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CLINICAL STUDIES

Stage progression of small hepatocellular carcinoma after radical therapy: comparisons of radiofrequency ablation and surgery using the Markov model

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Keywords
hepatocellular carcinoma – Markov model – radiofrequency ablation – recurrence – surgery – survival

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Abstract

Background: Stage progression of 374 small hepatocellular carcinomas (HCC) was retrospectively analysed. *Patients and methods:* During 8 years, 236 patients with the early stage of HCC received radiofrequency ablation (RFA), and 138 underwent surgery as an initial therapy. More patients of young age and with better liver function tended to undergo surgical treatment. Based on 1892 patient-year data, the Markov model analysed the stepwise progression of early stage (multiple up to three nodules, 3 cm or less each) to intermediate stage (four nodules or more, or larger than 3 cm), to advanced stage (portal invasion, extrahepatic metastasis or Child–Pugh C) and to death. *Results:* The recurrence rates after RFA and surgery were 53.3 and 40.6% in the third year. The annual progression rates from the early stage to the intermediate stage, advanced stage and death were 5.40, 1.63 and 1.73% in the RFA group and 3.90, 1.87 and 0.62% in the surgery group respectively. The progression rate from the early to the intermediate stage was significantly lower (2.34% annually) in the younger patient group (< 60 years) than that in the older group (≥ 60 years, 5.70%, $P = 0.0053$). In contrast, the progression rate from the intermediate to the advanced stage was significantly higher in the younger patient group (< 60 years, 37.50% annually) than that in the older groups (60–69 years, 30.30%, 70 years or older 22.09%, $P = 0.0011$). Multivariate hazard analysis showed that initial treatment did not significantly affect the stage progression rate (hazard ratio of RFA 1.09, $P = 0.70$) and the survival rate (hazard ratio of RFA 1.09, $P = 0.73$). *Conclusion:* Although the recurrence rate was slightly higher in the RFA group, additional ablation procedures could control the progression of HCC, with a rate comparable to the surgical group.

Hepatocellular carcinoma (HCC) is one of the most common neoplasms in the world today (1). Although routine imaging check-ups can often detect a small HCC at an early stage in high-risk patients with chronic hepatitis and cirrhosis, surgical resection is performed only in 20% or less of the cases because of the association of cirrhosis and tumour multiplicity (2–5). In the management of patients with HCC associated with cirrhosis, treatment repetition is common and inevitable for newly appearing multicentric tumours (6–8), and many practitioners hope each ablation procedure to be less invasive, less expensive and with a shorter hospitalization period.

Radiofrequency ablation (RFA) is currently considered the most effective percutaneous therapy for small HCCs, and certain centres now use it as a first-line treatment option (9), even in patients suitable for surgery. Indeed, RFA is sometimes considered as a less radical therapy compared with surgical resection because of the relatively high rate of local recurrence (10–12), but most of the local tumour progression can be completely treated through an additional RFA procedure. Surgical therapy, on the other hand, is an invasive mode of treatment with a higher cost (10), but achieves a lower recurrence rate. Only a few studies have evaluated the long-term outcome and prognostic factors of percutaneous RFA in comparison with surgical therapy (12–14).

When a recurrent tumour shows relatively advanced characteristics at an intermediate stage with a large tumour or multiples of four or more, transcatheter arterial chemoembolization (TACE) is preferred to surgical therapy or local ablation (15). We introduced the

Markov model to simulate the steps of stage progression of patients with small HCC under an intensive medical intervention. Here, we retrospectively evaluated the progression of HCC and the long-term prognosis of patients who had undergone RFA or surgical resection as the initial therapy for small HCCs, and assessed the prognostic factors of those patients.

The purposes of this study were, therefore, (i) to compare the recurrence rates, progression of tumour stage and survival rates between those patients who received percutaneous RFA and those who underwent surgery and (ii) to elucidate the significance of the selection of initial therapy for small HCCs from the viewpoints of stage progression and prognosis.

Patients and methods

Patients

A total of 468 patients were diagnosed as having a small HCC 3 cm or less in diameter, from March 1999 to April 2006, at the Department of Hepatology, Toranomon Hospital, Tokyo, Japan. Of these 468 patients, 236 patients (50.4%) underwent percutaneous RFA therapy as a curative mode of treatment and the remaining 138 patients (29.5%) received surgical resection, 52 had TACE and the remaining 42 patients were treated with ethanol injection, microwave coagulation or other palliative methods of treatment.

A total of 374 consecutive patients with a small HCC, who underwent either RFA or surgery, were analysed in this study. None had been treated previously for HCC, and all had single or multinodular (up to three) HCCs 3 cm or less in diameter each, absence of portal venous thrombosis and known extrahepatic metastases, and Child–Pugh class A or B liver function.

The patients included 246 men and 128 women, and ranging in age from 29 to 87 years, with a median age of 65 years. The demography, laboratory data and features of cancer were compared between the two therapy groups (Table 1). Patients' age was lower in the surgery group by 4.5 years. The rate of HBV-positive disease was significantly higher in the surgery group, and liver function tests were also significantly better in the surgery group.

Hepatocellular carcinoma

Patients were required to have HCC with a definitive diagnosis by either typical hypervascular radiological features or histology through needle biopsy. Tumours had to be measurable by ultrasonography (US), computerized tomography (CT) and digital subtraction angiography. In order to elucidate the detailed characteristics of the HCC, CT during arterial portography and CT hepatic arteriography were performed in all the patients. Among 374 patients, HCC was confirmed by a resected specimen in 138 patients, by typical hypervascular characteristics on at least two modalities of imagings in 219 and by a fine-needle biopsy in 17.

Most patients (82.2%, 309 of 376) had a single tumour, and the median tumour diameter was 19 mm, ranging from 5 to 30 mm. The characteristics of the tumour in the subgroup of RFA and surgery are given in Table 1. The median size of the largest tumour was 18 mm in the RFA group and 20 mm in the surgery group ($P < 0.001$).

Table 1. Clinical features of the patients with small liver cancer

Initial therapy	Radiofrequency ablation ($n = 236$)	Hepatic resection ($n = 138$)	P
Demography			
Men:women	145:91 (38.6%)	101:37 (26.8%)	0.0021
Age (median, range)	67 (38–87)	62.5 (29–80)	< 0.001
Decompensated cirrhosis	16 (6.8%)	5 (3.6%)	0.20
HBsAg	24 (10.2%)	46 (33.3%)	< 0.001
Antibody to HCV	197 (83.5%)	84 (60.9%)	< 0.001
History of alcohol intake > 500 kg	21 (8.9%)	16 (11.6%)	0.40
Observation period (year)	3.7 (0.1–9.9)	4.5 (0.1–10.0)	0.041
Laboratory data (median, range)			
ICG R15 (%)*	28 (1–100)	21 (3–68)	< 0.001
Bilirubin (mg/dl)	1.0 (0.2–3.1)	1.0 (0.3–2.2)	0.003
Albumin (g/dl)	3.5 (2.2–4.2)	3.6 (2.8–4.4)	< 0.001
Aspartic transaminase (IU)	55 (17–311)	45 (17–386)	0.006
Platelet count ($\times 10^3/mm^3$)	97 (19–253)	127 (38–272)	< 0.001
Prothrombin time (%)	84 (31–125)	91 (59–115)	0.001
Liver cancer			
Median size (mm)	18 (8–30)	20 (5–30)	< 0.001
Single/multiple	195/41 (17.4%)	114/24 (17.4%) 1.00	
α-fetoprotein (ng/ml)	19 (1–2080)	17 (1–2610)	0.84
PIVKA-II (AU/L)†	17 (7–1470)	20 (9–1650)	0.008

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

†PIVKA-II, protein induced by vitamin K antagonist-II.

HCV, hepatitis C virus.

Treatment for initial hepatocellular carcinoma

Physicians and surgeons usually held a conference about the choice of therapy in individual patients. RFA or surgical therapy were selected considering the site, size and number of tumours, liver function and the patient's general status. Both RFA and the surgical procedure were explained fully to all the patients, and informed consent was obtained. Despite the feasibility and availability of surgery, some patients voluntarily preferred RFA under informed consent.

Radiofrequency ablation therapy was performed percutaneously under US or CT guidance, under conscious sedation with fentanyl citrate (0.1–0.2 mg, Fentanyl; Daiichi-Sankyo, Tokyo, Japan) or pethidine hydrochloride (35–70 mg, Opystan; Tanabe-Mitsubishi, Osaka, Japan) administered intravenously. RFA was performed using three kinds of apparatus: a radiofrequency interstitial tumour ablation system (RITA, RITA Medical Systems Inc., Mountain View, CA, USA), a cool-tip system (Tyco Healthcare Group LP, Burlington, VT, USA) and a radiofrequency tumour coagulation system (RTC system, Boston-Scientific Japan Co., Tokyo, Japan).

Hepatic resection was performed under intra-operative US monitoring and guidance. In the cases of small and superficial HCC, arterial and portal vein clumping at the hepatic hilum was not usually performed for maintenance of liver perfusion.

Evaluation of the therapeutic effect

To evaluate the efficacy of local ablation, a dynamic CT was performed at 2–7 days after treatment with RFA, and 8–21 days after surgery. CT findings were confirmed by consensus among at least two hepatologists and radiologists. On dynamic CT images, the non-enhancing area was measured as the ablated area. When the diameter of the non-enhancing area was greater than that of the ablated nodule, RFA was considered to have had a complete effect, and the treatment was terminated. When patients had a smaller ablated area or a positively enhanced area in the original tumour based on CT results after RFA therapy, they usually underwent an additional RFA within several days.

Follow-up of patients

Physicians observed the patients every 4–8 weeks after the first treatment. Liver function test, haematology and tumour markers were measured every 1–2 months. After the completion of eradication of HCC, recurrence was surveyed with CT or magnetic resonance imagings (MRI) every 3–4 months. Serum α-fetoprotein (AFP) and des-γ-carboxy prothrombin were also measured every 1–2 months to detect recurrence as early as possible.

During a median observation period of 4.2 years, four patients (1.1%) were lost to follow-up.

Statistical analysis and the Markov model

Standard statistical measures and procedures were used. The χ^2-test, Fisher's exact test and Mann–Whitney's *U*-test were used to analyse the differences in the demography, laboratory findings and tumour characteristics between the RFA group and the surgery group. The recurrence rate, progression rates and survival rate were analysed using the Kaplan–Meier technique (16) with the log-rank test. Cox's proportional hazard analysis was performed to evaluate independent predictors of the outcomes.

The Markov model (17) was adopted to analyse the transition rates from the early stage to the intermediate stage of HCC, intermediate to advanced stage and advanced stage to death. A homologous Markov chain consisted of four states (Fig. 1). These were the early stage of HCC (solitary or multiple up to three nodules, 3 cm or less each), the intermediate stage (four nodules or more, or larger than 3 cm), the advanced stage (portal vein

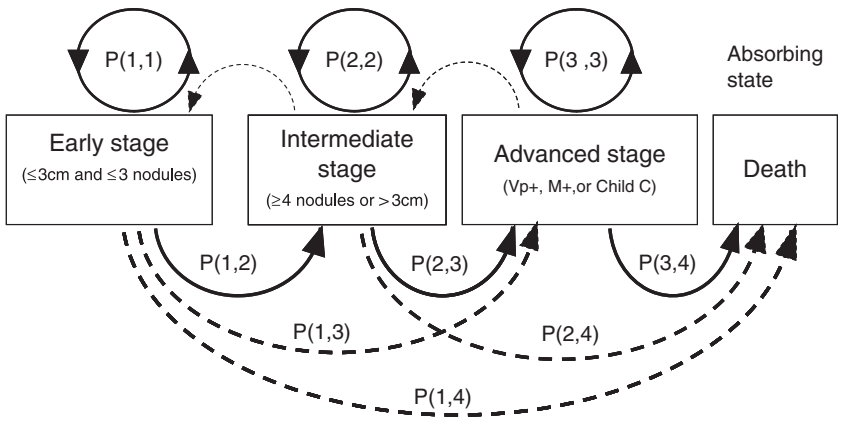

Fig. 1. The Markov state transition diagram of hepatocellular carcinoma. Four states were defined: early stage (solitary or multiple up to three nodules, 3 cm or less in diameter each), intermediate stage (multiple nodules of four or more, or 3.1 cm or more), advanced stage (main portal vein invasion, extrahepatic metastasis or Child–Pugh C) and death. Of these, death was the absorbing state from which no transitions to the other states occurred. The transition in one cycle (1 year) is shown. Arrows connecting two different states indicate the transitions observed.

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^{TM}, 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

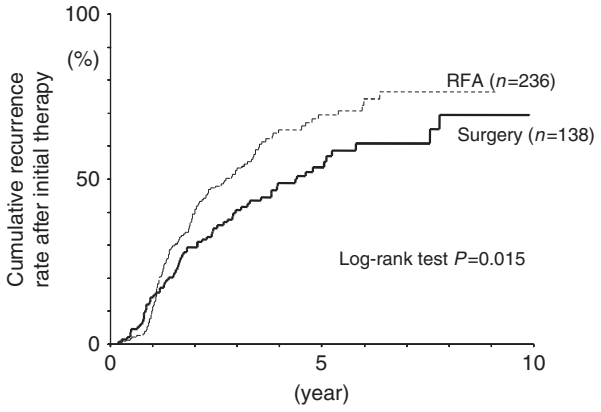

Fig. 2. Cumulative recurrence rates after therapy in patients with an early stage of hepatocellular carcinoma, according to initial therapy. RFA, radiofrequency ablation.

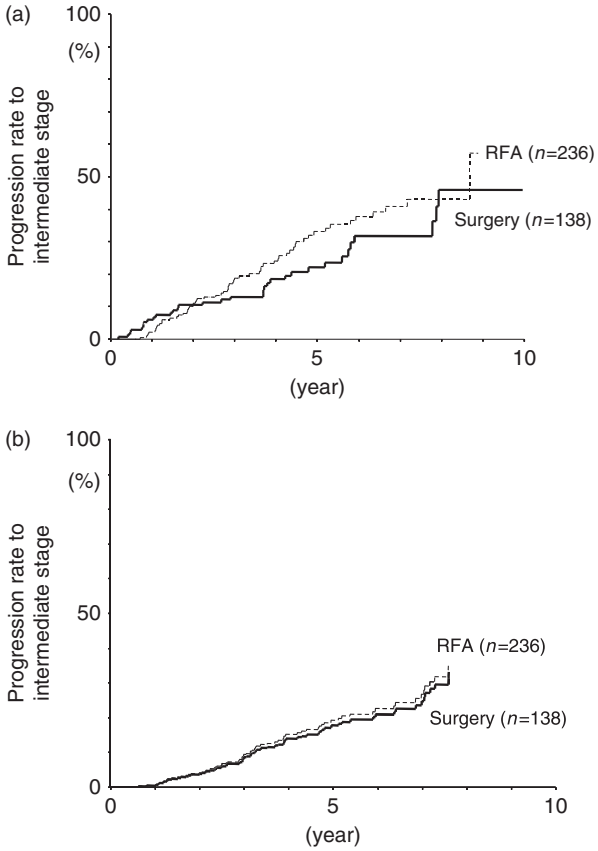

Fig. 3. (a) Crude development rates to the intermediate stage of hepatocellular carcinoma according to initial therapy. (b) Adjusted development rates to the intermediate stage, using proportional hazard analysis. RFA, radiofrequency ablation.

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: $\geq 100\,000/mm^3$	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).

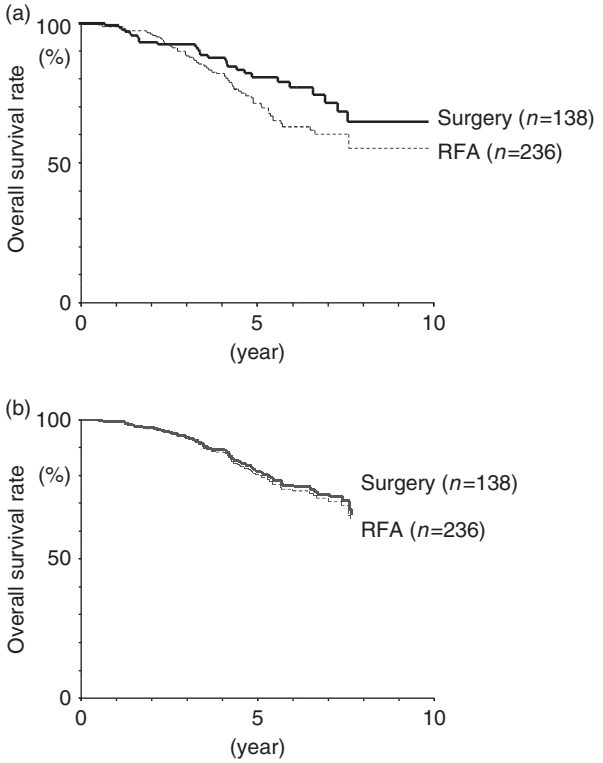

Fig. 4. (a) Crude survival rates in patients receiving radiofrequency ablation and those undergoing surgery as the initial therapy. (b) Adjusted survival rates in the radiofrequency group and surgery group, using proportional hazard analysis. RFA, radiofrequency ablation.

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

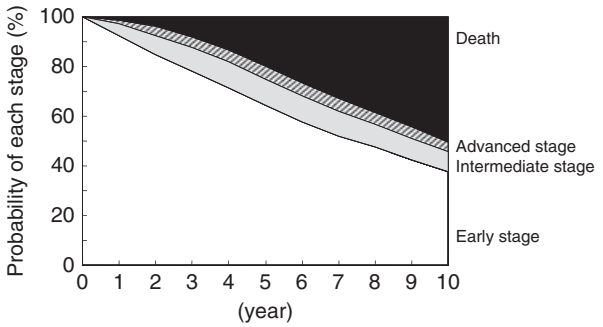

Fig. 5. Illustrated transition probabilities of patients, from the early stage of hepatocellular carcinoma, to the intermediate stage, the advanced stage and to death.

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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