current and other studies. Taken together, we suspect that the apparent relation between anti-HBc positivity and risk of HCC development is spurious.

Indeed, anti-HBc seropositivity was not shown to be a significant risk factor in the subset analysis among female patients, nor among male patients further stratified by age. In each subset the risk ratio was about 1. Confounding is strongly suggested when each subset reveals similar risk ratios that are different from the one obtained in the full set analysis. In the present study the gender and age of patients, which are strongly associated with both anti-HBc seropositivity and risk of HCC development, acted as confounding factors.

The hazard ratio attributed to anti-HBc seropositivity was slightly higher than 1 among female patients (OR = 1.24) and among younger male patients (OR = 1.23). Although neither was statistically significant, it is still possible that as the number of events decreased in subset analyses this reduced the power of analysis. In particular, crude Kaplan–Meier estimation of cumulative incidence differed between anti-HBc positive and negative younger male patients (Fig. 4). Although not statistically significant ($P = 0.27$), a hazard ratio of 1.23 was attributed to anti-HBc seropositivity in this subset of patients in multivariate analysis. We cannot exclude the possibility that some cases of HCC development in this subpopulation were affected by past HBV infection. HBV related HCC has a relative preponderance in young male patients as compared to HCV related HCC [6]. Thus, the influence of past HBV infection on HCC development among HCV positive patients, if any, would be most prominent among young male patients. However, this putative influence cannot be so strong even in this subpopulation as previously reported by some investigators [17,29].

The reason for the high seropositivity of anti-HBc among Japanese chronic hepatitis C patients is not well established but there is the possibility that the same route of blood-borne transmission was shared by HCV and HBV. Because genotype C is highly prevalent among HBV strains in Japan [30], HBV infection in adulthood rarely becomes chronic. We suspect that chronic occult HBV infection is more common in areas where other genotypes are prevalent, and the effect of anti-HBc seropositivity on HCC development in HCV-infected patients may be different in such areas. The way of acquiring anti-HBc positivity with HBsAg negativity may be divided into two patterns: former HBV carriers with spontaneous HBsAg loss and resolved acute hepatitis B. Since the prevalence of HBsAg positivity in 40–60 year old Japanese is approximately 1.5% [31], anti-HBc seropositivity among chronic hepatitis C patients is too high to be explained by the inclusion of former HBV carriers and must be mainly due to horizontal transmission. Transmission through blood transfusion and medical and paramedical practices with inadequately sterilized needles and syringes, considered to be responsible for HCV spread in Japan, may have contributed also to the spread of HBV. However, the reason why anti-HBc positivity is male dominant is not well known. Use of intravenous metamphetamine among workers around the end of World War II and sexual contact with commercial sex workers were suspected to be the cause of this phenomenon [32].

Patients positive for both HBsAg and HCV RNA are sometimes considered to be at higher risk for hepatocarcinogenesis because HBV DNA may be directly integrated into host hepatocyte DNA, causing potentially carcinogenic mutations [29]. However, Shiratori et al. [33] reported that the risk of HCC development was not significantly different between HBsAg positive HCV-infected patients and HCV mono-infected patients. Suppression of HBV replication in HCV co-infection has been suggested in previous studies [34] and clinical features were reportedly similar in co-infected patients and HCV mono-infected patients [33]. Thus, the effect of past HBV infection on hepatocarcinogenesis among chronic hepatitis C patients cannot be so profound, if any.

HBV-DNA, including covalently closed circular DNA, can infrequently be detected in the liver of HBsAg-negative anti-HBc-positive patients [35,36], and this form of HBV infection may be clinically important as shown in viral reactivation in cases of post-transplant immunosuppression and administration of rituximab [37]. HBV-DNA may have been present in the liver of some of anti-HBc-positive patients in this study. However, the results indicated that the effect of such HBV infection, if any, on hepatocarcinogenesis among HCV-infected patients is weak, as compared to the confounding effects of age and gender.

In conclusion, the current data showed that the apparent difference in an HCC incidence between anti-HBc positive and negative patients with HCV infection was confounded by differences in gender and age. Past HBV infection, as indicated by anti-HBc seropositivity, was not a significant risk factor of HCC.

## CONFLICTS OF INTEREST

The authors have nothing to disclose and no conflicts of interest exist.

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ORIGINAL ARTICLE

# Ultrasound surveillance for early detection of hepatocellular carcinoma among patients with chronic hepatitis C

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**Abstract**
*Background and aims* Ultrasonography is the most frequently used modality in surveillance for HCC among patients with chronic hepatitis C. However, the optimal surveillance interval is still controversial and the usefulness of supplementary tumor marker determination has not been confirmed.
*Methods* A total of 243 cases of naive HCC were detected among 1,431 patients with chronic hepatitis C under outpatient-based surveillance. The mode of HCC detection, including ultrasound surveillance interval, was retrospectively examined and the relation between the interval and detected tumor size was analyzed. Tumor volume doubling time was estimated from exponential increase in serum tumor marker levels when applicable.
*Results* HCC was first detected by ultrasonography in 221 patients. Ultrasound surveillance interval, ranging between 2 and 8 months, was not correlated with the size of tumor at detection. Patients with cirrhosis were likely to be surveyed at shorter intervals. The size of tumor exceeded 30 mm only in three (1.4%) cases. They were all positive for a biomarker and the estimated tumor doubling time was short. In 14 cases, HCC was first detected by CT indicated by abnormal rise in tumor marker levels despite negative ultrasound findings. In the remaining eight cases, ultrasonography had been replaced by CT as surveillance modality because of excessive obesity or coarseness of liver parenchyma.
*Conclusions* Ultrasound surveillance at 6-month intervals was appropriate in general for the detection of HCC at a size smaller than 30 mm. However, in patient with established cirrhosis, more frequent screening would be needed to detect tumors of the same size.

**Keywords** Hepatocellular carcinoma · Hepatitis C · Surveillance · Ultrasound · Tumor marker · Doubling time · Size of tumor · Surveillance interval

**Abbreviations**

| | |
|---|---|
| AFP | α-Fetoprotein |
| CT | Computed tomography |
| DCP | Des-γ-carboxy prothrombin |
| HBsAg | HBV surface antigen |
| HCC | Hepatocellular carcinoma |
| MRI | Magnetic resonance imaging |

## Introduction

HCC is one of the most common cancers worldwide [1–4]. Most HCC patients have a chronic liver disease in the background liver, among which chronic viral hepatitis due to hepatitis C virus (HCV) or hepatitis B virus (HBV) is very common [5–7]. Surveillance for HCC is now a part of standard clinical practice for patients with chronic viral hepatitis [8]. Considering recent advances in HCC treatments, surveillance is required to detect HCC while tumors are small enough for the indication of curative treatments such as surgical resection and radiofrequency ablation [9–13].

Ultrasonography is usually used as the modality of HCC surveillance because of its cost-effectiveness and non-invasiveness. Contrast-enhanced CT or MRI is usually

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reserved for the confirmatory diagnosis of HCC [14]. The efficacy of ultrasound surveillance on HCC detection depends on both ultrasound resolution and surveillance interval. Although ultrasound resolution has been much improved technologically, the optimal interval of surveillance may be still controversial. In Japan, an official guideline, the Clinical Practice Guidelines for Hepatocellular Carcinoma 2005, recommends ultrasound surveillance with an interval of 6 months for patients at a risk of HCC and with a shorter interval, 3–4 months, for extremely high-risk patients [15]. On the other hand, the guideline of American Association for the Study of Liver Diseases has proposed that ultrasound surveillance should be preformed at a fixed interval of 6 months for patients at a risk of HCC, regardless of its magnitude [8]. The latter guideline explicitly indicates that the surveillance interval should depend on expected tumor doubling time.

Once HCC occurs, the nodule will grow at a speed that is independent of the former probability of HCC development. Thus, surveillance with a fixed interval, disregarding the magnitude of the risk of HCC, seems relevant if the aim of surveillance is to detect any HCC nodules that are satisfactorily small. However, there remain a couple of issues to be addressed. First, it is to be confirmed whether the 6-month interval is short enough for the detection of HCC while tumors are small enough for curative treatments. Second, the sensitivity of ultrasonography should be substantially high. A failure to detect HCC tumors will result in delayed detection of oversized tumors.

The Japanese guideline, which recommends distinct surveillance intervals according to the magnitude of the risk of HCC, has been generally, although not strictly, observed in the clinical practice in Japan. At the authors' institution, the interval of ultrasound surveillance on patients with chronic hepatitis C with suspected cirrhosis was usually shorter than 6 months. This provided us with the chance to investigate the relationship between ultrasound surveillance intervals and the tumor size at detection. Although one can expect that shorter surveillance intervals lead to the detection of smaller tumors, it is of interest to know whether the magnitude of difference is large enough to be clinically relevant. In the present study, we also sought to evaluate the role of HCC-specific tumor marker determination, which is recommended by the Japanese guideline but sometimes discouraged elsewhere.

## Patients and methods

### Patients

A total of 1,431 patients with chronic hepatitis C, excluding those also positive for HBsAg and those with a present or past history of HCC, were followed up at the authors' institution between 1994 and 2004. HCC developed in 340 of them during the follow-up period of 6.1 years on average [16]. Among these naive HCC patients, 97 had undergone HCC surveillance exclusively or alternatively at other institutions and were excluded from the present analysis. In the remaining 243 cases, we analyzed the relationship between the interval of ultrasound surveillance and the size of tumor at detection.

### Abdominal ultrasound

Abdominal ultrasonography was performed on outpatient basis with ultrasound devices SSA-250A or SSA-370A (Toshiba Medical Systems Corporation, Tokyo, Japan) or SSD-2000 (Aloka Co., Tokyo, Japan). The examination was performed after fasting of at least 6 h. The examiners, all highly experienced in abdominal ultrasonography, were aware of patients' clinical data including previous ultrasound reports. The ultrasound surveillance interval of each patient was determined by the outpatient clinic physician in charge. Although there were no rigid protocols for the surveillance interval, patients with more advanced liver disease were likely to undergo ultrasonography at a shorter interval. HCC-specific serum tumor markers, AFP and DCP, were determined every 1–3 months.

### Diagnosis of HCC

When an intrahepatic nodule suggestive of HCC was detected on ultrasonography, contrast-enhanced dynamic CT or MRI was ordered. On CT/MRI, a nodule was considered to be HCC when both hyperattenuation in the arterial phase and hypoattenuation in the late phase were evidenced [8, 17, 18]. When CT/MRI findings were not conclusive, the nodule was followed up with ultrasonography within 3 months. Ultrasound-guided tumor biopsy was performed when there was a definite increase in size of the nodule while CT/MRI remained inconclusive. CT/MRI was also performed when there was an abnormal elevation in an HCC-specific tumor marker while ultrasound findings were negative. In most patients, ultrasound-guided liver biopsy was also performed and histology was evaluated according to the classification of Desmet et al. [19].

### Calculation of surveillance interval

The surveillance interval was defined as the interval between the ultrasound surveillance that first detected a nodule, which was subsequently diagnosed to be HCC by CT/MRI, and the immediately previous surveillance with negative findings. Sometimes, an intrahepatic nodule detected by ultrasonography was not diagnosed as HCC on

the subsequent CT/MRI, followed up with ultrasonography, and later diagnosed to be HCC. The interval of subsequent follow-up ultrasonography in such cases was usually short and biased. Thus, we defined the surveillance interval as the interval between the ultrasonography that first detected the nodule and the immediately previous one. Sometimes, HCC was detected on CT/MRI that was ordered because of abnormal elevation in tumor marker levels. The ultrasound surveillance interval was not definable in such cases and they were analyzed separately.

### Estimation of tumor doubling time

There was usually an interval of 1–2 months between the detection of a tumor on ultrasonography and the treatment. The increase in tumor size as measured by ultrasonography was usually subtle, but there was a measurable increase in tumor marker levels, AFP or DCP, when they were positive. In such cases, we estimated tumor doubling time assuming exponential increase in tumor marker levels as follows: $C_2 = C_1 \times 2^{t/DT}$, where $C_1$ and $C_2$ are the first and second tumor marker levels, respectively, $t$ is the interval of determination, and DT is the estimated doubling time [20].

### Statistical analysis

Data were expressed as the mean ± standard deviation unless otherwise indicated. Continuous variables were compared with unpaired Student's $t$ test (parametric) and Mann–Whitney test (non-parametric). A trend in the tumor size at detection over the surveillance interval was assessed by Spearman's rank correlation coefficient and Jonckheere-Terpstra trend test. A $P$ value less than 0.05 on 2-tailed test was considered significant. Data were processed and analyzed by using the S-PLUS 2000 (MathSoft, Inc., Seattle, WA).

## Results

### Surveillance interval and tumor size at detection

The intrahepatic tumor was first detected by surveillance ultrasonography in 221 patients. In the remaining 22 patients, HCC was first detected by CT (see the following text). The relationship between the ultrasound surveillance interval in months, rounded off to whole numbers, and the size of tumor on the ultrasonography among these 221 patients is shown in Fig. 1. There was no significant trend in the tumor size over the surveillance interval: Spearman's rank correlation coefficient was 0.0283 ($P = 0.6753$) and Jonckheere-Terpstra trend test revealed no significant trend in tumor size ($P = 0.7072$). Note that most of the small

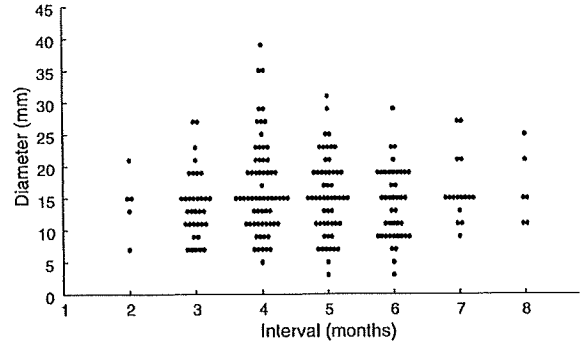


**Fig. 1** Size of tumors at detection. The mean size of tumors at detection was 16.5 ± 6.4 mm when the interval was shorter than 6 months and 15.8 ± 5.5 mm when the interval was 6–8 months ($P = 0.469$). Tumor was larger than 30 mm in diameter at detection in three patients, whose surveillance interval each was 4 months

nodules were not diagnosed as HCC immediately after the detection on ultrasonography but confirmed later in follow-up, usually after showing an increase in size The tumor size at detection was not different between the patients who had received surveillance at an interval shorter than 6 months ($N = 157$) and those at an interval of 6 months or longer, up to 8 months ($N = 64$) ($P = 0.50$ by Kruskal–Wallis test). Tumor was larger than 30 mm in diameter at detection in three patients in the former group and none in the latter ($P = 0.56$). Taken together, the tumor size at detection exceeded 30 mm in three of 221 (1.4%) patients.

Baseline characteristics of patients are shown in Table 1. Reflecting the characteristics of patients with chronic hepatitis C in Japan currently, the mean age reached 67 years. Those patients who had received surveillance at a shorter interval had significantly lower platelet count and albumin concentration and higher bilirubin concentration, suggesting that shorter surveillance interval had been applied to patients with more advanced liver disease. Background liver biopsy was performed at the time of HCC treatment in 174 (78.7%) patients. Cirrhosis was diagnosed in 89 of 123 (72.4%) patients who had been surveyed with a shorter interval and 26 of 51 (51.0%) patients with a longer interval ($P < 0.001$).

Thirty-two patients among them had had the ultrasound surveillance interval of exactly 6 months prior to HCC detection. Fibrosis stage was judged to be F1 in three, F2 in eight, F3 in six, and F4 in 15 patients. Tumor size was 14.1 ± 5.3 mm in non-cirrhotic (F1–F3) patients and 16.2 ± 5.7 mm in cirrhotic (F4) patients ($P = 0.279$ by Student's $t$ test; Fig. 2).

### Estimated doubling time

Tumor doubling time was estimated only in patients who were positive for AFP (≥100 ng/ml) or DCP (≥80 mAU/

**Table 1** Characteristics of patients

| Factors | Surveillance interval[a] | | *P* |
|---|---|---|---|
| | <6 months ($N = 157$) | 6–8 months ($N = 64$) | |
| Age[b] (year) | 66.9 ± 7.2 | 67.1 ± 8.4 | 0.86 |
| Male, *n* (%) | 93 (59.2) | 46 (71.9) | 0.092 |
| Aspartate aminotransferase[c] (IU/l) | 69.0 (51.0–98.0) | 66.5 (47.8–92.0) | 0.31 |
| Alanine aminotransferase[c] (IU/l) | 64.0 (44.0–90.0) | 62.0 (45.3–92.0) | 0.86 |
| Albumin[b] (g/dl) | 3.4 ± 0.5 | 3.6 ± 0.5 | 0.028 |
| Bilirubin[c] (mg/dl) | 0.9 (0.7–1.2) | 0.8 (0.6–1.0) | 0.017 |
| Prothrombin time[c] (%) | 71.0 (62.9–80.5) | 75.7 (67.4–84.5) | 0.050 |
| Platelet count[c] ($\times 10^3/\mu l$) | 79 (62–110) | 117 (81–151) | <0.001 |
| Ascites[d], *n* (%) | 26 (16.6) | 11 (17.2) | 1.00 |
| Size of tumors[b] (mm) | 16.5 ± 6.4 | 15.8 ± 5.5 | 0.47 |
| Number of tumors, *n* (%) | | | |
| 1 | 90 (57.3) | 40 (62.5) | 0.41 |
| 2–3 | 54 (34.4) | 21 (32.8) | |
| >3 | 13 (8.3) | 3 (4.7) | |
| Vascular invasion, present | 1 (0.6) | 0 (0) | 1.00 |
| Background liver[e], *n* (%) | | | |
| Cirrhosis | 98/123 (79.7) | 26/51 (51.0) | <0.001 |

[a] Exact trend test
[b] Expressed as mean ± SD
[c] Expressed as median (25th–75th percentiles)
[d] Those controlled by diuretics were included
[e] Liver biopsy was performed on 123 patients in less than 6-month interval group and 51 patients in 6- to 8-month interval group

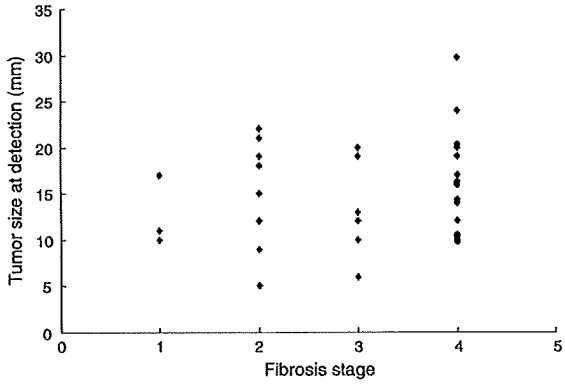


**Fig. 2** Relationship between the fibrosis stages and the tumor size at detection among patients who received ultrasonography at 6-month intervals and also underwent liver biopsy. Liver biopsy was performed in 124 patients. Thirty-two patients among them had had the ultrasound surveillance interval of 6 months prior to HCC detection. Fibrosis stage was judged to be F1 in three, F2 in eight, F3 in six, and F4 in 15 patients. Tumor size was 14.1 ± 5.3 mm in non-cirrhotic (F1–F3) patients and 16.2 ± 5.7 mm in cirrhotic (F4) patients ($P = 0.279$ by Student's *t* test)

ml). Among 80 such patients, sequential data were available in 67 of 221 (30.3%) patients. This is a biased subset because tumor marker is more likely to be positive when tumor is larger (Table 2). All the three cases in which tumor was larger than 30 mm in diameter at detection were positive for tumor markers. The association between the estimated tumor doubling time and tumor size at detection is shown in Fig. 3. Median tumor doubling time was 87.0 days, and 25th and 75th percentiles were 50.3 and 167.8 days, respectively. The estimated doubling time varied widely when tumor was relatively small at detection, whereas the doubling time was short for tumors that were detected at a large size. The three tumors larger than 30 mm in diameter at detection had a doubling time of 26.9, 44.8, and 80.1 days.

## Exceptional cases

Among the 243 patients studied, HCC was first detected not on ultrasonography but on CT in 22 (9.1%) patients. CT was used in surveillance instead of ultrasonography in

**Table 2** Size at detection and tumor marker positivity

| | ≤20 mm ($N = 171$) | 21–30 mm ($N = 47$) | >30 mm ($N = 3$) | Total ($N = 221$) |
|---|---|---|---|---|
| AFP (≥100 ng/ml) | 35 (20.5%) | 16 (34.0%) | 2 (66.7%) | 53 (24.0%) |
| DCP (≥80 mAU/ml) | 21 (12.3%) | 12 (25.5%) | 2 (66.7%) | 35 (15.8%) |
| At least one was positive | 54 (31.6%) | 23 (48.9%) | 3 (100%) | 80 (36.2%) |

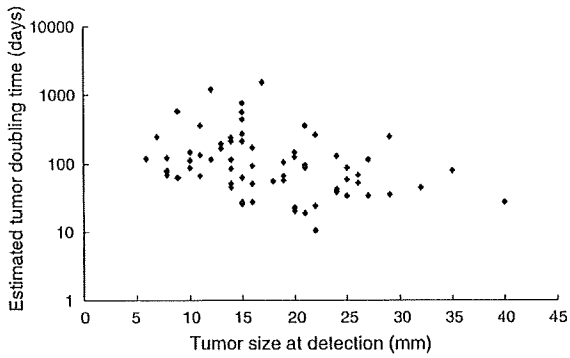


**Fig. 3** Association between tumor doubling time, estimated by exponential increase in tumor marker level, and tumor size at detection. Median tumor doubling time was 87.0 days; 25th percentile, 50.3 days, and 75th percentile, 167.8 days. The estimated doubling time varied widely in each case, but those tumors that were of large size at detection showed short doubling time. The three nodules that were larger than 30 mm in diameter at detection had a doubling time of 26.9, 44.8, and 80.1 days

eight (3.3%) patients because of extremely coarse liver parenchyma or excessive obesity. In the remaining 14 of 243 (5.8%) patients, CT was ordered because of abnormal elevation of tumor markers (AFP in nine, DCP in three, and AFP + DCP in two), although immediately previous ultrasonography had given negative findings (Fig. 4). Among these 14 patients, the size of tumor at detection was 12–43 mm (>30 mm in two patients), which was significantly larger than the size of tumor detected by ultrasound surveillance ($P = 0.0003$ by Mann–Whitney test).

## Discussion

This retrospective analysis indicated that ultrasound surveillance at 6-month intervals was generally acceptable as a means for detecting small-sized HCC among patients with chronic hepatitis C. Most HCC nodules were not exceeding 30 mm in diameter at detection. Such cases were suitable for receiving curative treatment such as surgical resection or radiofrequency ablation, although the actual indication depended also on the liver function reservoir of each patient [21, 22]. Shorter surveillance intervals did not provide further advantages in terms of tumor size (15.8 ± 5.5 mm with 6-month interval and 16.5 ± 6.4 mm with shorter interval).

In theory, a shorter surveillance interval will lead to detection at a smaller size. The reason why we found no difference is not clear. However, shorter surveillance interval was preferably assigned to patients with more advanced liver fibrosis (Table 1). Liver parenchyma of such patients might have coarse echogenicity, resulting in a larger threshold for tumor detection on ultrasonography. When compared among patients under 6-month surveillance interval, HCC nodules were detected at larger size in cirrhotic patients than in non-cirrhotic ones, although the difference was not statistically significant. Although not provable in this retrospective study, it is likely that those patients assigned to a shorter surveillance interval, among whom cirrhosis was dominant, would have had still larger tumors if surveyed within 6-month interval. This may bear greater importance when the quality of ultrasound devices or the skill of examiners has some shortcomings. Even under better external conditions, resolution of ultrasonography may be seriously impaired by patients' conditions such as extreme obesity. In the current study, ultrasonography had been replaced by CT in surveillance of such patients (8/243, 3.3%).

The current study suggested that tumor growth speed is an important factor affecting the tumor size at detection. Those tumors that were of large size at detection were positive for HCC-specific tumor markers and the deduced tumor growth speed was rapid. Although very few nodules (3/221, 1.4%) were larger than 30 mm in diameter at detection on ultrasound surveillance, other 14 cases were detected on CT that was ordered not because of ultrasound

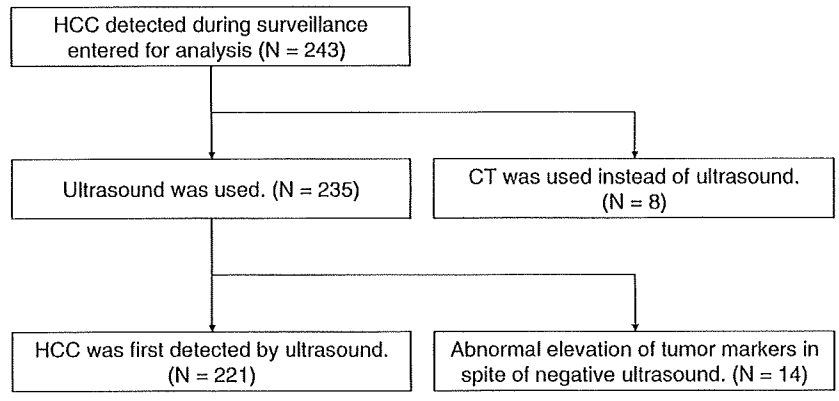


**Fig. 4** Schematic description of studied patients. *HCC* hepatocellular carcinoma, *CT* computed tomography

findings, which had been negative, but because of an abnormal rise in tumor markers. Tumor size was larger than 30 mm in two of these cases. For the remaining 12 patients, it is not known whether the tumor would have been smaller than 30 mm at detection without tumor marker determination. The ultrasound-based surveillance at the authors' institution failed to detect tumors while they were smaller than 30 mm in diameter in at least 2.1% (5/235) patients.

A simple solution to reduce the proportion of oversized detection would be to adopt shorter surveillance interval [23, 24]. However, the present study showed that the 4-month interval was not short enough, and it may not be practical to further shorten the surveillance interval in terms of cost-effectiveness. It should also be noted that the prognosis of patients with rapid growing tumor may be poor even after curative hepatectomy [25, 26]. Sheu et al. [23], by comparing tumor sizes on two ultrasound examinations at an interval of 36–860 days, reported a median tumor doubling time of HCC as 117 days (range = 29–398 days). Although the investigators proposed an optimal ultrasound interval of 4–5 months, some tumors may not be small enough at detection with this interval if the doubling time is at the shorter side of the range.

Although AFP has been known as an HCC-specific biomarker for more than 30 years, the usefulness of AFP in HCC surveillance has been questioned [27]. Serum AFP level is negative in more than half cases of HCC, and it may become positive in hepatitis or cirrhosis without HCC [28]. Thus, the evaluation of AFP based on a single-point value is of limited use. However, sequential elevation in serum AFP levels is more specific for HCC [29, 30]. Larger tumors, which are likely to have shorter doubling time, have higher positivity for AFP [31]. Thus, the sequential determination of AFP can be complementary to ultrasound surveillance. The determination of DCP, which is more specific to HCC than is AFP, may serve in a similar manner. These tumor markers should be measured at an interval shorter than that of ultrasound surveillance if the measurement is to supplement ultrasonography.

Ultrasonography had not been used as the mode of surveillance in eight patients because the resolution was judged not satisfactory. Contrast-enhanced CT was used instead and successful in finding HCC nodules at acceptable sizes. In the surveillance of patients with coarse liver parenchyma, modalities other than conventional ultrasonography are preferable. However, the cost-effectiveness and invasiveness of contrast-enhanced CT should be considered if its indication is to be broadened. Recently developed contrast-enhanced ultrasonography may be promising but is yet to be evaluated in future studies.

In conclusion, patients with chronic hepatitis C without cirrhosis could be appropriately screened at 6-month intervals, as recommended by various guidelines, and such a protocol would be able to detect small tumors in most cases. However, in patients with established cirrhosis, more frequent screening would be needed to detect tumors of the same size and the 6-monthly recommendations would result in the detection of larger tumors than that in patients without cirrhosis.

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# Image-guided percutaneous ablation therapies for hepatocellular carcinoma

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Image-guided percutaneous ablation therapies have been playing important roles in the treatment of hepatocellular carcinoma (HCC). In our department, we have treated 90% of previously untreated patients with ablation therapies. Among various local ablation therapies, radiofrequency ablation has been replacing ethanol injection as a standard therapy for patients who have unresectable HCC or who do not want surgery. Our randomized controlled trials and those of others proved that radiofrequency ablation is superior to ethanol injection. Radiofrequency ablation is potentially curative, minimally invasive, and easily repeated for recurrence. Long-term survival is notably high, and mortality and morbidity are low, in radiofrequency ablation. Further investigations are necessary to determine whether radiofrequency ablation can replace surgery for resectable hepatocellular carcinoma. In such trials, the primary endpoint must be overall survival. Recurrence-free survival can be misleading and cannot be a surrogate endpoint. There are still effective therapies after recurrence, and the first recurrence does not cause death in most cases. Furthermore, hepatectomy has theoretically better disease-free survival than radiofrequency ablation because it removes a larger amount of liver tissue. The better cure rate of resection can be canceled, however, by deterioration of liver function.

**Key words:** image-guided, percutaneous, ablation therapy, radiofrequency ablation, hepatocellular carcinoma

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## Introduction

Hepatocellular carcinoma (HCC) is the fifth most common malignant neoplasm in the world, and it is estimated to cause approximately half a million deaths annually.[1] HCC is on the increase in Western countries.[2,3] Surgery plays a limited role in the treatment of HCC in contrast to other solid tumors.[4–6] Only 20%–30% of patients can be candidates for hepatectomy because of underlying cirrhosis or multiple lesions. Furthermore, this cancer frequently recurs, even after apparently curative resection,[7] because of latent metastasis or metachronous multicentric carcinogenesis. Liver transplantation achieves excellent results in patients with solitary HCC less than 5 cm or with up to three nodules smaller than 3 cm, these criteria being known as the Milano criteria,[8] but its feasibility is restricted by organ donor shortage.[9,10]

Consequently, various nonsurgical therapies have been introduced. Among them, image-guided percutaneous ablation therapies, such as percutaneous ethanol injection,[11–13] microwave coagulation,[14] and radiofrequency ablation,[15–17] have been playing important roles in the treatment of small HCC. They have been widely accepted as the best treatment option for patients with early-stage HCC who do not undergo resection or transplantation. They are potentially curative, minimally invasive, and easily repeatable. At our institute, we have treated 90% of previously untreated patients with HCC by percutaneous ablation therapies. We have performed ethanol injection for a total number of 2000 since 1985, and microwave coagulation for a total of 200 patients since 1995, with satisfactory long-term results. However, since the introduction of radiofrequency ablation into clinical practice in 1999, there has been a drastic shift from ethanol injection and microwave coagulation to radiofrequency ablation (Fig. 1).[17] Our randomized controlled trial[18] and those of others[19,20] have proved that radiofrequency ablation has higher

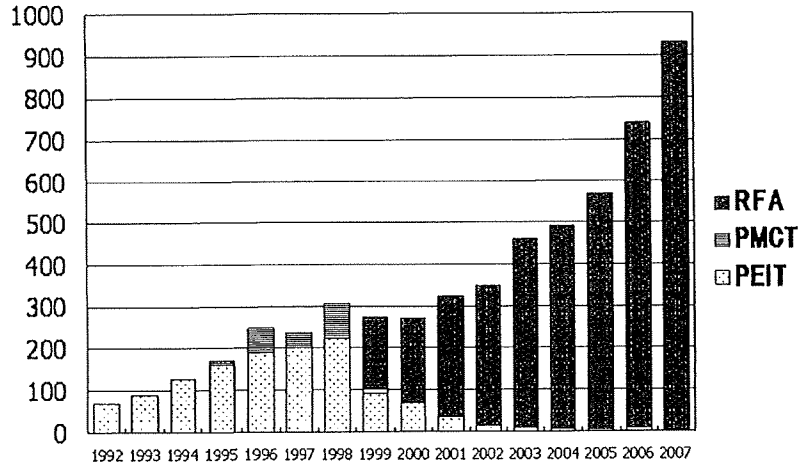


**Fig. 1.** Transition of image-guided percutaneous ablation therapies for liver tumors at the Department of Gastroenterology, University of Tokyo. At our institute, 90% of previously untreated patients with hepatocellular carcinoma have been treated by ablation therapies. Since the introduction of radiofrequency ablation into clinical practice in 1999, there has been a drastic shift from ethanol injection and microwave coagulation to radiofrequency ablation. In 2007, we performed radiofrequency ablation for a total of 929 patients with liver tumors; in contrast, we did ethanol injection for 2. *PEIT*, percutaneous ethanol injection therapy; *PMCT*, percutaneous microwave coagulation therapy; *RFA*, radiofrequency ablation

survival and lower recurrence than ethanol injection in the treatment of HCC.

In this article, I first describe ethanol injection and microwave coagulation briefly, and then radiofrequency ablation in more detail.

## Percutaneous ethanol injection

In percutaneous ethanol injection, absolute ethanol is injected directly into lesions through 21- to 22-gauge needles that are inserted under ultrasound guidance.[21] This method can destroy a considerably large volume of tissue in one ablation. Ethanol injection was introduced into clinical practice in the early 1980s.[11–13] It has enabled us to treat HCC potentially curatively by nonsurgical measures. Ethanol injection has been widely performed as a standard therapy for small HCC, such as those 3 cm or less in diameter.[21,22]

Histopathological examinations after the therapy have revealed that ethanol injection can destroy the tumor completely when it is performed properly.[23] Some investigators have reported that its long-term survival may be similar to that of surgery.[24–27] According to the report of the 17th nationwide follow-up survey of the Liver Cancer Study Group of Japan, the 1-, 2-, 3-, 4-, 5-, 7-, and 10-year survival rates of all 14726 patients treated by ethanol injection were 91.3%, 77.5%, 63.0%, 50.2%, 39.4%, 24.4%, and 12.3%, respectively.[28] At our institute, the cumulative survival rates of 685 patients for whom ethanol injection was performed as the initial treatment were 91.0%, 80.5%, 67.6%, 57.0%, 49.0%, 34.5%, and 17.4% at 1, 2, 3, 4, 5, 7, and 10 years, respectively.[29] A recent randomized controlled trial showed that there is no statistical significance for recurrence and survival between ethanol injection and surgical resection.[30]

Ethanol injection requires repeated injection on separate days. Its efficacy is not very reliable, furthermore, because spread of injected ethanol is largely restricted by the capsule or septa of the lesion (Fig. 2).[23] Thus, the number of patients treated by ethanol injection has sharply decreased since the recent introduction of radiofrequency ablation.[17] Our randomized controlled trial[18] and others[19,21] showed that radiofrequency ablation is superior to ethanol injection for small HCC from the point of view of not only treatment response but also recurrence and survival.

Nowadays, ethanol injection is a treatment of choice only in cases in which radiofrequency ablation cannot be performed safely, such as those in whom enteric-biliary reflux is observed, so that radiofrequency ablation may develop a liver abscess, or those in whom adhesion exists between the lesion and the gastrointestinal tract, so that radiofrequency ablation may cause gastrointestinal tract perforation or penetration even using the artificial ascites technique.

## Percutaneous microwave coagulation

In percutaneous microwave coagulation, the cancer tissue is ablated by dielectric heat produced by microwave energy emitted from the inserted bipolar-type electrode (16 gauge).[14] Microwave coagulation has been used in liver surgery to control bleeding from liver transaction planes during resection. Heat may be conducted considerably homogeneously in all directions; the capsule or septa of the lesion may not prevent the conduction appreciably. Microwave coagulation can certainly destroy a certain amount of tissue, although its necrotic area is smaller (2 cm in diameter and 2.5 cm in length) compared with ethanol injection. Microwave coagulation became popular in Japan in the late 1990s.

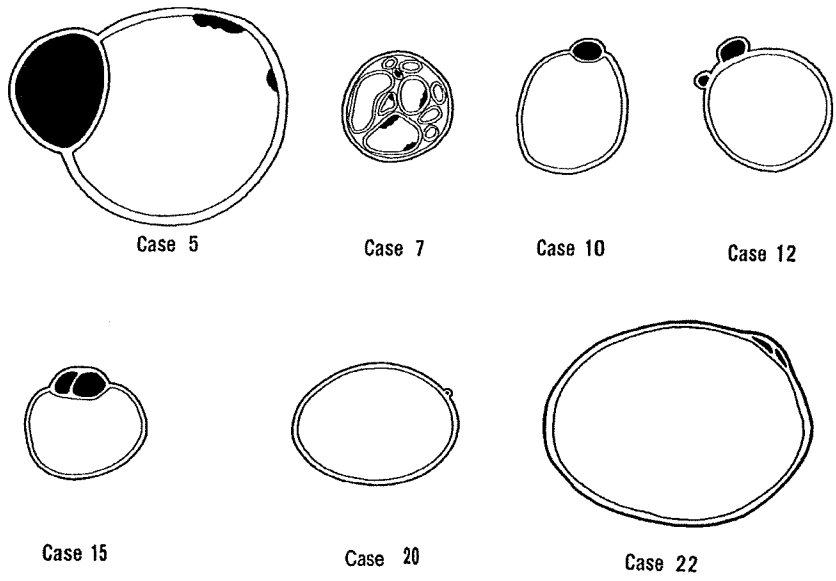


**Fig. 2.** Scheme of cases of incomplete necrosis treated by ethanol injection. In an early period of our study, we histopathologically examined 24 lesions of hepatocellular carcinoma treated by ethanol injection and found that the lesion was completely necrotic in 17 lesions, 90% necrotic in 6 lesions, and 70% necrotic in the remaining lesion. Viable cancer tissue remains in small nodules around the main lesion, along the edge of the lesion, or in portions isolated by septa; this occurs because spread of injected ethanol is largely restricted by the capsule or septa of the lesion, which results in less reliable efficacy in ethanol injection than thermal ablation

However, since the spread of radiofrequency ablation, microwave coagulation has rarely been performed.[17] According to the report of the 15th nationwide follow-up survey of the Liver Cancer Study Group of Japan, the 1-, 2-, 3-, 4-, and 5-year survival rates of all 828 patients treated by microwave coagulation were 93.8%, 85.6%, 77.1%, 67.3%, and 57.2%, respectively.[31]

## Radiofrequency ablation

In radiofrequency ablation, the electrode is inserted into the tumor under image guidance. Then, radiofrequency energy emitted from the exposed portion of the electrode is converted into heat and causes necrosis of the tumor. Radiofrequency ablation can ablate a tissue of as much as 3 cm in diameter or more as expected. Thus, radiofrequency ablation has the advantage of ethanol injection; it can ablate a large volume of tissue in one treatment. It also has the advantage of microwave coagulation; it can definitely destroy a certain size of tissue.

Radiofrequency ablation is mainly performed percutaneously under ultrasound guidance; however, it can also be used under laparotomy,[32] laparoscopy,[33] or thoracoscopy.[34]

Several types of radiofrequency ablation systems are commercially available.[35] In RITA (Mountain View, CA, USA) and Boston Scientific (Natick, MA, USA) systems, expandable-type electrodes are used; multiple thin curved monopolar electrodes extend from the central cannula (14–18 gauge) of the electrode (Fig. 3A). Radiofrequency emanates from each of these hooks, resulting in increased coagulation. In the Valley Lab (Boulder, CO, USA) system, cooled-tip electrodes (17 gauge) are used. These electrodes have two hollow lumens that permit continuous internal cooling of the tip with a chilled perfusate (Fig. 3B). As a result, heating of tissues nearest to the electrode is reduced, which allows for greater current deposition without tissue charring or impedance increase. We use the cooled-tip electrodes almost exclusively at our institute because some lesions can be ablated with these electrodes but not with the expandable-type ones.[36] In Japan, where more than 1400 institutes have introduced radiofrequency ablation in clinical practice, the system with the cooled-tip electrodes has an 80% share of the market; in other countries, however, those systems with expandable-type electrodes are more widely used.

Among various local ablation therapies, radiofrequency ablation has been replacing ethanol injection as a standard therapy for patients who have unresectable HCC or who do not want to undergo surgery. There have been a few randomized controlled trials to compare radiofrequency ablation with ethanol injection. In a study by Lin et al., 157 patients with 186 HCCs of 4 cm or less were randomly assigned to radiofrequency ablation, conventional ethanol injection, and higher-dose ethanol injection.[20] Radiofrequency ablation was superior to conventional ethanol injection and higher-dose ethanol injection from the aspects of local tumor progression, overall survival, and cancer-free survival. In another study by Lin et al., 187 patients with HCC were assigned to radiofrequency ablation, ethanol injection, or acetic acid injection.[37] Radiofrequency ablation was superior to ethanol injection and acetic acid injection with respect to local recurrence, overall survival, and

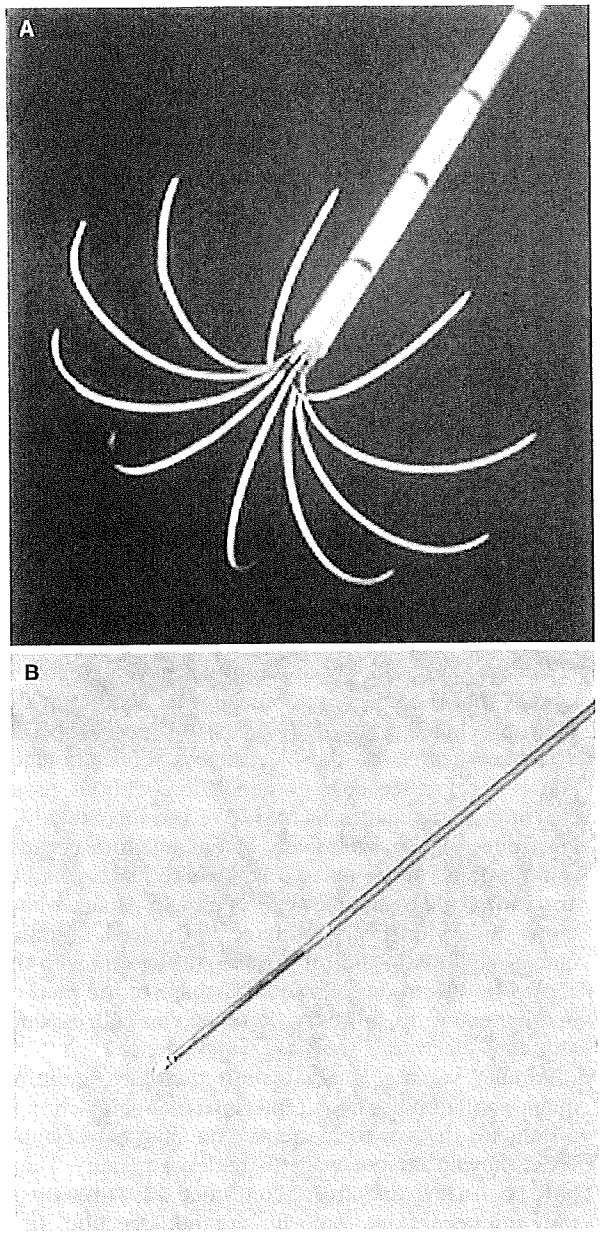


**Fig. 3. A** Tip of an expandable-type electrode. A 16-gauge needle is introduced into a lesion, and then ten retractable tines are deployed. Radiofrequency emanates from each of these hooks, resulting in increased coagulation. **B** Tip of a single needle type electrode; these are called cool-tip electrodes, because the electrode's internal circulation of water cools the tissue adjacent to the exposed electrode, maintaining low impedance during the treatment cycle. Low impedance permits maximum energy deposition for a larger ablation volume

cancer-free survival rates, but radiofrequency ablation also caused more major complications.

In our study, 232 patients with HCC who had three or fewer lesions, each 3 cm or less in diameter, and liver function of Child-Pugh class A or B were entered into a randomized controlled trial.[18] The primary endpoint was survival, and the secondary endpoints were overall recurrence and local tumor progression. Radiofrequency ablation had a 46% smaller risk of death, a 43% smaller risk of overall recurrence, and an 88% smaller risk of local tumor progression than ethanol injection. The incidence of adverse events was not different between the two therapies.

Recently, a randomized controlled trial to compare radiofrequency ablation with surgical resection reported that there was no difference between these two treatments from the aspects of overall survival and disease-free survival, whereas posttreatment complications were more frequent and more severe after surgery.[38]

## Patient selection

The general requirements for radiofrequency ablation are as follows:

1. Histopathologically confirmed HCC or characteristic imaging features of HCC
2. Unresectable lesions or refusal of surgery
3. Absence of apparent vascular or biliary invasion
4. Absence of refractory ascites
5. Absence of marked bleeding tendency (prothrombin times should be 50 % or more; platelet transfusion must be used if a patient has a platelet count of less than 50000/mm$^3$)
6. Serum bilirubin level of less than 3.0 mg/dl
7. Lesions located in portions where the electrode can be inserted and held safely
8. Informed consent

With regard to the size of the lesions, radiofrequency ablation is usually performed for small lesions up to 3 cm in diameter, because the size of necrosis achieved by each ablation is limited. Larger tumors can be treated by radiofrequency ablation, however, with overlapping of ablated areas. The combination of transcatheter arterial chemoembolization and radiofrequency ablation is often useful for large tumors.

With regard to the number of the lesions, most investigators have performed radiofrequency ablation on patients with three or fewer lesions. It is impractical to treat very many lesions with radiofrequency ablation because of the number of necessary treatment sessions. In addition, it is very likely that there are also small undetectable metastases in cases of many lesions, and

therefore, even if all detected lesions are treated by radiofrequency ablation, complete cure cannot be expected in those cases. In cases of more than three lesions, in which complete cure cannot be expected, radiofrequency ablation may still be performed combined with transcatheter arterial chemoembolization. Chemoembolization is first performed to treat all lesions, and then radiofrequency ablation may be performed against main lesions.

The anatomic location of the tumor may have potential influence on the efficacy and complication of radiofrequency ablation, although we have put no restrictions on lesion location, and we have successfully performed radiofrequency ablation on more than 99% of patients at our institute.[36] It is risky to perform ablation for lesions adjacent to the Glisson's capsule; this frequently causes biliary injury, which results in biliary stricture or biloma. It may also damage the hepatic artery and the portal vein, which results in hepatic infarction. A "heat-sink" effect caused by blood flow may cause incomplete necrosis of lesions contiguous with large vessels. It is also risky to do ablation near other organs, such as the gallbladder and the heart. Lesions near the gastrointestinal tract may be treated safely if the artificial ascites technique can separate the lesion from the tract.[39] Subcapsular lesions are reported to be a high risk of malignant cell seeding[40] and thus, if possible, the lesion should be punctured through the nontumorous part of the liver. Lesions beneath the diaphragm can be ablated successfully if the artificial pleural effusion technique is available.[41]

Radiofrequency ablation can be used even in cases in which complete cure cannot be expected, because it is not very invasive and definitely reduces the tumor mass. In those cases, only main lesions may be treated by radiofrequency ablation to reduce the tumor burden, and some lesions may be treated by other therapies.

## Technique

Planning ultrasound should be performed carefully to select the optimal approach. In Japan, radiofrequency ablation is performed on an inpatient basis.[17] The patients should fast at least 4 h before the treatment and should be given premedications for analgesia and sedation.

In radiofrequency ablation, grounding is achieved by attaching two pads to the patient's thighs. An 17-gauge, cooled-tip electrode with a 2- or 3-cm exposed tip is attached to a radiofrequency generator (CC-1 Cosman Coagulator; Valley Lab). After local anesthesia, the electrode is inserted under ultrasound guidance (Fig. 4). During ablation, the temperature is measured with a thermocouple in the electrode. Tissue impedance is also monitored by circuitry incorporated into the generator. A peristaltic pump infused 0°C saline into the electrode lumen to maintain the tip temperature below 20°C. Radiofrequency energy is usually delivered for 6–12 min for each application as follows: after measurement of baseline impedance, generator output is gradually increased to 1400 mA. This level is maintained until the impedance is increased more than 10 ohms from the baseline. Then the current is temporarily reduced until impedance becomes stabilized. Output is decreased and increased repeatedly for the remainder of the session to avoid tissue charring. A 12-min ablation using a 3-cm exposed-tip electrode produces a quasi-spherical necrotic volume 3 cm in diameter. For large lesions, the electrode is repeatedly inserted into different sites, so that the entire lesion can be enveloped by assumed necrotic volumes. Following the procedure, the patients should remain in bed until the next morning.

If the entire lesion is assumed to have become necrotic, enhanced computed tomography (CT) is performed (Fig. 5). When any possible undestroyed portions remain, the therapy is repeated until CT demonstrates the entire tumor necrosis.

## Local tumor progression and distant recurrence

Although many investigators have reported that radiofrequency ablation could achieve complete tumor necrosis in most cases on CT, local tumor progression is not infrequent; local tumor progression rate at 3 years was reported to be 1.7%–20.4%.[18,20,42,43] The most important factor associated with failure of local tumor control is tumor size.[42–44] It is not easy to obtain a certain amount of safety margin all around a large tumor in three dimensions. Although various new radiofrequency ablation devices to increase the ablation volume have been introduced, a large tumor of 3 cm or more still requires multiple overlapping ablations.

Although local tumor progression is related to incomplete tumor ablation, distant intra- and extrahepatic recurrence is mainly determined by the biological characteristics and natural history of HCC. The incidence of distant intra- and extrahepatic recurrence ranges from 41% to 73%.

## Survival

According to the report of the 17th nationwide follow-up survey of the Liver Cancer Study Group of Japan, the 1-, 2-, 3-, 4-, and 5-year survival rates of all 5478 patients treated by radiofrequency ablation were 94.9%, 85.7%, 76.7%, 67.2%, and 57.3%, respectively.[28] At our

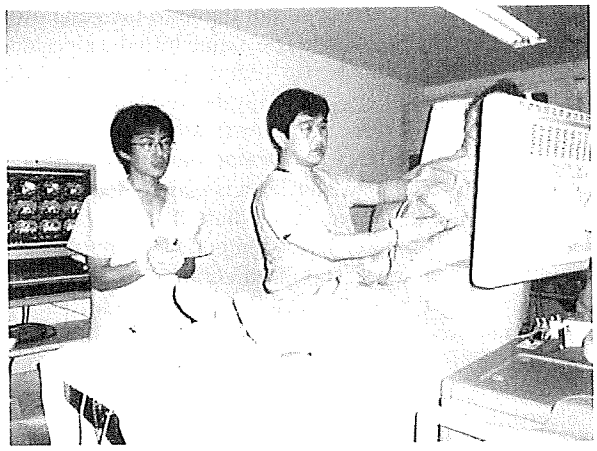

**Fig. 4.** A view of radiofrequency ablation. An electrode is inserted percutaneously into the lesion under ultrasound guidance

institute, the cumulative survival rates of 909 patients on whom radiofrequency ablation was performed as the initial treatment were 96.5%, 88.6%, 81.8%, 71.1%, 60.6%, and 34.1% at 1, 2, 3, 4, 5, and 8 years, respectively.[27] In other studies, survival rates of patients treated by radiofrequency ablation range from 75% to 97% at 1 year, from 50% to 78% at 3 years, and from 33% to 54% at 5 years.[45–50] Survival depends on not only tumor factors but also liver function.

## Adverse effects and complications

Mortality and morbidity rates are much lower in radiofrequency ablation than in surgery. Knowledge of the broad spectrum of adverse effects and complications and relevant management is, however, mandatory to perform radiofrequency ablation safely.

Common adverse effects of radiofrequency ablation were pain, fever, nausea, and asymptomatic right pleural effusion. Mulier et al. reviewed 82 articles and reported that the mortality and morbidity rates of 3670 patients treated by radiofrequency ablation were 0.5% and 8.9%, respectively.[51] There were 20 deaths reported, as a result of sepsis ($n$ = 7), liver failure ($n$ = 7), cardiac complications ($n$ = 4), peritoneal hemorrhage ($n$ = 1), and bile duct stricture ($n$ = 1). Major complications were abdominal bleeding (1.6%), abdominal infection (1.1%), bile tract damage (1.0%), liver failure (0.8%), dispersive pad skin burn (0.6%), hepatic vascular damage (0.6%), visceral damage (0.5%), cardiac complications (0.4%), myoglobinemia or myoglobinuria (0.2%), tumor seeding (0.2%), coagulopathy (0.2%), and other. The complication rate was similar for the percutaneous (7.2%), laparoscopic (9.5%), and simple laparotomic (9.9%) approach whereas the laparotomic approach combined with cryotherapy or hepatic or extrahepatic resection had a morbidity rate of 31.8%.

A multicenter study in Italy reported that 6 deaths (0.3%) were noted among 2320 patients treated with the cooled-tip electrode, including multiorgan failure following intestinal perforation ($n$ = 2), septic shock following *Staphylococcus aureus*-caused peritonitis ($n$ = 1), massive hemorrhage following tumor rupture ($n$ = 1), liver failure following stenosis of right bile duct ($n$ = 1), and sudden death of unknown cause 3 days after the procedure ($n$ = 1).[52] Fifty patients (2.2%) had additional major complications. Common complications were peritoneal hemorrhage (0.5%), neoplastic seeding (0.5%), intrahepatic abscess (0.3%), and intestinal perforation (0.2%). An increased number of treatment sessions were related to a higher rate of major complications.

A multicenter survey in Korea revealed one procedure-related death (0.09%) resulting from peritoneal hemorrhage and 37 major complications (2.4%) among 1139 patients in 11 centers.[53] Reported complications were hepatic abscess (0.7%), peritoneal hemorrhage (0.5%), biloma (0.2%), ground pad burn (0.2%), pneumothorax (0.2%), vasovagal reflex (0.1%), and other.

A multicenter survey in Japan reported that 9 patients (0.3%) died within 3 months and 207 complications (7.9%) were encountered in 2614 patients treated by radiofrequency ablation.[54] Causes of death were liver failure in 3, rapid progression and sarcomatous changes in 3, biliary injury in 1, gastrointestinal (GI) bleeding in 1, and myocardial infarction in 1. The survey reported that departments that treated larger numbers of patients per month had a smaller number of complications and deaths.

## Ablation and resection

In the *Clinical Practice Guidelines for Hepatocellular Carcinoma 2005 in Japan*,[55] resection is considered superior to percutaneous local ablation (Fig. 6). A scientific statement is as follows: if there is only one tumor, hepatectomy is recommended, irrespective of the diameter of the tumor (percutaneous local therapy may also be selected if the severity of liver damage is class B and the diameter of the tumor is not more than 2 cm). This scientific statement is based upon a report which said that in clinical stage I (fair liver function) cases with a solitary tumor less than 2 cm in diameter, and in all clinical stages with a solitary tumor greater than 2 cm and in the clinical stage II (moderately impaired liver function) cases with two tumors greater than 2 cm, the hepatic resection group showed higher survival rates than the nonsurgical groups.[56]

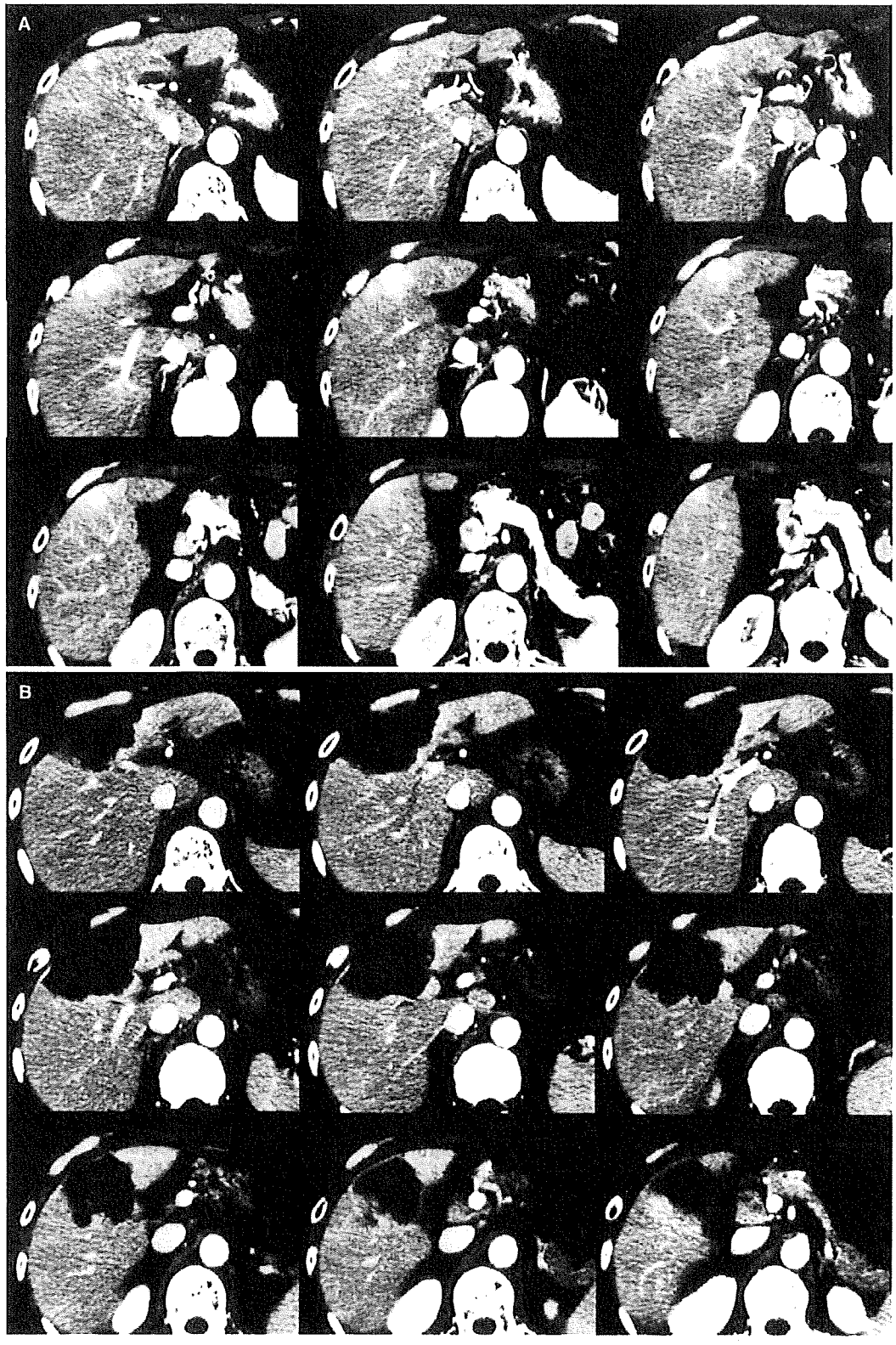


**Fig. 5.** **A** A 62-year-old man had confluent multinodular type hepatocellular carcinoma of 4 cm on the surface in S4. **B** Computed tomography scan taken after two sessions of radiofrequency ablation demonstrated that not only the lesion but also some amount of surrounding tissue had become necrotic. We judged that a local cure was certainly achieved even for this confluent multinodular type lesion

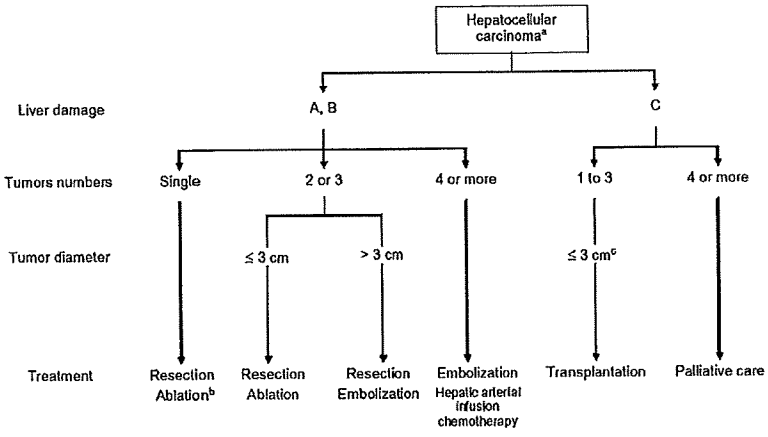


**Fig. 6.** Treatment algorithm for hepatocellular carcinoma from *Clinical Practice Guidelines for Hepatocellular Carcinoma 2005* in Japan.[55] *a* Presence of vascular invasion or extrahepatic metastasis to be indicated separately. *b* Selected when the severity of liver damage is class B and tumor diameter is ≤2 cm. *c* Tumor diameter ≤5 cm when there is only one tumor

However, those findings were not based on randomized controlled trials, and the different survival rates may result from bias of background. The report said that the hepatic resection group had a younger mean age than the ethanol injection group. Furthermore, even in the same clinical stage I group, most patients with normal liver or chronic hepatitis seemed to undergo resection whereas many with cirrhosis seemed to receive ethanol injection. This difference may result in lower recurrence from multicentric carcinogenesis and less frequent development of liver failure in the resection group. Moreover, the trend that patients with severe complications, such as cardiopulmonary disease, received not resection but ethanol injection may explain some part of the survival gap. A randomized controlled trial said that there is no statistical significance for recurrence and survival between surgical resection and ethanol injection.[30] In addition, there are several nonrandomized controlled trials that report that ethanol injection had similar or even better overall survival than resection.[57–59]

In addition, those findings were only from comparison of resection with ethanol injection. It is improper to consider them as findings from comparison of resection with all kinds of percutaneous local ablation therapies and to conclude hepatectomy is recommended more than any percutaneous local ablation. Our randomized controlled trial demonstrated that radiofrequency ablation had higher survival and lower recurrence rates than ethanol injection whereas adverse events were similar between the two therapies.[18] Other randomized controlled trials also showed that radiofrequency ablation was superior to ethanol injection in the treatment of HCC.[19,20,37] Furthermore, a randomized controlled trial reported that there were no difference in overall survival and disease-free survival between resection and radiofrequency ablation, whereas posttreatment complications occurred more often and were more severe after surgery.[38]

Further trials are necessary to determine whether radiofrequency ablation can replace surgery for operable HCC. In those trials, the primary endpoint should be overall survival. As the AASLD practice guideline clearly describes,[60] recurrence-free survival can be misleading and cannot be a surrogate endpoint. In HCC, in contrast to other solid tumors, there are still effective therapies after recurrence, and the first recurrence does not cause death in most cases. Furthermore, surgery has theoretically better disease-free survival than radiofrequency ablation because it removes a larger amount of liver tissue. The better cure rate of hepatectomy can be canceled, however, by deterioration of liver function.

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

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

**Key words:** hepatocellular carcinoma, radiofrequency ablation, survival analysis

## Introduction

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

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

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

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