invasion, extrahepatic metastasis or Child–Pugh score C) and death as an absorbing state from where no transitions to the other states occurred. The model was based on the following principles: (i) the four states are mutually exclusive and collectively exhaustive; (ii) the Markov assumption for the current state without any memories of prior states; (iii) time intervals are uniform; and (iv) transition probabilities are constant and time independent. Items (i) and (ii) define a Markov chain, whereas items (iii) and (iv) characterize a homogenous Markov chain (18).

A *P*-value of $< 0.05$ in a two-tailed test was considered significant. Data analysis was performed using the computer program IBM SPSS STATISTICS ver. 18 (19).

## Results

### Effect of initial treatment

After the initial session of RFA or surgery, complete ablation for entire tumour nodules was obtained in 232 patients (98.3%) in the RFA group and in 138 patients (100%) in the surgery group. Among four patients (1.7%) with incomplete ablation after the initial session of RFA, two achieved complete necrosis by re-RFA performed after a few months, and the other two underwent TACE for the residual tumour nodules.

### Complications of treatment (Table 2)

After the initial therapy with RFA or surgery, 12 patients developed major complications after treatment: seven in the RFA group and five in the surgery group. There was no treatment-related death within 6 months after therapy in any of the patients in the RFA and surgery groups. Although abdominal pain, mild aggravation of liver function test, low-grade fever, transient elevation of aminotransferases and bilirubin values were often found after RFA therapy, significant deterioration of performance status and prolonged stay in the hospital were not observed.

### Cumulative recurrence rates and treatment for recurrent hepatocellular carcinoma

The initial recurrence rates were compared between the two groups according to the initial therapy. The initial recurrence rates after treatment in the RFA and the surgery group were 11.3 and 14.2% at the end of the first year, 40.4 and 29.3% in the second year, 53.3 and 40.6% in the third year, 65.0 and 48.8% in the fourth year and 69.5 and 53.7% in the fifth year respectively. The recurrence rate in the RFA group was significantly higher than that of the surgery group (log-rank test, $P = 0.015$) (Fig. 2).

For the treatment of a recurrent tumour, we fundamentally adopted RFA or surgical treatment when patients had an early stage of HCC with sufficient liver function. Although initial therapy included surgery, patients with a recurrent tumour tended to receive RFA therapy more frequently. When a tumour progressed to the intermediate stage with a large tumour and/or multiple nodules, TACE was usually performed using anti-tumour agents, iodinated poppy seed oil fatty acid (Lipiodol Ultra-Fluide™, Guerbet Japan, Tokyo) and gelatin sponge particles. When the tumour progressed to the advanced stage (portal invasion, extrahepatic metastasis, or Child–Pugh C) during repeated local ablation or TACE therapy, anti-tumour therapy was usually not performed, except for systemic or intra-arterial chemotherapy. Anti-molecular targeted agents were not available during the study period in Japan.

**Table 2.** Complications after the initial treatment

| Complication | Initial therapy | |
|---|---|---|
| | Radiofrequency ablation ($n = 236$) | Hepatic resection ($n = 138$) |
| Perforation of jejunum | 2 | 0 |
| Biloma and/or biliary infection | 3 | 1 |
| Prolonged ascites | 1 | 2 |
| Jaundice | 0 | 1 |
| Haemorrhage requiring transfusion | 1 | 1 |

### Cumulative progression rates from the early to the intermediate stage

A total of 98 (26.2%) developed to the intermediate stage during the observation: 65 (27.5%) in the RFA group and 33 (23.9%) in the surgery group.

Crude development rates to the intermediate stage in the RFA and surgery groups were 18.2 and 13.0% in the third year, 33.1 and 22.1% in the fifth year, and 40.9 and 31.8% in the fifth year respectively. The development rate of the RFA group was slightly higher ($P = 0.14$) (Fig. 3a).

Independent factors associated with the stage development rate were explored in the patients. Multivariate hazard analysis showed that the rate is independently associated with positive HBsAg ($P = 0.041$) and a high platelet count ($P = 0.032$). The factor of initial therapy

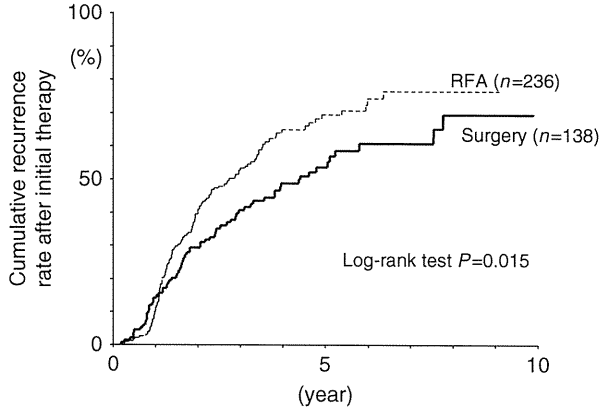


**Fig. 2.** Cumulative recurrence rates after therapy in patients with an early stage of hepatocellular carcinoma, according to initial therapy. RFA, radiofrequency ablation.

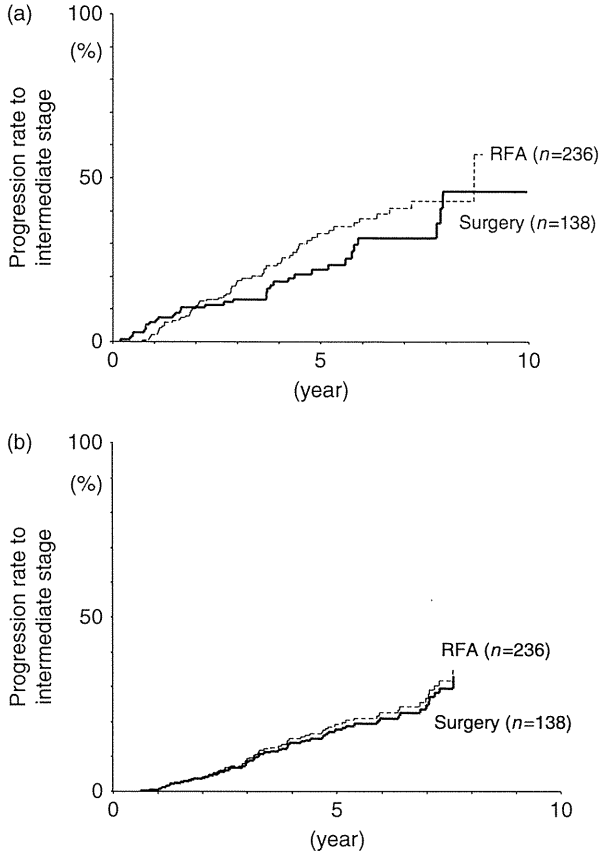


**Fig. 3.** (a) Crude development rates to the intermediate stage of hepatocellular carcinoma according to initial therapy. (b) Adjusted development rates to the intermediate stage, using proportional hazard analysis. RFA, radiofrequency ablation.

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

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

### Survival rates and predictive factors

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

The crude survival rates in the RFA group and the surgery group were 88.5 and 92.6% in the third year, 71.7 and 80.9% in the fifth year and 60.6 and 74.6% in the seventh year respectively (Fig. 4a). The survival rate of

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

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

RFA, radiofrequency ablation.

the surgical therapy group was higher but statistical significance was not obtained ($P = 0.071$).

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

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

### Probabilities for transition among four disease states of hepatocellular carcinoma

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

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

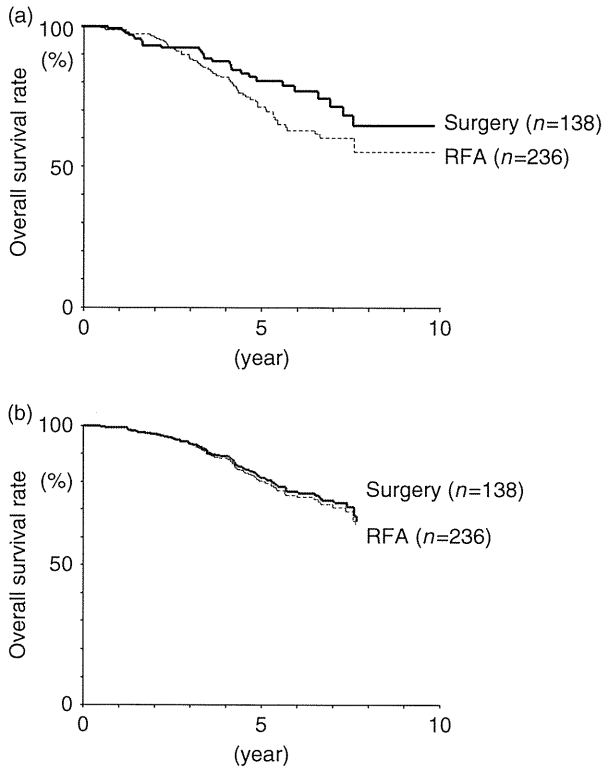


**Fig. 4.** (a) Crude survival rates in patients receiving radiofrequency ablation and those undergoing surgery as the initial therapy. (b) Adjusted survival rates in the radiofrequency group and surgery group, using proportional hazard analysis. RFA, radiofrequency ablation.

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

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

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

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

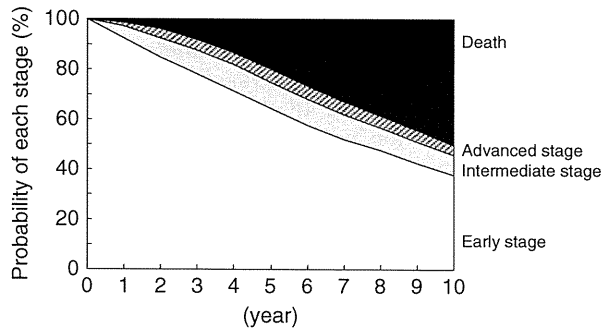


**Fig. 5.** Illustrated transition probabilities of patients, from the early stage of hepatocellular carcinoma, to the intermediate stage, the advanced stage and to death.

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

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

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

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

### Probabilities for transition according to the initial treatment

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

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

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

## Discussion

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

## Materials and Methods

### *Study Population*

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

### *Contrast Infusion and CT Protocol*

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

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

### *Diagnosis of HCC*

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

### *Imaging Analysis of Hepatocellular Carcinoma and Definition of Enhancement Pattern*

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

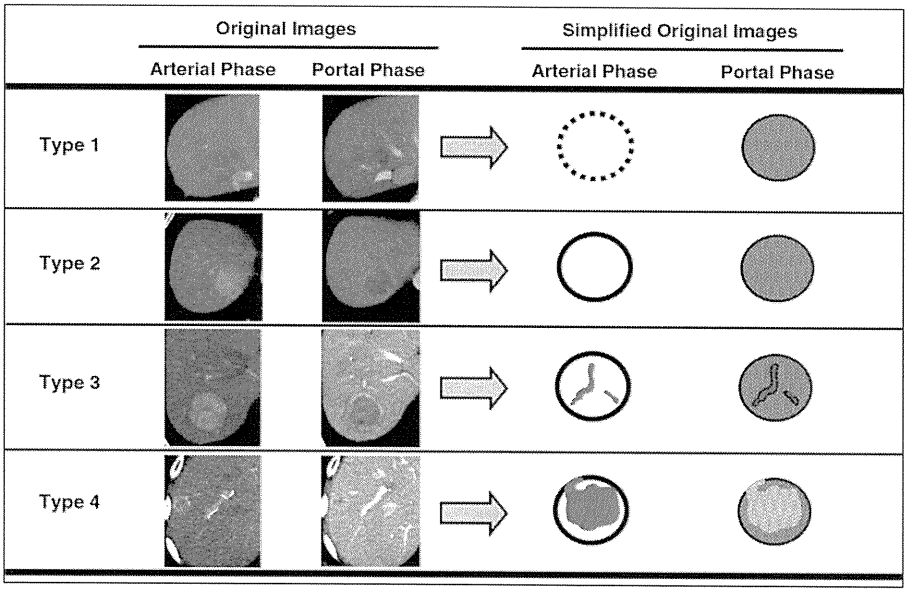


**Fig. 1**—Sample of original dynamic CT images and simplified images for each enhancement pattern. (Reprinted and modified with permission from John Wiley and Sons [19])

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

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

### *Treatment Methods*

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

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

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

### *Definition of Multinodular Recurrence of HCC*

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

### *Follow-Up Protocol*

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

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

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

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

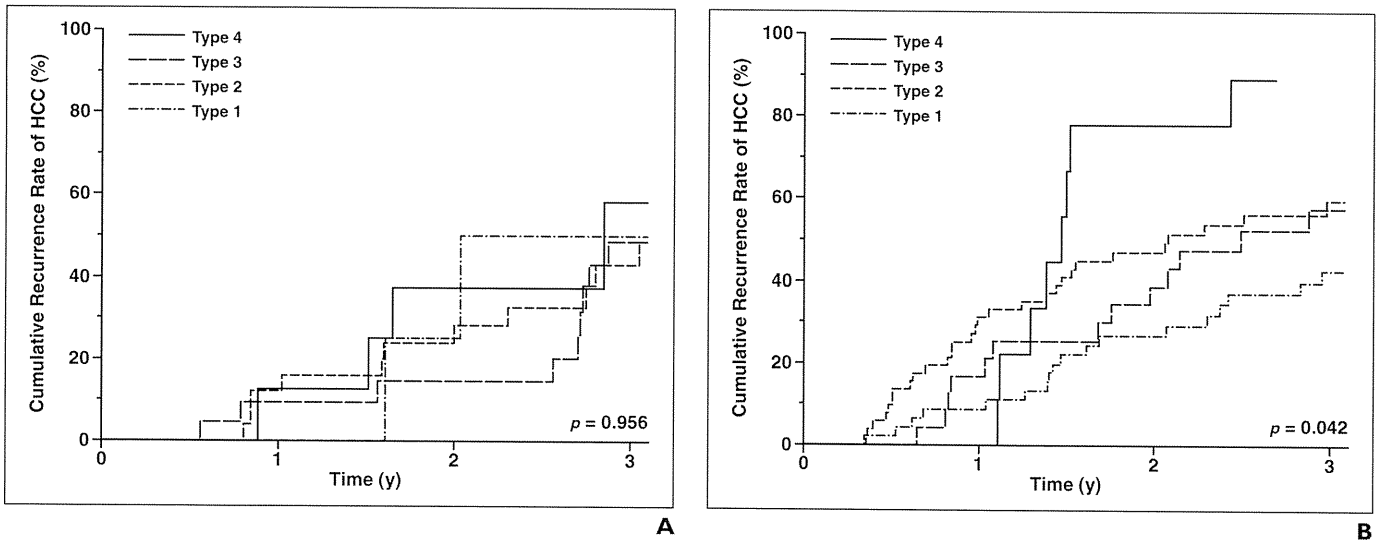


**Fig. 2**—Correlation between cumulative recurrence rates and enhancement patterns of pretreatment dynamic CT after each treatment procedure.
**A** and **B**, Graphs show associations between cumulative hepatocellular carcinoma (HCC) recurrence rate after surgical resection (**A**) and after radiofrequency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

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

### *Statistical Analysis and Ethical Considerations*

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

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

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

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

**(Table 2 continues on next page)**

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

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

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

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

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

## Results

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

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

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

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

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

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

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

### *Predictive Factors for Initial Recurrence After Surgical Resection or Radiofrequency Ablation*

Multivariate Cox proportional hazards analysis revealed that the following independent

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

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

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

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

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

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

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

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

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

## Discussion

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

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

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

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

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

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

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

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

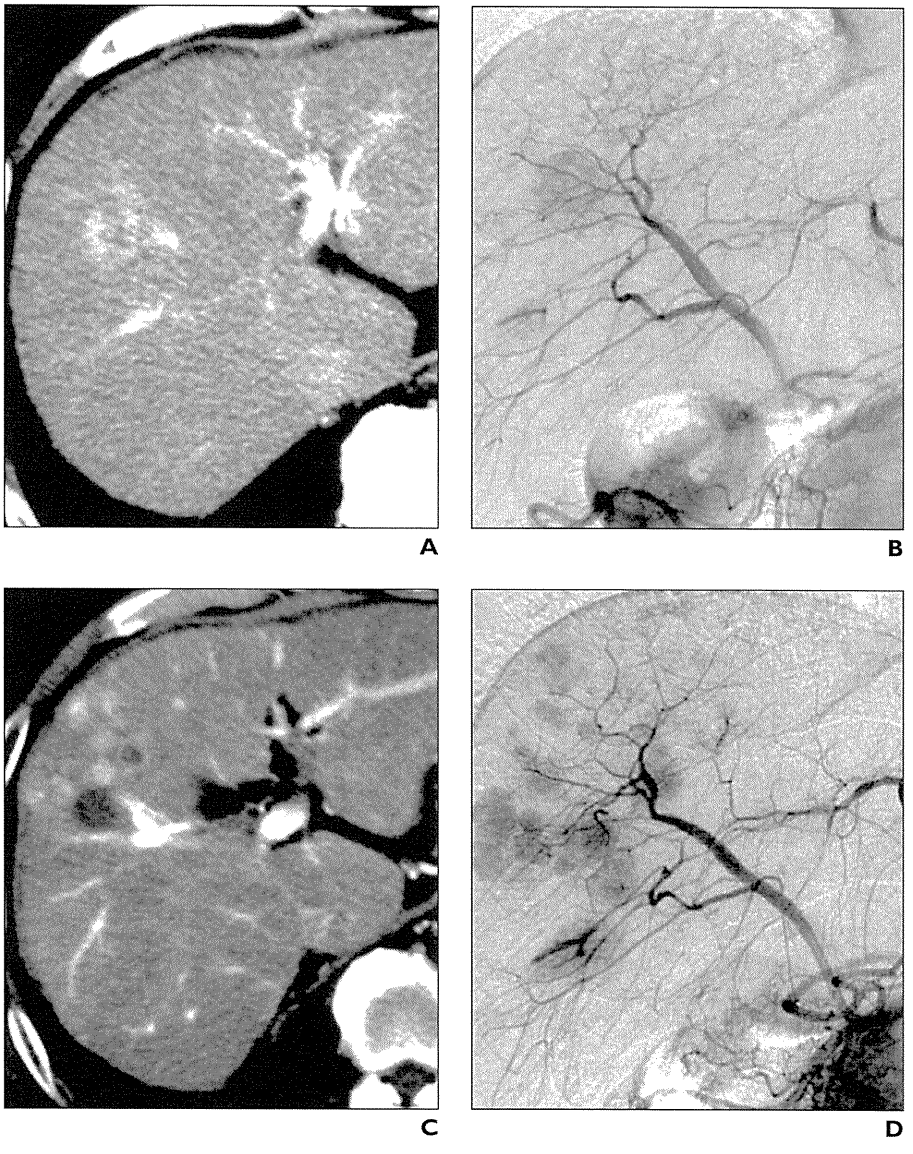


**Fig. 3**—83-year-old man with hepatocellular carcinoma (case 7 in Table 3).
**A,** Pretreatment dynamic CT (arterial phase) image. Tumor shows heterogeneous enhancement pattern with irregular ringlike structures—that is, type 4 enhancement pattern.
**B,** Pretreatment digital subtraction angiography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

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

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

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

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

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

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

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

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

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

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

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

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治療の新たな取り組み　臓器別集学的治療—EBMに基づいて—

# 肝細胞癌の最新治療

池田健次

**Current therapy of hepatocellular carcinoma**

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**Abstract**

Multimodality treatment is applied according to varied stages of hepatocellular carcinoma (HCC), and to varied status of liver function. Surgical resection is regarded as the most radical way of therapy for an early stage of HCC (single large tumor, or small tumor of 3 cm or less with 3 nodules or less). Among percutaneous local ablation therapies, radiofrequency ablation is the most effective from the viewpoint of local recurrence and survival rate. Transcatheter arterial chemoembolization prolongs the survival period of those patients with an intermediate stage of HCC (tumors of more than 3 cm and/or 4 nodules or more). Sufficient evidence of the efficacy of chemotherapy is still lacking for advanced stages of HCC with or without portal vein invasion. Although sorafenib is the first molecular targeted medicine approved for the advanced HCCs, its usefulness remains unknown in Japanese patients.

**Key words**: hepatocellular carcinoma, local ablation, surgery, transcatheter arterial chemoembolization (TACE), radiofrequency ablation

## はじめに

肝癌治療に関する先進国である我が国では，C型肝炎の新規感染の激減を受けて，肝癌死亡が横ばいから減少傾向を示し始めている．しかし，実際の臨床の場ではいまだ肝癌治療のニーズは衰えず，肝癌治療・肝癌予防の努力が続けられている．

本稿では各種肝癌の治療に関する治療法について，肝細胞癌の治療アルゴリズムとして総論を述べたのち，外科切除，局所治療，経動脈的治療，抗癌剤治療の順にエビデンスとしての観点から最新の知見を示す．

## 1. 肝細胞癌の治療法選択の基準

肝細胞癌の病態に応じた治療法の選択基準として幕内班の‘肝細胞癌治療アルゴリズム’(**図1**)が推奨されている[1]．この肝癌治療に関するアルゴリズムは，肝障害度・腫瘍数・腫瘍径の3因子を基に設定されており，種々の治療法選択基準の中で最も単純化されている．

肝障害度AまたはBの症例においては，①腫瘍が単発ならば腫瘍径にかかわらず肝切除が推奨される(ただし，肝障害度Bの症例で腫瘍径

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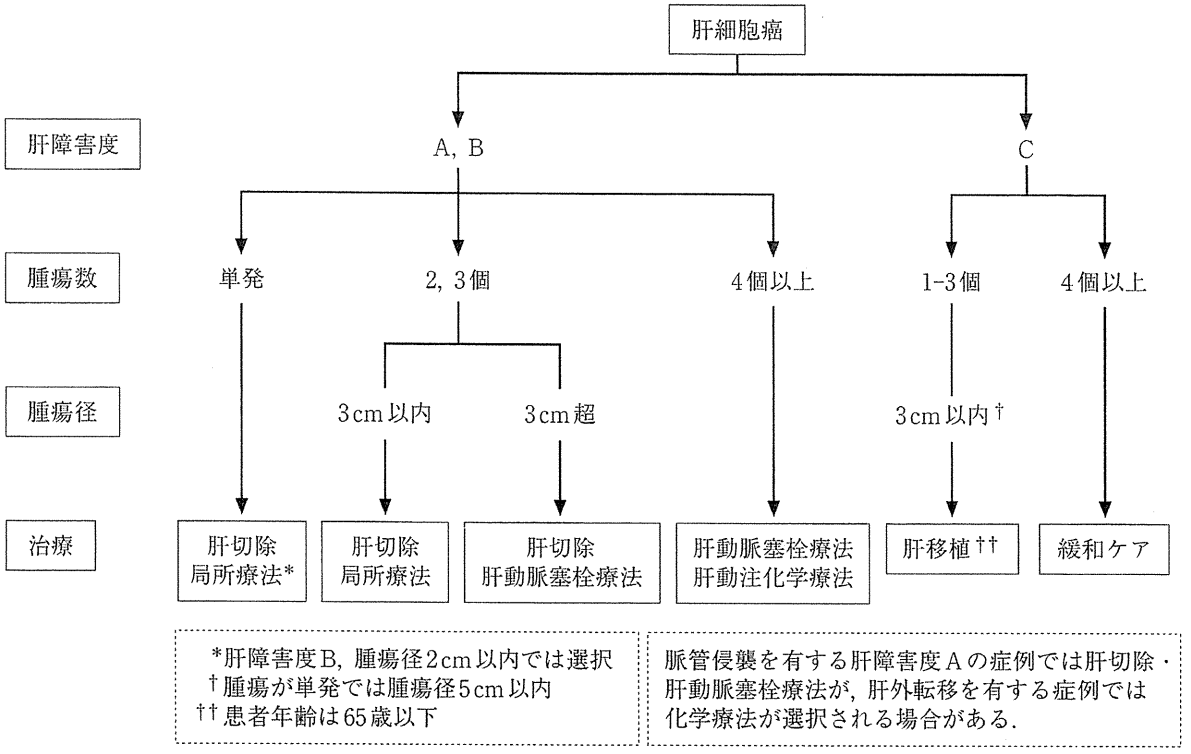


**図1 肝細胞癌治療アルゴリズム**(文献[1]より引用)

が2cm以内ならば経皮的局所療法も選択される), ②腫瘍数が2個または3個で腫瘍径が3cm以内ならば肝切除または経皮的局所療法が推奨される, ③同腫瘍数で腫瘍径が3cm超ならば肝切除または肝動脈塞栓療法が推奨される, ④腫瘍数が4個以上ならば肝動脈塞栓療法または肝動注化学療法が推奨される. 肝障害度Cの症例においては, ①腫瘍数が3個以下で腫瘍径が3cm以内(および腫瘍が単発で腫瘍径が5cm以内)で, 患者年齢が65歳以下ならば肝移植が推奨される, ②腫瘍数が4個以上ならば緩和ケアが推奨される. なお, 脈管侵襲を有する肝障害度Aの症例では肝切除・肝動脈塞栓療法が, 肝外転移を有する症例では化学療法が選択される場合がある.

## 2. 肝癌の外科治療

### a. 外科治療の進歩

日本肝癌研究会による25年前の全国調査では, 原発性肝癌における肝切除症例の手術死亡率は27.5%, 5年生存率は11.8%であったが, 最近の第16回調査(2000-01年)では手術死亡率は0.9%, 5年生存率は54.6%と飛躍的に改善した. この治療成績向上は, 術前評価, 手術手技, 周術期管理などの総合的な外科診療の進歩によると考えられている.

### b. 肝癌外科治療の適応決定

手術適応の決定は, 肝細胞癌の進行度評価と肝機能評価が必須である. 肝癌進行度は, 腫瘍の大きさ, 数, 血管侵襲, リンパ節転移, 遠隔転移の有無によって規定されるが, 治療法選択においては, 腫瘍の存在部位や過去の治療歴も考慮される. 肝機能からみた適応評価では, ICG 15分値(インドシアニン・グリーン15分停滞率)が単独の臨床検査値の中では優れるとされているほか, これら検査値の組み合わせによる計算式による様々な肝切除の基準が提唱され, 利用されている. 肝癌外科切除術式においては, 腫瘍根治と肝機能温存の両面から妥当と考えられる手術法が我が国から多数開発されてきた.

### c. 系統的亜区域切除と部分切除

従来から議論のあった, 系統的亜区域切除の臨床的意義に関して, 同時期に2種類の見解が

示されている．一つはTanakaら[2]，Kaiboriら[3]の系統的切除の有用性を認めないとする報告であり，他は肝癌研究会集計[4]の多施設のretrospectiveな5,781例のデータである．前者のうち，Tanakaらは125例のretrospectiveなデータであり，系統的亜区域切除を行った群では再発率・生存率のいずれをとっても非解剖学的局所切除を行った群と差がないため，肝機能温存を主眼とした手術を行うことが重要としている．Jaubiriらも単一施設で247例のC型関連肝細胞癌の切除術式を検討し，解剖学的切除の有用性がなく，肝実質温存を目指す部分切除が良いとしている．一方後者の多施設データの集計では，系統的切除が行われた2-5cmの肝癌では，無再発生存率が有意に高いため，'系統的切除の方が推奨される'と結論付けている．後者は大規模な集積比較研究であるが，相対的に再発率の低い軽度の肝障害症例に系統的切除が選ばれているという，retrospectiveな研究としてのバイアスを払拭するには至っていない．肝細胞癌治療ガイドライン[1]では，'非肝硬変肝細胞癌に対する肝切除範囲に際しては，治癒切除が可能であれば必ずしも拡大切除は必要とせず，肝機能と腫瘍の進展に応じて部分切除でも十分'，'肝切除において肝切離断端距離は必要最低限でよい'と記載している一方，'予後の観点から肝切除では系統的に行うことが推奨される'としている．

## 3. 経皮的(穿刺)局所療法

肝癌に対する内科的な経皮的局所治療としては，ラジオ波凝固療法(RFA)，マイクロ波凝固療法(MCT)，エタノール局注療法(PEI)が保険診療で認可されているほか，最近では収束超音波治療(HIFU)，冷凍凝固治療などが応用され始めている．

### a. 経皮的局所治療の適応

肝細胞癌治療ガイドライン[1]によると，穿刺局所療法の良い適応は，Child-Pugh分類AあるいはBの肝機能，腫瘍径3cm以下腫瘍数3個以下である．肝細胞癌治療における穿刺局所療法は肝切除に代わる第一選択の治療になりうるかについての結論は現在のところ出ていない．種々のデータ・報告より，経皮的局所治療の中ではRFAの成績が最も良好であるとされている[5,6]．

### b. 経皮的局所治療と他治療との比較

日本肝癌研究会の解析(n=12,888)では，単発2cm未満で臨床病期(CS)Iでは肝切除の治療成績がPEIより良好(p=0.01)だが，CS II以上では肝切除とPEIで有意差はない．一方，単発で2cmより大きい症例では肝切除の治療成績が良好である．2cmより大きいCS IIにおいても肝切除の成績が良好であった[7]．国内18施設の肝癌症例(n=3,225)のretrospectiveな集計では，3cm以下3個以下の症例でCS Iでは5年生存率は肝切除とPEIで同等だがCS IIではPEIの生存率が高かった[8]．Livraghiら[9]は多施設共同研究で，2cm以下単発の218例の肝細胞癌治療について，RFAと肝切除を比較した．ここでは局所の持続制御率と治療関連合併症について検討しているが，局所の持続制御率は中央値31カ月で216例(97.2%)に得られ，治療侵襲も少ないことより，RFAが小型肝癌の基本的治療であるとしている．良質の無作為化試験で肝切除と経皮的局所治療を比較した研究は今のところ発表されていない．

Murakamiら[10]は，3cm以下3個以下もしくは5cm以下単発の肝癌に対してRFAまたは肝動脈化学塞栓療法(TACE)で治療された連続258症例について局所再発率を検討し，有意にRFAがTACEに勝っていた(p=0.013)データを示している．

### c. RFAと他治療の併用，その他RFAの最近の知見

新しいタイプのRFA機器として，電極冷却型バイポーラ電極を使用した大型肝癌治療の初期成績が報告されている[11]．肝癌は5-9cmの26例で，1症例1-2回の治療が行われた．27結節中22個(81%)で完全壊死が得られ，平均14カ月の観察期間で14%の局所再発，24%の異所再発がみられたとしている．肝機能良好で脈管侵襲のない大型肝癌では，肝切除以外に治療オプションとして今後広く行われる可能性がある

と思われる.

RFA施行後の新規肝癌の増殖速度は無治療の自然経過の病変より早いことがParkら[12]により報告されている. 彼らはこのmultiphasic CTを繰り返し行って算出した増殖速度から, RFA後の画像経過観察は2.5カ月ごとに行うことが望ましいとしている.

Lencioniら[13]は, 3.3-7cm(平均5.0cm)のやや大型の肝癌に対して, ドキソルビシン溶出ビーズ(DEB: ドキソルビシン50-125mg)肝動注併用RFA治療のパイロット試験を20例に行った. RFA治療後の壊死域は48$cm^3$であったが, DEB動注後には75.5$cm^3$に増大した. 重大な合併症はなく, 肝機能の増悪もみられず, 目標病変が12例(60%)で完全壊死に陥ったとしている. Chengら[14]は, 3cmを超えるやや大型の肝癌に対して, RFA+TACE, TACE単独, RFA単独の無作為化比較試験を行った. 併用治療96例, TACE単独95例, RFA単独100例に割り付けられ, 生存率・直接治療効果が検討された. 生存期間の中央値は, それぞれ37カ月(治療4.4コース), 24カ月(3.4コース), 22カ月(3.6コース)で, 併用治療を行った群の生存率が最も良好であったとしている. Yamakadoら[15]も, RFA+TACE治療を行い, これを肝切除の成績と比較している. これは104例の早期の肝癌についてretrospectiveな検討を行ったもので, 内科的なRFA+TACE治療で無再発生存率・全体生存率ともに外科とほぼ同じ成績が得られたとしている.

Zhangら[16]は, RFAにPEI併用を行う・行わないの無作為化比較試験を行った. RFA+PEI併用群66例, RFA単独群67例での1年・2年・3年・4年・5年生存率は, 併用群で95.4%, 89.2%, 75.8%, 63.3%, 49.3%, RFA単独群で89.6%, 68.7%, 58.4%, 50.3%, 35.9%で, 併用群の生存率が有意に良好であった($p=0.04$). 全再発率に関しては, 併用群23例, 単独群33例で, 両群間に有意差はなかったが, 局所再発は, 併用群4例, 単独群14例で, RFA+PEI併用群が有意に優れていた($p=0.012$). 著者らは腫瘍径が予後に最も影響する因子であったとしており, 大型肝癌では併用療法の有用性があるとしている.

Kobayashiら[17]は, RFA時に肝動脈のバルーン閉塞を行う意義を無作為化比較試験で検討した. 動脈閉塞の意義が壊死領域を大きくすることは既に広く知られているが, 本論文では同亜区域内の再発率に影響するとする長期成績を示したところが重要である. 一方, Sudheendraら[18]は, RFA治療の際に間欠的に肝静脈をバルーン閉塞させることの意義を検討した. 中央値4.2cmの肝腫瘍8例に治療を行い, 平均径6.3cmの壊死域が作成でき, 静脈血栓などの合併症は起こらなかったとしている.

**d. RFA治療の副作用・合併症**

Kasugaiら[19]は, 大阪地区多施設の2,614例, 3,891回のRFA治療について副作用の頻度をまとめた. 治療症例中合併症を認めたのは207例(7.9%)であった. うち3カ月以内死亡9例(0.3%)がみられ, その死因は肝不全3例, 肝癌急速進行3例, 胆管損傷1例, 消化管出血1例, 急性心筋梗塞1例という内訳で, 治療経験数が増せばその頻度を減少させることができるとしている. Kimら[20]は, 872例1,120セッションのRFA(cool-tip電極)を行い, 20回(1.8%)の肝梗塞がみられたと報告している. このうち2例はbiloma, 2例は肝膿瘍, 1例は門脈血栓, 1例は肝葉単位の梗塞から肝不全死に至った. 多変量解析では高齢・腫瘍径が肝梗塞発症に関連し, 頻度は少ないが注意すべきであると記載している.

Kimら[21]は, 非代償期肝硬変合併肝癌19例26結節に対してcool-tip電極を用いたRFAを行った. 治療6カ月後に腫瘍が完全壊死と判定されたのは23結節(88.5%)で, 50%生存期間12カ月であった. 2例は肝不全死(1例は2カ月後, 1例は4カ月後)で, 他は6カ月以上生存した. 第1週目, 第2週目のトランスアミナーゼ・ビリルビンは有意に上昇し, 肝障害の増悪がみられることもあり, 非代償期肝硬変合併肝癌患者に対するRFAは適切な患者選択を行うべきであるとしている.

### e. そのほかの肝癌局所療法

Ohmotoら[22]は，RFAとマイクロ波凝固療法(MCT)とのretrospectiveな比較で，侵襲度・局所再発の低さ・高い生存率・少ない回数で大きな壊死域など，多くの点でRFAが勝っているとした．少数例のretrospectiveな比較であり，またRFAの方が最近行われた治療という'練習効果'の影響などがあり，長期予後までの効果は十分に示されているとはいえないが，腫瘍が大きく焼灼できるという点に加えて，RFAでは胆管障害や胸水貯留などの副作用が経皮的MCT群に比べて少なかったとしている．

経皮的治療のうち，針を穿刺しなくてもすむ無侵襲の治療として収束超音波治療(HIFU)が徐々にその臨床成績を示しつつある．Liら[23]は，これまで主として小型肝癌が対象とされてきたHIFU治療を，切除不能大型肝癌151例に対して施行し，CR 43例(28.5％)，PR 91例(60.3％)の成績を示した．これはHIFUと他の支持療法の併用での成績ではあるものの，対照群30例ではそれぞれ0％，16.7％であった結果と比較してHIFUが良好な効果を示しているとした．また，1年・2年生存率がそれぞれ50.5％・30.9％と優れていたと長期成績についても論じているが，長期成績の評価には，他の支持療法・継続的な集学的治療の効果を十分に考慮する必要があると考えられる．

Hanajiriら[24]は，治療前にmicrobubbleの投与を行うとHIFUの抗腫瘍効果を高めるとする動物実験データを示しており，将来の臨床応用への有用性を示唆した．

肝癌に対する冷凍凝固療法は1990年頃より欧米・中国などで試みられているが，機器が一般的でなく，プローブも3-10 mmと太いこともあって外科的に行われるなど，我が国ではPEI・RFAなどのように広く行われていない．このようななかで，イタリアのOrlacchioら[25]は，超音波ガイド下経皮的に17ゲージの冷凍凝固プローブを複数本穿刺し，これをCTでモニターする方法を示し，経皮的な治療が可能であることを示した．

## 4. 肝動脈(化学)塞栓療法(TACE/TAE)

肝臓は肝硬変になっていても動脈・門脈の2血流の支配を受けているのに対し，進行した肝細胞癌は肝動脈のみの血流に依存していることを利用して，肝動脈末梢部を経カテーテル的に塞栓することで肝細胞癌のみを壊死に陥らせることを目指す治療である．TACEは肝細胞癌に特有な治療法で，原発性肝癌である胆管細胞癌や転移性肝癌での治療効果は劣る．

### a. 肝動脈化学塞栓療法の有効性

我が国では1980年頃から1990年代中頃までは切除不能と判断された腫瘍濃染像を有する肝細胞癌の大多数はTACE/TAE療法が施行されていた．その後種々の経皮的凝固療法の導入により，切除不能肝細胞癌でかつ経皮的凝固療法の対象外とされている肝細胞癌がTACE/TAEの適応となってきた．1990年代のランダム化比較成績では，TACE/TAEの有用性は証明されなかったが，2000年代に入り2編の無作為化比較試験論文とメタアナリシスでTACE/TAEは切除不能肝細胞癌の予後向上に寄与することが証明された[26,27]．

### b. 肝動脈化学塞栓療法の適応

肝細胞癌診療ガイドライン[1]では，腫瘍径3 cm，3個以内の肝癌は肝切除や経皮的局所治療の適応，また単発では大型のものまで肝切除の適応があるので，これら'根治的な治療'が困難な症例に対して肝動脈化学塞栓療法・肝動注化学療法が適応と考えられる．一方，門脈浸潤・閉塞が起こっている進行肝癌ではTACEにより肝不全をきたすため，禁忌である．肝機能からは，高度の腹水や肝性脳症のあるChild-Pugh分類Cの症例，ビリルビン3 mg/dL以上の肝予備能不良の症例は適応外である．TACEは様々な治療法の中では，根治療法不能の'中等度進行肝癌'の広い適応範囲をもった治療法である．

まとめて示すと，TACE/TAEはChild-Pugh分類A，Bの進行肝癌(手術不能で，かつ経皮的凝固療法の対象とならないもの)に対する治療として推奨されている．安全で有効なTACEのためには，化学塞栓される非癌部肝容積の非癌

部全肝容積に占める割合と残肝予備能を考慮したTACE/TAEが推奨される.

**c. 肝動脈化学塞栓療法の具体的な方法**

担癌区域(肝癌の存在する区域)・亜区域までカテーテルを挿入し,これより抗癌剤・脂溶性造影剤(リピオドール™)懸濁液を動注した後,ゼラチンスポンジ細片(ジェルパート™)により塞栓する.肝両葉に腫瘍が存在する場合には,固有肝動脈からTACEを行う場合もあるが,腫瘍の栄養血管を同定し末梢動脈までカテーテルを挿入して,抗癌剤+リピオドール懸濁液を強く注入した後に塞栓を行う(亜)区域性Lp-TACEの治療効果は高く,腫瘍の完全壊死も期待できる.

[**症例1**(通常のTACE,小型少数で限局した腫瘍)] エピルビシン40mg+リピオドール3mL,その後ジェルパートで塞栓

[**症例2**(両葉多発,進行肝障害,門脈末梢部腫瘍塞栓合併例)] シスプラチン100mg(70mL溶解液),リピオドール4mLを少量ずつ交互に肝動注

[**症例3**(両葉多発,進行肝障害,門脈末梢部腫瘍塞栓合併例)] ミリプラチン80mg+リピオドール4mL懸濁液を担癌区域動脈に動注

## 5. 進行肝癌に対する動注化学療法と分子標的薬

早期肝癌(3cm以下少数),中期肝癌(3cm超,3個超だが脈管浸潤なし)に対しては,肝切除・経皮的局所治療,TACEなどの有力な治療が存在するため,抗癌剤治療は主として進行肝癌に対して適応を考慮する.

肝細胞癌に対する化学療法に関する論文は,他の悪性腫瘍に対する化学療法のように多数の症例を検討したランダム化比較試験といったエビデンスレベルの高いものは少ない.進行肝癌を中心に様々な化学療法が報告されているが,対照群を伴わない症例集積研究や後ろ向き研究が多い.

**a. 動注化学療法**

単剤での肝動注療法による奏効率は,シスプラチンで37%,ドキソルビシンで60%というコホート研究があるが,進行肝癌に対する治療効果はこれより劣る.進行肝癌に対する良好な直接治療効果として報告されているのは,①シスプラチン肝動注とインターフェロン全身療法併用[28,29],②5-FU持続肝動注+インターフェロン全身投与併用[30,31],③5-FU持続肝動注+シスプラチン併用療法の組み合わせ[32]である.

進行肝細胞癌に対する動注化学療法は我が国を中心に盛んに行われているが,生命予後まで示した無作為化比較試験というものは報告されておらず,エビデンスとしての標準的な治療としては確立されていない.

**b. 分子標的薬**

2008年7月にソラフェニブ(ネクサバール™)の進行肝細胞癌への有効性が大規模二重盲検ランダム化比較試験[33]で示され,2009年5月より我が国でも進行肝癌(門脈浸潤,肝外転移のある肝機能良好例)に対する治療薬として保険診療が可能となった.しかし我が国では使用開始後短期間での肝不全・肝性脳症が多くみられる一方,2009年12月には,中期進行肝癌に対して我が国で行われた'TACE施行例に対するソラフェニブの無作為化比較試験で有効性が示されなかった'とのデータが開示された.日本人におけるソラフェニブの有効性や副作用に関してはまだ十分なデータがない状態であり,副作用に十分な注意を払いながら慎重に有用性を検討していく必要がある.

現在世界中で20種類を超す分子標的薬が肝癌に対して治験がなされている状況であり,今後の分子標的薬の位置づけは個々の薬剤で検討していく必要がある.

## 文　献

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