1.0 mg/dl, 44 IU/L, 26 ng/ml and $10.8 \times 10^4/mm^3$ respectively.

Among 165 patients, 26 patients (15.8%) had multiple tumours before resection. We conducted percutaneous ablation therapy, including ethanol injection, microwave coagulation

Table 1. Clinical characteristics of 165 patients before hepatic resection

Variables	$n = 165$
Age	62 (38–80)*
Gender (male:female)	127:38
Hepatitis B surface antigen-positive	46 (27.9%)
Anti-hepatitis C virus-positive	109 (66.1%)
Child–Pugh classification (A:B:C)	125:38:1
Serum albumin (g/dl)	3.6 (2.6–4.6)*
Serum bilirubin (mg/dl)	1.0 (0.3–2.7)*
Aspartate transaminase (IU/L)	44 (12–386)*
Prothorombin time (%)	90.8 (58.9–112.8)*
ICG R15 (%)	21 (8–68)*
Platelet count (10^4/mm^3)	12.6 (3.9–26.0)*
α-foetoprotein (ng/ml)	23 (1–7960)*
Des-γ-carboxy prothorombin (mAU/ml)	22 (< 10–1650)*
Tumour size (mm)	20 (7–30)*
Tumour number (solitary:multiple)	139:26
Vascularity positive	153 (92.7%)
ASRI	1.2 (0.03–345)*

*Values are medians (range).
ASRI, α-foetoprotein–size ratio index = AFP (ng/ml)/tumour size (mm); ICG R15, indocyanine green retention test at 15 min.

and radiofrequency ablation, for another tumour before surgery if another tumour existed in a lobe distant from the resected tumour. The term 'curative resection' indicated that no tumours were left in the remnant liver irrespective of the width of margin around the tumour; this was confirmed using (i) intra-operative US and (ii) combined US and dynamic CT conducted after 1 month of surgery.

This study was conducted in accordance with the guidelines of the Declaration of Helsinki and its subsequent amendments, and informed consent was obtained from every patient. This study was approved by the Local Ethics Committee of Toranomon Hospital.

Follow-up and recurrence of hepatocellular carcinoma

Patients were followed up on a monthly or a bi-monthly basis after surgery by monitoring AFP and other biochemical data, and conducting US or helical dynamic CT every 3 months. The median observation period for the entire patient cohort was 6.0 years, with a range of 0.3–16.4 years. Recurrence of HCC was diagnosed by typical hypervascular characteristics on angiography and/or histological examination with fine needle biopsy specimens, in addition to certain features of CT and US.

The modes of cancer recurrence were classified into two categories: (i) advanced recurrence and (ii) minor recurrence. The patterns of recurrence were morphologically judged from the images of CT and angiography, and from histopathological findings. The pattern of recurrent tumour number > 3, tumour size > 3 cm, involving vascular invasion and/or extrahepatic metastasis was defined as advanced recurrence. The recurrent pattern, except for those described above, was defined as minor recurrence.

Imaging analysis

Ultrasonography or helical dynamic CT was carried out every 3 months for follow-up and examined for a change in imaging findings. Dynamic CT scans were performed using a single-detector helical CT scanner (Hi-Speed advantage SG; GE Yokogawa Medical Systems, Tokyo, Japan). The radiological studies included intra-arterial digital subtraction angiography (celiac and mesenteric angiography) and selective angiography of the common hepatic artery. CT arterial portography (CT-AP) and CT hepatic angiography (CT-HA) were carried out in almost all patients before surgery. HCC was diagnosed by typical hypervascular characteristics on angiography and/or CT-HA, and hypo-attenuation on CT-AP. If hepatic nodules showed iso-hypo-attenuation on CT-HA and iso-hypo-attenuation on CT-AP, histological examination was carried out with fine needle biopsy specimens before surgery.

Table 2. Pathological characteristics of small hepatocellular carcinoma

Variables	$n = 165$
Tumour differentiation (early:well:moderately:poorly)	11:32:100:22
Growth type (Eg:Ig)	138:27
Capsular formation	99 (60.0%)
Capsular infiltration	52 (31.5%)
Septum formation	42 (25.5%)
Portal vein invasion	26 (15.8%)
Intrahepatic extent of tumour	5 (3.0%)
Presence of cirrhosis	114 (69.1%)

Eg, expansive growth (well-demarcated border); Ig, infiltrative growth (poorly demarcated border).

Histopathological examination

Macroscopic and microscopic examinations were performed according to the classification of the Liver Cancer Study Group of Japan (17). All resected specimens were analysed histopathologically for tumour size, growth type, tumour differentiation, capsular formation, portal vein invasion, satellite nodules and fibrosis staging of surrounding liver. The tumour characteristics are summarized in Table 2. We categorized well-differentiated HCC that had histological features of the early stage into early HCC. Early HCC was defined as follows: macroscopically, the tumours had an indistinct margin that replaced the liver cell cords at the tumour–non-tumour boundary; microscopically, increased cell density with an increased nuclear to cytoplasm ratio and an irregular thin-trabecular pattern, and the portal tracts were involved inside the tumours together with tumour cell invasion into the portal tracts (18–20).

α-foetoprotein–size ratio index

In this study, there were patients with very high AFP levels regardless of the cohort of small HCC measuring 3 cm or less in greatest dimension. We hypothesized that HCCs with high AFP levels had more malignant potential than those with low AFP levels if each tumour size was equal. And so, we created a simple index to closely evaluate the malignant potential of small HCC, named the AFP–size ratio index (ASRI). The numerical formula of ASRI was defined as follows: ASRI = AFP levels (ng/ml)/tumour size (mm). For example, the calculated value of ASRI of HCC, with tumour size = 20 mm and AFP levels = 400 ng/ml, is 20.

Statistical analysis

Standard statistical measures and procedures were used. We used the χ^2-test to assess the significant association of risk

factors with tumour recurrence after resection. All factors found to be at least marginally associated with recurrence ($P < 0.15$) were tested by multivariate analysis. Independent factors, associated with the recurrence of HCC and prognosis, were calculated using stepwise Cox regression analysis. The χ^2-test was used to analyse differences between the clinical characteristics of HCC and the patterns of tumour recurrences. The cumulative overall survival rates after resection of small HCC were analysed using the Kaplan–Meier method, and differences in the curves were tested using the log-rank test. A P value of < 0.05 in a two-tailed test was considered significant. Data analysis was performed using the SPSS software, version 11.0 (Chicago, IL, USA).

Results

Factors associated with tumour recurrences

Univariate analysis showed that tumour recurrence was significantly associated with tumour multiplicity ($P < 0.001$), ASRI ≥ 20 ($P = 0.004$), AFP levels ≥ 1000 ng/ml ($P = 0.024$), portal vein invasion ($P = 0.035$) and serum albumin levels ≥ 3.5 g/dl ($P = 0.041$), and marginally significantly with HCV positivity ($P = 0.058$), HBV negativity ($P = 0.072$), hypervascularity of tumour ($P = 0.076$) and serum AST levels ≥ 50 IU/L ($P = 0.088$) (Table 3). Because these variables were associated, multivariate analysis was performed using the nine variables mentioned above in the model (Table 4a). The following two variables were significantly associated with overall tumour recurrence: tumour multiplicity [hazard ratio (HR) 3.06, 95% confidence interval (CI): 1.84–5.10; $P < 0.001$], ASRI ≥ 20 (HR 2.42, 95% CI: 1.41–4.18, $P = 0.001$). To evaluate risk factors except for tumour multiplicity, subgroup analysis was conducted in solitary tumour cases (Table 4b). Independent risk factors affecting the overall recurrence of HCC were the presence of portal vein invasion (HR 2.35, 95% CI: 1.31–4.20, $P = 0.004$), ASRI ≥ 20 (HR 2.23, 95% CI: 1.19–4.18, $P = 0.013$) and serum albumin < 3.5 g/dl (HR 1.74, 95% CI: 1.05–2.88, $P = 0.030$).

Predictive factors of advanced recurrences after curative resection

Tumour recurrence was diagnosed in 102 (61.8%) of the 165 patients, with a median interval of 2.77 years after curative resection. Of these, 22 (13.3%) were categorized into advanced recurrence, 80 (48.4%) were minor recurrence and the remaining 63 (38.1%) were no recurrence. The median interval to recurrence after resection was 1.82 years in the minor recurrence group and 1.01 years in the advanced recurrence group respectively. Univariate analysis showed that advanced recurrence was significantly associated with the following four factors: poorly differentiation of tumour ($P < 0.001$), ASRI ≥ 20 ($P = 0.005$), tumour multiplicity ($P = 0.017$) and AFP levels ≥ 1000 ng/ml ($P = 0.025$) (Table 5). Multivariate analysis by the Cox model was performed using the four variables mentioned above. Predictive factors of advanced recurrences after curative resection were tumour multiplicity (HR 5.65, 95% CI: 1.77–18.1, $P = 0.003$), ASRI ≥ 20 (HR 4.04, 95% CI: 1.16–14.1, $P = 0.028$) and poor differentiation of tumour (HR 2.70, 95% CI: 1.51–4.82, $P = 0.001$) (Table 6).

We compared values of ASRI by patterns of recurrences (Fig. 1). The median values of ASRI were 0.68 (minimum: 0.07–maximum: 73.0) in the no recurrence group, 1.64 (0.06–344) in the minor recurrence group and 3.28 (0.03–318) in the advanced recurrence group respectively. The values of ASRI were marginally significantly higher in the minor recurrence and the advanced recurrence group than in the no recurrence group. However, there was no significance of ASRI values stratified by tumour number.

Furthermore, we categorized the following three subgroups into the advanced recurrence group: tumour number > 3, or tumour size > 3 cm without vascular invasion and extrahepatic metastasis (multi/large nodular recurrence group), recurrent tumour with vascular invasion (vascular invasion group) and

Table 3. Factors associated with overall recurrence of small hepatocellular carcinoma by univariate analysis

Factors	Hazard ratio (95% CI)	*P*
Age (≥ 65 vs. < 65 years)	0.79 (0.52–1.22)	0.288
Gender (female vs. male)	0.78 (0.48–1.26)	0.316
HBV (negative vs. positive)	1.52 (0.96–2.41)	0.072
HCV (positive vs. negative)	1.53 (0.99–2.36)	0.058
Serum albumin (< 3.5 vs. ≥ 3.5 g/dl)	1.53 (1.02–2.31)	0.041
Serum bilirubin (≥ 1.5 vs. < 1.5 mg/dl)	1.11 (0.62–2.00)	0.713
AST levels (≥ 50 vs. ≥ 50 IU/L)	1.41 (0.95–2.10)	0.088
Prothorombin time (≥ 70 vs. $< 70\%$)	0.67 (0.31–1.45)	0.311
ICG R 15 (≥ 30 vs. $< 30\%$)	1.37 (0.89–2.12)	0.158
count ($\geq 10^5$ vs. $< 10^5$/mm^3)	0.81 (0.54–1.22)	0.304
AFP levels (≥ 1000 vs. < 1000 ng/ml)	2.01 (1.10–3.67)	0.024
ASRI (≥ 20 vs. < 20)	2.16 (1.28–3.64)	0.004
DCP levels (≥ 100 vs. < 100 mAU/ml)	1.19 (0.70–2.04)	0.517
Fibrosis stage (F4 vs. F1, 2, 3)	1.09 (0.72–1.66)	0.681
Tumour size (≥ 21 vs. < 21 mm)	1.088 (0.73–1.63)	0.680
Tumour number (multiple vs. solitary)	2.85 (1.74–4.65)	< 0.001
Vascularity (positive vs. negative)	2.48 (0.91–6.76)	0.076
Tumour differentiation (poorly vs. early, well, moderately)	1.15 (0.87–1.51)	0.333
Eg	1.00 (0.60–1.68)	0.987
Capsular formation	1.01 (0.68–1.52)	0.948
Infiltration to capsular	1.39 (0.92–2.10)	0.121
Septum formation	0.99 (0.63–1.56)	0.969
Portal vein invasion	1.70 (1.04–2.78)	0.035
Intrahepatic extent of tumour	1.57 (0.58–4.26)	0.380

AFP, α-foetoprotein; ASRI, α-foetoprotein–size ratio index; AST, aspartic transaminase; DCP, des-γ-carboxy prothorombin; Eg, expansive growth (well-demarcated border); HBV, hepatitis B virus; HCV, hepatitis C virus; ICG R15, indocyanine green retention test at 15 min.

Table 4a. Independent risk factors affecting the overall recurrence of hepatocellular carcinoma after curative resection of small hepatocellular carcinoma by multivariate analysis

Factors	Category	Hazard ratio (95% CI)	*P* value
Tumour number	1: solitary	1	
	2: multiple	3.06 (1.84–5.10)	< 0.001
ASRI	1: < 20	1	
	2: ≥20	2.42 (1.41–4.18)	0.001

ASRI, α-foetoprotein–size ratio index; CI, confidence interval.

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Table 4b. Independent risk factors affecting the overall recurrence of hepatocellular carcinoma after curative resection of small hepatocellular carcinoma by multivariate analysis (solitary cases only)

Factors	Category	Hazard ratio (95% CI)	*P* value
Portal vein invasion	1: –	1	
	2: +	2.35 (1.31–4.20)	0.004
ASRI	1: < 20	1	
	2: ≥20	2.23 (1.19–4.18)	0.013
Serum albumin	1: ≥3.5	1	
	2: < 3.5	1.74 (1.05–2.88)	0.030

ASRI, α-foetoprotein–size ratio index; CI, confidence interval.

Table 5. Univariate analysis for clinical factors associated with advanced recurrence

Factors	Advanced recurrence, *n* = 22 (%)	Minor recurrence, *n* = 80 (%)	No recurrence, *n* = 63 (%)
Age			
< 65 years	13 (59)	59 (73.8)	35 (55.6)
≥65 years	9 (41)	21 (26.2)	28 (44.4)
Gender			
Male	19 (86.4)	62 (77.5)	46 (73)
Female	3 (13.6)	18 (22.5)	17 (27)
HBV			
Positive	5 (22.7)	19 (23.8)	22 (34.9)
Negative	17 (77.3)	61 (76.2)	41 (65.1)
HCV			
Negative	5 (22.7)	23 (28.8)	28 (44.4)
Positive	17 (77.3)	57 (71.2)	35 (55.6)
Serum albumin			
≥3.5	11 (50)	49 (61.3)	41 (65.1)
< 3.5	11 (50)	31 (39.7)	22 (34.9)
Serum bilirubin			
< 1.5	21 (95.5)	67 (83.8)	56 (88.9)
≥1.5	1 (4.5)	13 (16.2)	7 (11.1)
AST levels			
< 50	17 (77.3)	40 (50)	42 (66.7)
≥50	5 (22.7)	40 (50)	21 (33.3)
Prothorombin time			
< 70	2 (9.1)	5 (6.3)	14 (22.2)
≥70	20 (90.9)	75 (93.7)	49 (77.8)
ICG R 15			
< 30	15 (68.2)	58 (72.5)	48 (76.2)
≥30	7 (31.8)	22 (27.5)	15 (23.8)
Platelet count			
$< 10^5$	7 (31.8)	28 (35)	30 (47.6)
$\geq 10^5$	15 (68.2)	52 (65)	33 (52.4)
AFP levels			
< 1000	17 (77.3)	73 (91.3)	61 (96.8)
≥1000	5 (22.7)*	7 (8.7)	2 (3.2)
ASRI			
< 20	15 (68.2)	70 (87.5)	60 (95.2)
≥20	7 (31.8)*	10 (12.5)	3 (4.8)
DCP levels			
< 100	18 (81.8)	68 (85)	54 (85.7)
≥100	4 (18.2)	12 (15)	9 (14.3)
Fibrosis stage			
F1, 2, 3	9 (41)	23 (28.8)	19 (31.7)
F4	13 (59)	57 (71.2)	41 (68.3)
Tumour size			
< 21	11 (50)	53 (66.3)	37 (58.7)
≥21	11 (50)	27 (33.7)	26 (41.3)
Tumour number			
Solitary	14 (63.6)	67 (83.8)	58 (92.1)
Multiple	8 (36.4)*	13 (16.2)	5 (7.9)
Vascularity			
Negative	1 (4.5)	3 (3.8)	8 (12.7)
Positive	22 (95.5)	77 (96.2)	55 (87.3)
Tumour differentiation			
Early, well, moderately	13 (59.1)	74 (92.5)	56 (88.9)
Poorly	9 (40.9)*	6 (7.5)	7 (11.1)
Eg			
Eg	21 (95.5)	63 (78.8)	54 (85.7)
Ig	1 (4.5)	17 (21.2)	9 (14.3)
Capsular formation			
Absence	6 (27.3)	33 (41.3)	22 (34.9)
Presence	16 (72.7)	47 (58.7)	41 (65.1)
Infiltration to capsular			
Absence	13 (59.1)	54 (67.9)	46 (73)
Presence	9 (40.9)	26 (32.1)	17 (27)
Septum formation			
Absence	16 (72.7)	61 (76.2)	46 (73)
Presence	6 (27.3)	19 (23.8)	17 (27)
Portal vein invasion			
Absence	17 (77.3)	65 (81.3)	54 (85.7)
Presence	5 (22.7)	15 (18.7)	6 (14.3)
Intrahepatic extent of tumour			
Absence	20 (90.9)	78 (97.5)	59 (98.3)
Presence	2 (9.1)	2 (2.5)	1 (1.7)

*Significantly higher than the other groups ($P < 0.05$).

AFP, α-foetoprotein; ASRI, α-foetoprotein–size ratio index; AST, aspartic transaminase; DCP, des-γ-carboxy prothorombin; Eg, expansive growth (well-demarcated border); HBV, hepatitis B virus; HCV, hepatitis C virus; ICG R15, indocyanine green retention test at 15 min; Ig, infiltrative growth (poorly demarcated border).

Table 6. Predictive factors of advanced recurrence after curative resection by multivariate analysis using the Cox model

Factors	Category	Hazard ratio (95% CI)	*P* value
Tumour number	1: solitary	1	
	2: multiple	5.65 (1.77–18.1)	0.003
ASRI	1: < 20	1	
	2: ≥20	4.04 (1.16–14.1)	0.028
Tumour differentiation	1: early, well, moderately	1	
	2: poorly	2.70 (1.51–4.82)	0.001

ASRI, α-foetoprotein–size ratio index; CI, confidence interval.

presence of extrahepatic metastasis (extrahepatic metastasis group). The multi/large nodular recurrence group had 17 cases (77.3%), the vascular invasion group had three (13.6%) and the

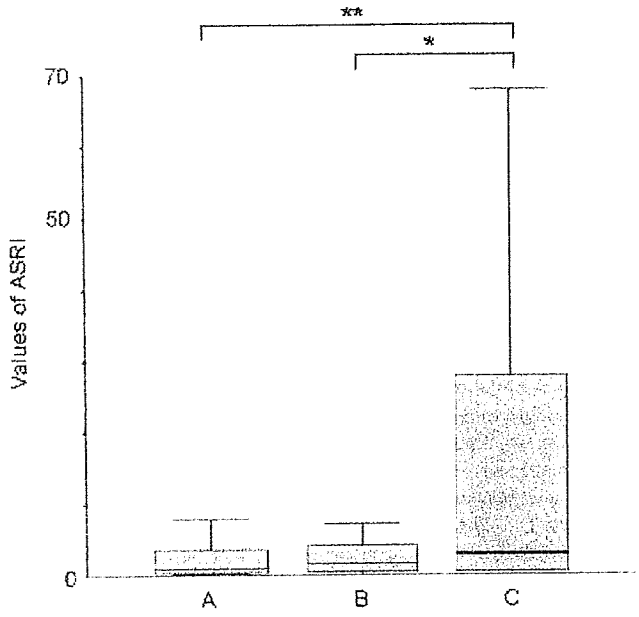

Fig. 1. Comparison with values of ASRI by patterns of recurrences. (A) No recurrence group, (B) minor recurrence group, (C) advanced recurrence group. *P=0.032, **P=0.028.

extrahepatic metastasis group had two (9.1%) in 22 cases of advanced recurrence. In particular, patients in the vascular invasion group had significantly higher pre-operative des-γ-carboxy prothorombin levels than those in the other two groups (P=0.008). Meanwhile, there was no significant difference of ASRI among the three groups.

Survival rate after curative resection by patterns of recurrences

Figure 2 shows the overall survival rates by patterns of recurrences. The overall survival rates of patients were 98.5, 93.6 and 91.8% for the first, third and fifth year in the no recurrence group; 98.8, 96.5 and 85.6% in the minor recurrence group; and 91.3, 64.5 and 35.1% in the advanced recurrence group respectively. The overall survival rates of the advanced recurrence group were significantly lower than those of the minor recurrence and the no recurrence groups (advanced recurrence vs. no recurrence: $P < 0.0001$, advanced recurrence vs. minor recurrence: P=0.001). Furthermore, the overall survival rates of the minor recurrence group were significantly lower than those of the no recurrence group (P=0.009). However, the overall survival rates of both the minor recurrence and the no recurrence groups were similar for the first 5 years after surgery.

Discussion

Our study identified the clinical, radiological and histological factors associated with advanced tumour recurrence and prognosis after curative resection of small HCC. Predictive factors of advanced recurrence were tumour number, ASRI and tumour differentiation. ASRI, which was made to reflect the malignant potential of HCC precisely, was easy to calculate and useful to predict the overall and advanced recurrence of HCC. Patients in the advanced recurrence group had a poorer prognosis than those in the minor recurrence and the no recurrence groups. On the other hand, patients in the minor recurrence group had a

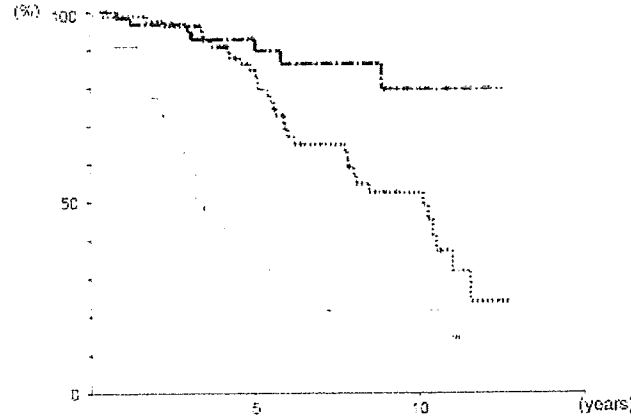

Fig. 2. Overall survival rates by patterns of recurrences; thick broken line: no recurrence group, dot line: minor recurrence group, solid line: advanced recurrence group.

prognosis similar to that of the no recurrence group for the first 5 years after resection.

Some predictors of survival and recurrence after resection were reported previously (21–24). These reports showed that the main predictors of recurrence were tumour size, tumour number, serum AFP levels, tumour differentiation, vascular invasion, etc. In the present study, we intended for patients with small HCC within 3 cm to pick up cases with high malignant potential. Therefore, tumour size was not associated with recurrence, but the other factors mentioned above were associated with recurrence as well as previous reports. However, we recently showed that ASRI was associated with both overall and advanced recurrence after resection. Small HCC with a high ASRI value may have a high malignant potential and may be likely to cause intra- or extrahepatic metastasis.

The high recurrence rate of HCC after curative resection and ablation is attributable to two principal characteristics: intrahepatic metastasis and de novo multicentric carcinogenesis. Some studies have shown that intrahepatic metastasis is an important mechanism of early recurrence after resection (13, 16, 24). In the present study, time to advanced recurrence was short: just 1 year. Furthermore, a previous study showed that tumour differentiation, which was a predictive factor of advanced recurrence in this study, was associated with intrahepatic metastasis (22). This is probably because potential metastasis depends on biological tumour factors, such as tumour differentiation. Considering these facts, a main mechanism of advanced recurrence is assumed intrahepatic metastasis. High AFP levels have been reported as a poor prognosis factor after resection of HCC (25, 26). On the other hand, it is assumed that AFP levels may increase in patients with acute or chronic active inflammation in background hepatocytes without HCC (27, 28). It is difficult to distinguish these mechanisms of AFP elevation. We created ASRI to evaluate the malignant potential of HCC by calculating AFP values per unit tumour diameter. Although it is impossible to distinguish neoplastic and inflammatory AFP elevation using this index, ASRI may mainly reflect neoplastic AFP elevation because ASRI is a predictive factor of advanced recurrence of HCC. In addition, Imamura *et al.* (24) reported that high AFP levels were associated with early recurrence within 2 years after resection, and this fact also supports our result.

α-foetoprotein levels usually tend to be higher in HBV-related HCC than those related to HCV, and this tendency has been reported by researchers in Japan, where HCV is

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