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Authors' contributions
YO, TK, SS, AS, and TI participated in the design of the study and performed the statistical analysis; RK helped to draft the manuscript. EI, SA, YK, TI, HT, FM, JN, KH, and SH collected the data. All authors have read and approved the final manuscript.

Competing interests
The authors declare that they have no competing interests. None of the authors has had within the past 12 months any financial relationship with a biotechnology manufacturer, a pharmaceutical company, or other commercial entity that has any interest in the subject matter, materials, or processes discussed in the manuscript.

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Percutaneous Radiofrequency Ablation for Hepatocellular Carcinoma: Clinical Outcome and Safety in Elderly Patients

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Abstract

Background & Aims. We aimed to compare clinical outcomes and safety of radiofrequency ablation (RFA) in single hepatocellular carcinoma (HCC) patients aged >75 years (elderly group) versus patients aged <75 years (control group). **Patients and methods.** There were 130 patients in the elderly group and 238 in the control group. Clinical outcomes including overall survival (OS), recurrence free survival (RFS) and local tumor progression (LTP), and safety were analysed for these two groups after initial RFA. **Results.** The mean (± standard deviation [SD]) tumor diameter in the elderly and the control groups was 2.13 ± 0.86 cm and 1.92 ± 0.63 cm, respectively; the mean (± SD) observation period was 2.5 ± 1.8 years and 3.2 ± 2.0 years, respectively. The 1 and 3 year OS rates were 90.0 and 64.1%, respectively, in the elderly group and 97.6 and 83.7%, respectively, in the control group (P=0.001); the corresponding RFS rates were 66.9 and 21.3%, respectively, in the elderly group and 80.5 and 40.0%, respectively, in the control group (P=0.001). The 1 and 3 year LTP rates were 15.0 and 43.0%, respectively, in the elderly group and 8.3 and 26.3%, respectively, in the control group (P=0.002). In terms of duration of hospitalization (P=0.807) and serious adverse events related RFA (P=0.670), there was no significant difference between these two groups. **Conclusion.** The clinical outcomes in the elderly group were poorer than those in the control group, although RFA in the elderly patients was a safe procedure.

Key words

Hepatocellular carcinoma – radiofrequency ablation – elderly patients – clinical outcome – safety.

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Introduction

Hepatocellular carcinoma (HCC) ranks fifth among th most prevalent cancers in the world, and is the third mos common cause of cancer related death [1-4]. The incidenc of cancer has been reported to increase markedly with age with >60% of all cancers developing in patients aged >6 years [5]. In fact, the risk of developing HCC is know to be age dependent [6]. Thus, there will be an increasin number of elderly HCC patients in the coming years owin to the increased longevity of the population. In Japan, th adjusted HCC mortality rate has increased in recent year [7]. Moreover, the average age of HCC patients in Japa is increasing and the proportion of elderly HCC patients i therefore rising [8].

Radiofrequency ablation (RFA) therapy, an alternativ technique to percutaneous ethanol injection (PEI) tha was introduced in Japan in 1999, has been widely use as a curative treatment for HCC and has evolved into a important therapeutic tool for the treatment of HCC [1-3 9-12]. An area of <3 cm in diameter can be ablated with single application of RFA. This technique has proven t be a safe and effective modality for the treatment of smal HCC in patients who are considered unsuitable for surgica intervention because of insufficient hepatic reserve [1-3] More recently, several investigators have used RFA to trea selected patients with resectable HCC with favorable clinica outcomes, and RFA is gradually gaining popularity in th treatment of resectable HCC in many countries, in additio to Japan [13].

In general, elderly patients have a high incidence o comorbid diseases and are considered high-risk patients fo surgical resection. Thus, radical surgical resection of HC is less feasible in elderly patients than in younger patients and RFA therapy may be an acceptable alternative [14] However, to our knowledge, there have been few reports or clinical outcomes and safety in elderly HCC patients treate with RFA, although there have been several reports regardin patients treated with other therapies such as surgica resection, PEI and transcatheter arterial chemoembolizatio (TACE) [15-31]. The aim of the present study was to evaluat

clinical outcomes and safety after RFA treatment in HCC patients aged >75 years as compared with HCC patients aged <75 years.

Patients and methods

Patients

We performed RFA therapy in 395 treatment-naïve patients diagnosed with solitary HCC in the Department of Gastroenterology and Hepatology, Osaka Red Cross Hospital, Japan between January 2004 and January 2012. Of these patients, 27 were lost in follow-up and were excluded from the present study. Thus, the current study consisted of a total of 368 patients with single HCC. Our criteria of RFA therapy are as follows: (a) ineligible for surgical resection or liver transplantation; (b) patient refusal for surgery; (c) tumor size up to about 3cm and tumor number up to 3 nodules; (d) absence of uncontrollable ascites; (e) no extrahepatic metastases or vascular invasion.We categorized patients into two groups, namely the elderly group (≥75 years old) and the control group (<75 years old).The breakpoint of 75 years of age was chosen because it enabled comparison with other relevant previous reports. Moreover, in our country, patients aged ≥75 years are covered by a health insurance system which is different from that for patients aged <75 years. We compared the clinical outcomes including overall survival (OS), recurrence free survival (RFS) and local tumor progression (LTP) and safety between these two groups after initial RFA. Prior to RFA, written informed consent was obtained from all patients. The current study comprised a retrospective analysis of patient records and all treatments were conducted in an open-label manner. The Ethics Committee of our department approved the current study protocol and this study protocol complied with all of the provisions of the Declaration of Helsinki.

HCC diagnosis

Hypervascular HCC was diagnosed using abdominal ultrasound and dynamic computed tomography (CT) scans (hyperattenuation during the arterial phase in all or some part of the tumor and hypoattenuation in the portal-venous phase). Arterial and portal phase dynamic CT images were obtained at approximately 30 s and 120 s, respectively, after the injection of contrast material. In all cases of hypovascular HCC, percutaneous tumor biopsy was performed according to the diagnostic criteria for HCC proposed by the Japan Society of Hepatology [32]. There were 336 hypervascular HCCs and 32 hypovascular HCCs in the current study. For all patients, abdominal angiography was performed before RFA. We confirmed solitary HCC with no vascular invasion and no satellite nodules using CT during hepatic arteriography (CTHA) and arterial-portography (CTAP) [33].

Assessment of treatment efficacy

To assess treatment efficacy, we performed dynamic 16-column multi-detector CT (MDCT) using 3-mm slice scans within 1 week after RFA. The patients were then classified into four groups as follows: Grade A (absolutely curative), a ≥5 mm ablative margin around the entire tumor; Grade B (relatively curative), an ablative margin around the tumor but <5 mm in diameter in some places; Grade C (relatively non-curative), only an incomplete ablative margin around the tumor although no residual tumor was apparent; Grade D (absolutely non-curative), the tumor was not completely ablated. We referred to this classification system as Radicality Grading (R grades: A, B, C and D) [34]. Decisions with regard to R grading were made by three radiologists experienced in liver imaging modalities.

In our department, during abdominal angiography, we routinely perform arterial infusion of iodized oil (Lipiodol Ultra-Fluid, Schering Japan, Osaka, Japan). Lipiodol was injected to intensify the radiologic visibility of the target tumor [34]. In patients where the tumor location could be determined because of the dense accumulation of lipiodol, we assessed treatment efficacy using dynamic CT scans. However, in patients where it was difficult to determine the exact location of the tumor because of insufficient lipiodol accumulation (e.g. hypovascular HCC), and for those where lipiodol had only accumulated in part of the tumor (e.g. nodule-in-nodule HCC), we measured the ablative margin using CTHA with a CTAP image as the reference image.

Definition of HCC recurrence

We defined LTP as the presence of a recurrent nodule adjacent to the ablated area after RFA using dynamic CT scanning. Recurrence that occurred distantly from the ablated area in the same segment was included as distant recurrence. Extrahepatic recurrence was determined using chest CT scan, whole abdominal CT scan and bone scintigraphy. LTP, distant recurrence and extrahepatic recurrence were determined by the same three radiologists mentioned above.

RFA procedure

The details of our RFA procedure have been described previously [34]. Briefly, we routinely used a cool-tip needle (Radionics Corp., Burlington, MA, USA) while performing RFA. Using the intercostal or subcostal approach a 17-gauge, 2 or 3 cm long cooled-tip electrode was inserted under real-time ultrasound guidance. The duration of a single ablation session using RFA was 12 min for the 3-cm electrode and 6 min for the 2-cm electrode. All procedures were performed under ultrasound guidance by one of five operators who had at least 3 years of experience performing RFA. We used the artificial ascites technique to prevent collateral thermal injury when the anticipated RFA zone was in contact with a critical organ, such as the hepatic flexure of the colon. We also used this technique to improve visibility when the index tumor was located in the hepatic dome area.

Complete ablation of HCC was defined as hypoattenuation of the lesion, including the surrounding liver parenchyma. Therefore, we routinely performed additional RFA treatment until we had confirmed that the ablative margin surrounded the entire circumference of the tumor (R grade: Grade A or B), provided that patient consent had been obtained. The reasons for not attempting to perform additional RFA in patients with R grading scores of Grade C or D have been detailed elsewhere [34].

Comorbid diseases

The presence of hypertension, cardiovascular diseases, respiratory diseases, cerebrovascular diseases, diabetes mellitus and renal dysfunction, all of which with potential impact on the prognosis, were recorded.

Follow up

Follow-up after initial RFA consisted of periodic blood tests and monitoring of tumor markers, including alpha-fetoprotein (AFP) and des-γ-carboxy prothrombin (DCP), which was measured using a chemiluminescent enzyme immunoassay (Lumipulse PIVKAII Eisai, Eisai, Tokyo, Japan). Dynamic CT scans and/or magnetic resonance imaging (MRI) were obtained every 3-4 months after RFA.

Statistical analysis

Data were expressed as the mean ± standard deviation (SD). Differences between the two groups were analyzed using the unpaired *t* test for continuous variables, and categorical variables were analyzed using Fisher's exact test. Data were analyzed using univariate and multivariate analysis. Time to recurrence was defined as the interval between initial RFA and first confirmed recurrence. For analysis of OS, follow-up ended at the time of death from any cause, censoring the remaining patients at the last follow-up visit. For analysis of RFS and LTP, follow-up was terminated at the time of first recurrence; other patients were censored at their last follow-up visit and at the time of death from any cause without recurrence. The cumulative OS rate, RFS rate and LTP rate between the two groups were calculated using the Kaplan-Meier method, and tested using the log-rank test. The Cox proportional hazard model was used for multivariate analysis of factors that were considered significant by univariate analysis. These statistical methods were used to estimate the interval from initial RFA treatment. Values of $P<0.05$ were considered to be statistically significant.

Results

Clinical characteristics

The baseline clinical characteristics of the two groups are shown in Table I. The mean tumor diameter and the mean observation period between the elderly group and the control group were 2.13 ± 0.86 cm and 1.92 ± 0.63 cm, respectively, and 2.5 ± 1.8 years and 3.2 ± 2.0 years, respectively. There was a significantly higher proportion of female patients, a lower positivity rate for hepatitis B surface antigen, larger tumor size, a greater number of RFA sessions, a lower body mass index and lower levels of hepatobiliary enzymes such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma glutamyl transpeptidase (GGT) and total bilirubin in the elderly group.

Comorbid diseases

The prevalence of hypertension, cardiovascular disease, respiratory disease, cerebrovascular disease was significantly higher in the elderly group than in the control group. Serum creatinine levels were significantly higher in the elderly group than in the control group (Table I).

Treatment efficacy in the two groups

In the elderly group using the proposed R grading system, 18 (13.8%) patients were classified as Grade A, 50 (38.5%) as Grade B, 40 (30.8%) as Grade C and 22 (16.9%) as Grade D. In the control group, 52 (21.8%) patients were classified as Grade A, 112 (47.1%) as Grade B, 60 (25.2%) as Grade C and 14 (5.9%) as Grade D. In terms of treatment efficacy, there was a significant difference between the two groups (P=0.001) (Table I).

Overall survival rates in the two groups

The 1, 3 and 5 year OS rates after initial RFA therapy were 90.0%, 64.1% and 44.8%, respectively, in the elderly group and 97.6%, 83.7% and 64.0%, respectively, in the control group. In terms of OS, there was a significant difference between the two groups (P=0.001) (Fig. 1).

Recurrence free survival rates in the two groups

The 1, 3 and 5 year RFS rates after initial RFA were 66.9%, 21.3% and 19.0%, respectively, in the elderly group and 80.5%, 40.0% and 19.5%, respectively, in the control group. In terms of RFS, there was a significant difference between the two groups (P=0.001) (Fig. 2).

Local tumor progression rates in the two groups

The 1, 2 and 3 year LTP rates after initial RFA were 15.0%, 29.0% and 43.0%, respectively, in the elderly group and 8.3%, 15.5% and 26.3%, respectively, in the control group. In terms of LTP, there was a significant difference between the two groups (P=0.002) (Fig. 3).

Univariate and multivariate analyses of factors contributing to OS

In the univariate analysis, age >75 years, tumor size >2 cm, Child-Pugh classification, cause of liver disease, serum albumin >3.5 g/dL, total bilirubin >1.0 mg/dL, prothrombin time >70 %, platelet count $>10\times10^4/mm^3$, post-RFA antiviral therapy, serum creatinine >1 mg/dL, HCC recurrence within 1 year after RFA and R grade A or B were significant factors contributing to OS (Table II). In the multivariate analysis involving 12 factors that were found to be significant in the univariate analyses, age >75 years, prothrombin time >70 %, platelet count $>10\times10^4/mm^3$ and serum creatinine >1 mg/dL were significant factors contributing to OS. The hazard ratios (HRs) and 95% confidence interval (CI) for these factors are detailed in Table III.

Univariate and multivariate analyses of factors contributing to RFS

In the univariate analysis, age >75 years, Child-Pugh classification, cause of liver disease, AST >40 IU/L, GGT >80 IU/L, serum albumin >3.5 g/dL, total bilirubin >1 mg/dL, platelet count $>10\times10^4/mm^3$, presence of cardiovascular disease and R grade A or B were significant factors contributing to RFS (Table II).

Table I. Baseline characteristics between the elderly group and the control group

Variables	Elderly group (n=130)	Control group (n=238)	P value
Age (years)	78.6 ± 3.3	65.2 ± 7.5	<0.001[a]
Gender, male/female	67 / 63	150 / 88	0.036[b]
Tumor size (cm)	2.13 ± 0.86	1.92 ± 0.63	0.008[a]
Child-Pugh classification			
Chronic hepatitis / Child-Pugh A / B / C	27 / 87 / 16 / 0	53 / 145 / 36 / 4	0.358[b]
Causes of liver disease			
Hepatitis B/hepatitis C/non B non C	2 / 113 / 15	27 / 176 / 35	0.002[b]
Session number of RFA	1.32 ± 0.56	1.21 ± 0.43	0.025[a]
R grading			
Grade A/B/C/D	18 / 50 / 40 / 22	52 / 112 / 60 /14	0.001[b]
AST (IU/L)	52.2 ± 24.2	60.5 ± 32.8	0.012[a]
ALT (IU/L)	42.1 ± 24.3	54.1 ± 46.2	0.007[a]
ALP (IU/L)	317.1 ± 112.6	380.1 ± 233.9	0.004[a]
GGT (IU/L)	59.5 ± 44.1	80.7 ± 81.5	0.006[a]
Serum albumin (g/dL)	3.74 ± 0.47	3.82 ± 0.53	0.123[a]
Total bilirubin (mg/dL)	0.78 ± 0.36	1.04 ± 0.60	<0.001[a]
Prothrombin time (%)	86.5 ± 14.5	84.6 ± 16.2	0.280[a]
Platelets ($\times 10^4$/mm^3)	11.3 ± 4.4	10.8 ± 5.3	0.301[a]
AFP (ng/mL)	159.9 ± 572.7	145.3 ± 942.2	0.872[a]
DCP (mAU/mL)	587.8 ± 3668.2	227.0 ± 1216.9	0.167[a]
Duration of hospitalization (days)	13.7 ± 5.6	13.5 ± 6.6	0.807[a]
Body mass index (kg/m^2)	22.8 ± 3.4	23.8 ± 3.6	0.013[a]
Comorbid diseases			
Hypertension, yes/no	92 / 38	131 / 107	0.004[b]
Cardiovascular disease, yes/no	45 / 85	36 / 202	<0.001[b]
Respiratory disease, yes/no	33 / 97	33 / 205	0.007[b]
Cerebrovascular disease, yes/no	23 / 107	23 / 215	0.032[b]
Diabetes mellitus, yes/no	37 / 97	83 / 155	0.245[b]
Serum creatinine (mg/dL)	1.03 ± 0.82	0.84 ± 0.43	0.004[a]

Data are expressed as number or mean ± standard deviation. RFA; radiofrequency thermal ablation, R; radicality, AST; aspartate aminotransferase, ALT; alanine aminotransferase, ALP; alkaline phosphatase, GGT; gamma glutamyl transpeptidase, AFP; alpha-fetoprotein, DCP; des-γ-carboxy prothrombin, a; unpaired *t* test, b; Fisher's exact test

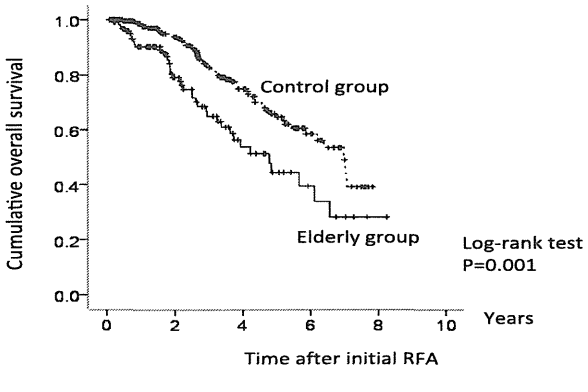

Fig 1. Cumulative overall survival (OS) rates in the elderly group (n=130) and the control group (n=238). The 1, 3 and 5 year OS rates after initial radiofrequency ablation (RFA) were 90.0%, 64.1% and 44.8%, respectively, in the elderly group and 97.6%, 83.7% and 64.0%, respectively, in the control group..

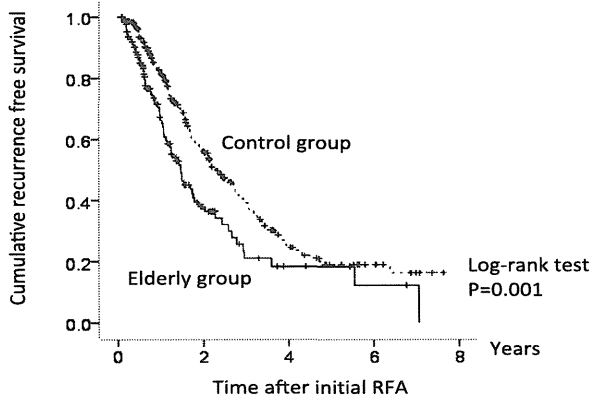

Fig 2. Cumulative recurrence free survival (RFS) rates in the elderly group (n=130) and the control group (n=238). The 1, 3 and 5 year RFS rates after initial radiofrequency ablation (RFA) were 66.9%, 21.3% and 19.0%, respectively, in the elderly group and 80.5%, 40.0% and 19.5%, respectively, in the control group.

Table II. Univariate analysis of factors contributing to overall survival and recurrence free survival after initial RFA

Variables	n	Overall survival P value[a]	Recurrence free survival P value[a]
Age (>75 years), yes/no	130 / 238	0.001	0.001
Gender (male), yes/no	217 / 151	0.786	0.884
Tumor size (>2 cm), yes/no	139 / 229	0.040	0.065
Child-Pugh classification			
Chronic hepatitis/C-P A/C-P B or C-P C	89 / 223 / 56	<0.001	0.049
Cause of liver disease			
Hepatitis B/hepatitis C/nonB nonC	29 / 289 / 50	0.010	0.032
AST (>40 IU/L), yes/no	256 / 112	0.103	0.013
ALT (>40 IU/L), yes/no	185 / 183	0.200	0.695
ALP (>340 IU/L), yes/no	146 / 222	0.863	0.124
GGT (>80 IU/L), yes/no	106 / 262	0.920	0.019
Serum albumin (>3.5 g/dL), yes/no	215 / 154	< 0.001	0.004
Total bilirubin (>1 mg/dL), yes/no	107 / 261	0.046	0.019
Prothrombin time (>70 %), yes/no	307 / 61	< 0.001	0.059
Platelets (>10×10^4/mm^3), yes/no	192 / 176	< 0.001	< 0.001
AFP (>100ng/mL), yes/no	64 / 304	0.720	0.635
DCP (>200mAU/mL), yes/no	46 / 322	0.127	0.296
Post-RFA antiviral therapy, yes/no	48 / 320	0.014	0.689
Body mass index (>25 kg/m^2), yes/no	111 / 257	0.616	0.604
Diabetes mellitus, yes/no	119 / 249	0.261	0.155
Hypertension, yes/no	223 / 145	0.924	0.249
Cardiovascular disease, yes/no	81 / 287	0.111	0.005
Respiratory disease, yes/no	66 / 302	0.760	0.519
Cerebrovascular disease, yes/no	46 / 322	0.741	0.307
Serum creatinine >1mg/dL, yes/no	90 / 278	0.004	0.239
HCC recurrence within 1 year after RFA, yes/no	76 / 292	< 0.001	
R grade, A or B/C or D	232 / 136	0.009	< 0.001

RFA, radiofrequency thermal ablation; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; GGT, gamma glutamyl transpeptidase; AFP, alpha-fetoprotein; DCP, des-γ-carboxy prothrombin; HCC, hepatocellular carcinoma; R, radicality; a, log-rank test

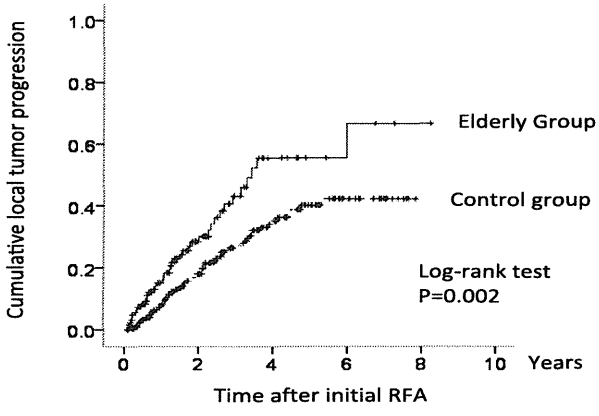

Fig 3. Cumulative local tumor progression (LTP) rates in the elderly group (n=130) and the control group (n=238). The 1, 2 and 3 year LTP rates after initial radiofrequency ablation (RFA) were 15.0%, 29.0% and 43.0%, respectively, in the elderly group and 8.3%, 15.5% and 26.3%, respectively, in the control group.

Table III. Significant factors for OS in the multivariate analysis

Variable	Hazard ratio	95% CI	P value[a]
Age (years)			
≥ 75 years	0.646	0.425-0.982	0.041
< 75 years	1.000		
Prothrombin time			
> 70%	2.196	1.045-4.614	0.038
≤ 70%	1.000		
Platelets count			
>10×10^4/mm^3	1.795	1.086-2.966	0.023
≤ 10×10^4/mm^3	1.000		
Serum creatinine			
≥ 1 mg/dL	0.530	0.338-0.831	0.006
< 1mg/dL	1.000		

95% CI, 95% confidence interval; a, Cox proportional hazard model

In the multivariate analysis involving the 10 factors that were significant in the univariate analysis, age >75 years, platelet count $>10\times10^4/mm^3$ and R grading A or B were significant factors contributing to RFS. The HRs and 95%CI for these factors are detailed in Table IV.

Table IV. Significant factors for recurrence free survival in the multivariate analysis

Variables	Hazard ratio	95% CI	P value[a]
Age (years)			
≥ 75 years	0.674	0.494-0.921	0.013
< 75 years	1.000		
Platelets count			
$> 10\times10^4/mm^3$	2.003	1.406-2.853	<0.001
$\leq 10\times10^4/mm^3$	1.000		
R grading			
Grade A or B	2.232	1.684-2.958	<0.001
Grade C or D	1.000		

R, radicality; 95% CI, 95% confidence interval; a, Cox proportional hazard model

HCC recurrence

In the present study, during the follow-up period, 71 (54.6%) patients in the elderly group and 143 (60.1%) patients in the control group had HCC recurrence. In the elderly group, LTP alone was found in five patients, LTP with distant recurrence in 35 patients and distant recurrence alone in the other 31 patients. In the control group, LTP alone was found in 7 patients, LTP with distant recurrence in 57 patients and distant recurrence alone in the other 79 patients.

The patterns of HCC recurrence after the initial RFA in the elderly group were as follows: single HCC recurrence in the liver (43 patients); multiple HCC recurrences in the liver (25 patients); multiple HCC recurrences in the liver with lung metastases (1 patient); and single lymph node metastasis (2 patients). In the control group, the patterns of HCC recurrence after the initial RFA were: single HCC recurrence in the liver (81 patients); multiple HCC recurrences in the liver (59 patients); single HCC recurrence with invasion of the inferior vena cava (1 patient); multiple HCC recurrences in the liver with lung metastases (1 patient) or peritoneal dissemination (1 patient) and single lymph node metastasis in 1 patient.

There were 36 (27.7%) patients who had HCC recurrence within 1 year after initial RFA in the elderly group and 40 (16.8%) patients in the control group. In no patient was neoplastic seeding identified. Treatment methods for the first recurrence in the elderly group were as follows: surgical resection in zero patients; RFA in 43 patients; TACE in 11 patients; PEI in 6; systemic chemotherapy in 2 patients and no specific treatment in 9 patients. In the control group, the treatment methods used were: surgical resection in 8 patients; RFA in 106 patients; TACE in 15 patients; PEI in 2 patients; systemic chemotherapy in 1 patient and no specific treatment in 11 patients.

Causes of death

Forty patients (30.8%) in the elderly group and 58 (24.4%) patients in the control group died during the follow-up period. The causes of death in the elderly group were as follows: HCC recurrence (12 patients); liver failure (15 patients); and miscellaneous (13 patients). In the control group the causes of death were: HCC recurrence (29 patients); liver failure (22 patients); and miscellaneous (seven patients). The miscellaneous causes of death in the elderly group were: myocardial infarction (2 patients); pneumonia (3); renal failure (1); lung cancer (1); cerebral hemorrhage (1); cerebral infarction in two patients and unknown causes (3) patients. The miscellaneous causes of death in the control group were: intestinal obstruction (1 patient); pneumonia (1); pulmonary hypertension (1); lung cancer (1); gastric cancer (1); rectal cancer (1); and unknown cause (1 patient).

Antiviral therapy after initial RFA

In the elderly group after initial RFA no patient received nucleotide analogue therapy for hepatitis B and only two patients received interferon (IFN) therapy for hepatitis C. In the control group after initial RFA, 23 patients received nucleotide analogue therapy for hepatitis B and 23 patients received IFN therapy for hepatitis C.

Duration of hospitalization and major adverse events related to the initial RFA

The mean duration of hospitalization was 13.7 ±5.6 days in the elderly group and 13.5 ±6.6 days in the control group. There was no significant difference between the two groups (P=0.807) (Table I). Major adverse events related to the initial RFA treatment as defined by current guidelines [35] were as follows: biloma (1 patient); refractory ascites (1 patient); and intra-abdominal bleeding (1) in the elderly group. In the control group major adverse events were: pneumothorax (1 patient); intra-abdominal bleeding (1); and liver abscess (1). There was no significant difference between the two groups (P=0.670). These serious adverse events improved during the same hospitalization. There was no needle tract seeding or deaths related to complications associated with RFA, and consequently the mortality rate was 0% in both groups.

Subgroup analyses in patients with radicality grade A and B

We performed subgroup analyses in patients with R grade A and B (n=232). There were 68 patients in the elderly group and 164 patients in the control group, respectively. In terms of OS, the difference between the two groups was significant (Fig. 4). In terms of RFS, lower RFS rate was observed in the elderly group, however, the difference did not reach significance (Fig. 5). In terms of LTP, there was no significant difference between the two groups (Fig. 6).

Discussion

In Japan, the proportion of elderly patients with HCC

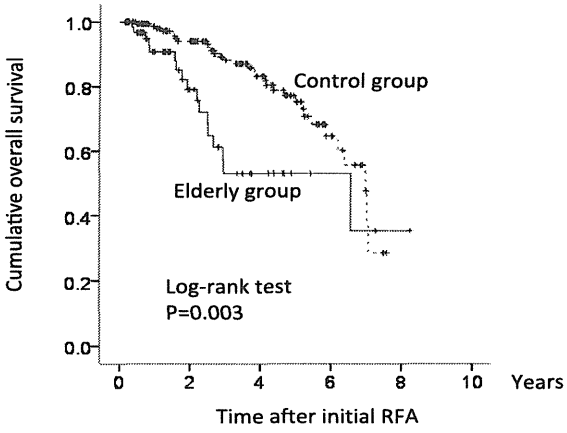

Fig 4. Subgroup analysis in patients with radicality (R) grade A and B (n=232) in terms of overall survival. The difference between the two groups was significant (P=0.003).

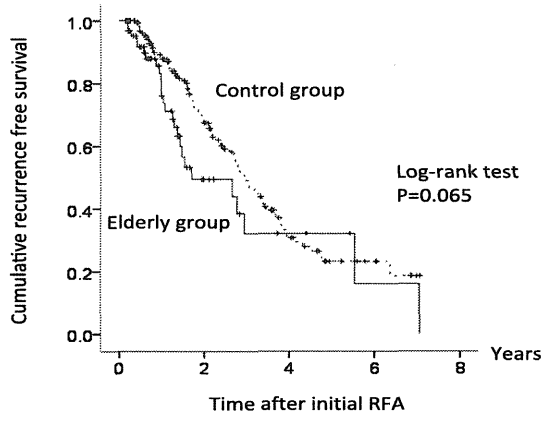

Fig 5. Subgroup analysis in patients with radicality (R) grade A and B (n=232) in terms of recurrence free survival (RFS). Although the elderly group had a lower RFS rate, the difference was not significant (P=0.065).

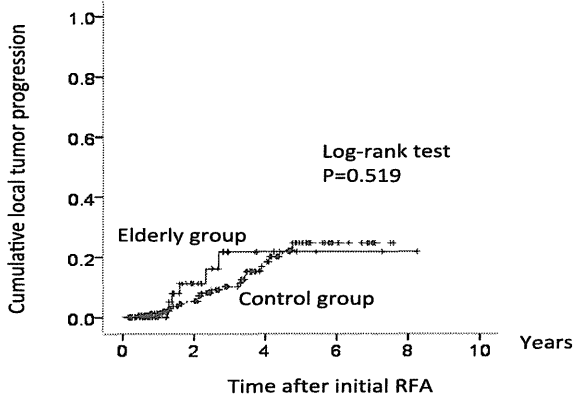

Fig 6. Subgroup analysis in patients with radicality (R) grade A and B (n=232) in terms of local tumor progression. There was no significant difference between the two groups (P=0.519).

and their average age is increasing [8]. These trends have led to a rising demand in our country for investigations related to the outcome of therapy in elderly HCC patients. Several comparative studies on clinical outcomes between elderly patients and younger patients treated with surgical resection, PEI or TACE have been reported. Most of these reports have demonstrated similar survival rates and safety in old and young patients [15-31]. However, to our knowledge, there have been few reports on the clinical outcome and safety of RFA treatment of elderly HCC patients; hence the reason for the current comparative study.

Takahashi et al reported that 3 year OS rate in elderly patients who underwent RFA was 82% and the corresponding RFS rate was 51%, while ours were 64.1% in OS and 21.3% in RFS [15]. Our results were poorer than those of their study, although the reasons for these were unclear.

In our study, in terms of OS, age >75 years was found to be a significant adverse prognostic factor using multivariate analysis. Moreover, in subgroup analysis in patients with R grade A and B, the difference was significant between the two groups in terms of OS. However, several other studies have reported that old age was not a significant factor associated with survival prognosis after RFA [15, 18]. One possible reason for this is that in the elderly patients that were analyzed in the current study there was a higher incidence of HCC recurrence than in the control group, as indicated in our analysis of RFS. Age is a well-known risk factor for HCC [36, 37]. Our results suggest that after the initial RFA therapy for HCC, old age is associated not only with hepatocarcinogenesis but also with recurrence. One of the other possible reasons is that the proportion of deaths from miscellaneous causes in the elderly group (13 out of 40 deaths; 32.5%) was higher than that in the control group (7 out of 58 deaths; 12.1%). In our study, comorbid diseases were more common in the elderly group. In order to optimize the clinical outcome of RFA, clinicians should be alert to the presence of comorbid diseases in elderly HCC patients. The other possible reason is that in 113 elderly patients with hepatitis C virus (HCV)-related HCC, only 2 (1.8%) patients had received IFN therapy after RFA, whereas in 176 patients with HCV-related HCC in the control group, 23 (13.1%) patients had received IFN therapy after RFA. IFN therapy cannot be tolerated in elderly patients owing to expected serious side effects, although it has been reported that IFN therapy after RFA can improve survival in HCV-related HCC patients treated with RFA [38, 39].

In relation to our proposed R grading system, the proportion of HCC patients with insufficient ablative margin (i.e. grade C or D) in the elderly patient group (62 out of 130 patients; 47.7%) was higher than that in the control patient group (74 out of 238 patients; 31.1%), leading to a higher LTP rate in the elderly patients [34]. In most of these patients, additional RFA therapy for obtaining a sufficient ablative margin was not performed for several reasons including the fear of potential toxicities, perceived minimal survival advantage, poor liver function, technical impossibility and physical burden. Our results seem to agree with previously reported findings regarding RFA therapy in elderly HCC patients.

In the multivariate analysis, R grade A and B was significant independent factor linked to RFS. Since poor

treatment efficacy may cause poor prognosis even in elderly patients, additional RFA therapy should be considered when it is safely feasible in elderly patients with insufficient ablative margin of RFA to optimize their clinical outcome.

In the present study, there were significantly more females than males in the elderly group. This may be related to the presence of a larger proportion of females than males in the elderly Japanese population owing to the longer life expectancy of women. Furthermore, there were significantly more hepatitis B virus (HBV)-associated HCC patients in the control group. Several investigators have reported that HBV-associated HCC was common in younger patients in Japan [40-42]. Our results are consistent with their reports.

A platelet count of $>10 \times 10^4/mm^3$ was found to be a significant favorable prognostic factor in terms of both OS and RFS. A lower platelet count reflects the progression of hepatic fibrosis, resulting in an increased risk of hepatocarcinogenesis [43]. In HCC patients treated with RFA, those with a lower platelet count should be closely monitored after RFA.

Serum creatinine level >1 mg/dL was a significant adverse factor linked to OS in the multivariate analysis. It was expected that the presence of comorbid diseases might be a poor prognostic factor. Several investigators have reported that renal insufficiency was associated with poor clinical outcomes for HCC patients [44, 45]. Our results were similar to those reported in these studies. We recommend that clinicians should notice the clinical course in HCC patients with poor renal function as well as those with low platelet count.

In the present study, there was no significant difference in terms of duration of hospitalization and serious complications related to RFA between the two groups. This was despite the fact that the number of RFA sessions in the elderly group was significantly higher than that of the control group. These results suggest that RFA is less invasive than other treatments and is safe in elderly HCC patients. Interestingly, when the first HCC recurrence after initial RFA treatment had developed, no patients in the elderly group had received surgical resection for HCC recurrence, whereas eight patients in the control group had undergone surgical resection. In general, the risks of surgical resection for HCC are higher in elderly patients than in younger patients [19-21, 24-30]. Our results in elderly HCC patients seem to support this finding.

There were several limitations to the current study. Firstly, this was a retrospective single center study. Secondly, the mean observation periods were too short to achieve optimal survival analysis. Thirdly, 27 patients lost in follow up were excluded from the current comparative study, leading to bias. Hence, a prospective comparative study with a longer observation period will be required. However, our results indicated that although RFA therapy in the elderly patients was considered to be a safe procedure, clinical outcomes in this group were poorer than those in the control group.

Conclusion

Since clinical outcomes in the elderly HCC patients treated with RFA are less favorable than those in younger patients, clinicians should observe the clinical course after RFA therapy, especially in elderly patients.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Acknowledgement

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Percutaneous Radiofrequency Ablation for Hepatocellular Carcinoma: Clinical Outcome and Safety in Elderly Patients

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Abstract

Background & Aims. We aimed to compare clinical outcomes and safety of radiofrequency ablation (RFA) in single hepatocellular carcinoma (HCC) patients aged >75 years (elderly group) versus patients aged <75 years (control group). **Patients and methods.**There were 130 patients in the elderly group and 238 in the control group. Clinical outcomes including overall survival (OS), recurrence free survival (RFS) and local tumor progression (LTP), and safety were analysed for these two groups after initial RFA. **Results.** The mean (± standard deviation [SD]) tumor diameter in the elderly and the control groups was 2.13 ± 0.86 cm and 1.92 ± 0.63 cm, respectively; the mean (± SD) observation period was 2.5 ± 1.8 years and 3.2 ± 2.0 years, respectively. The 1 and 3 year OS rates were 90.0 and 64.1%, respectively, in the elderly group and 97.6 and 83.7%, respectively, in the control group (P=0.001); the corresponding RFS rates were 66.9 and 21.3%, respectively, in the elderly group and 80.5 and 40.0%, respectively, in the control group (P=0.001). The 1 and 3 year LTP rates were 15.0 and 43.0%, respectively, in the elderly group and 8.3 and 26.3%, respectively, in the control group (P=0.002). In terms of duration of hospitalization (P=0.807) and serious adverse events related RFA (P=0.670), there was no significant difference between these two groups. **Conclusion.** The clinical outcomes in the elderly group were poorer than those in the control group, although RFA in the elderly patients was a safe procedure.

Key words

Hepatocellular carcinoma – radiofrequency ablation – elderly patients – clinical outcome – safety.

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Introduction

Hepatocellular carcinoma (HCC) ranks fifth among the most prevalent cancers in the world, and is the third most common cause of cancer related death [1-4]. The incidence of cancer has been reported to increase markedly with age, with >60% of all cancers developing in patients aged >65 years [5]. In fact, the risk of developing HCC is known to be age dependent [6]. Thus, there will be an increasing number of elderly HCC patients in the coming years owing to the increased longevity of the population. In Japan, the adjusted HCC mortality rate has increased in recent years [7]. Moreover, the average age of HCC patients in Japan is increasing and the proportion of elderly HCC patients is therefore rising [8].

Radiofrequency ablation (RFA) therapy, an alternative technique to percutaneous ethanol injection (PEI) that was introduced in Japan in 1999, has been widely used as a curative treatment for HCC and has evolved into an important therapeutic tool for the treatment of HCC [1-3, 9-12]. An area of <3 cm in diameter can be ablated with a single application of RFA. This technique has proven to be a safe and effective modality for the treatment of small HCC in patients who are considered unsuitable for surgical intervention because of insufficient hepatic reserve [1-3]. More recently, several investigators have used RFA to treat selected patients with resectable HCC with favorable clinical outcomes, and RFA is gradually gaining popularity in the treatment of resectable HCC in many countries, in addition to Japan [13].

In general, elderly patients have a high incidence of comorbid diseases and are considered high-risk patients for surgical resection. Thus, radical surgical resection of HCC is less feasible in elderly patients than in younger patients, and RFA therapy may be an acceptable alternative [14]. However, to our knowledge, there have been few reports on clinical outcomes and safety in elderly HCC patients treated with RFA, although there have been several reports regarding patients treated with other therapies such as surgical resection, PEI and transcatheter arterial chemoembolization (TACE) [15-31]. The aim of the present study was to evaluate

clinical outcomes and safety after RFA treatment in HCC patients aged >75 years as compared with HCC patients aged <75 years.

Patients and methods

Patients

We performed RFA therapy in 395 treatment-naïve patients diagnosed with solitary HCC in the Department of Gastroenterology and Hepatology, Osaka Red Cross Hospital, Japan between January 2004 and January 2012. Of these patients, 27 were lost in follow-up and were excluded from the present study. Thus, the current study consisted of a total of 368 patients with single HCC. Our criteria of RFA therapy are as follows: (a) ineligible for surgical resection or liver transplantation; (b) patient refusal for surgery; (c) tumor size up to about 3cm and tumor number up to 3 nodules; (d) absence of uncontrollable ascites; (e) no extrahepatic metastases or vascular invasion.We categorized patients into two groups, namely the elderly group (≥75 years old) and the control group (<75 years old).The breakpoint of 75 years of age was chosen because it enabled comparison with other relevant previous reports. Moreover, in our country, patients aged ≥75 years are covered by a health insurance system which is different from that for patients aged <75 years. We compared the clinical outcomes including overall survival (OS), recurrence free survival (RFS) and local tumor progression (LTP) and safety between these two groups after initial RFA. Prior to RFA, written informed consent was obtained from all patients. The current study comprised a retrospective analysis of patient records and all treatments were conducted in an open-label manner. The Ethics Committee of our department approved the current study protocol and this study protocol complied with all of the provisions of the Declaration of Helsinki.

HCC diagnosis

Hypervascular HCC was diagnosed using abdominal ultrasound and dynamic computed tomography (CT) scans (hyperattenuation during the arterial phase in all or some part of the tumor and hypoattenuation in the portal-venous phase). Arterial and portal phase dynamic CT images were obtained at approximately 30 s and 120 s, respectively, after the injection of contrast material. In all cases of hypovascular HCC, percutaneous tumor biopsy was performed according to the diagnostic criteria for HCC proposed by the Japan Society of Hepatology [32]. There were 336 hypervascular HCCs and 32 hypovascular HCCs in the current study. For all patients, abdominal angiography was performed before RFA. We confirmed solitary HCC with no vascular invasion and no satellite nodules using CT during hepatic arteriography (CTHA) and arterial-portography (CTAP) [33].

Assessment of treatment efficacy

To assess treatment efficacy, we performed dynamic 16-column multi-detector CT (MDCT) using 3-mm slice scans within 1 week after RFA. The patients were then classified into four groups as follows: Grade A (absolutely curative), a ≥5 mm ablative margin around the entire tumor; Grade B (relatively curative), an ablative margin around the tumor but <5 mm in diameter in some places; Grade C (relatively non-curative), only an incomplete ablative margin around the tumor although no residual tumor was apparent; Grade D (absolutely non-curative), the tumor was not completely ablated. We referred to this classification system as Radicality Grading (R grades: A, B, C and D) [34]. Decisions with regard to R grading were made by three radiologists experienced in liver imaging modalities.

In our department, during abdominal angiography, we routinely perform arterial infusion of iodized oil (Lipiodol Ultra-Fluid, Schering Japan, Osaka, Japan). Lipiodol was injected to intensify the radiologic visibility of the target tumor [34]. In patients where the tumor location could be determined because of the dense accumulation of lipiodol, we assessed treatment efficacy using dynamic CT scans. However, in patients where it was difficult to determine the exact location of the tumor because of insufficient lipiodol accumulation (e.g. hypovascular HCC), and for those where lipiodol had only accumulated in part of the tumor (e.g. nodule-in-nodule HCC), we measured the ablative margin using CTHA with a CTAP image as the reference image.

Definition of HCC recurrence

We defined LTP as the presence of a recurrent nodule adjacent to the ablated area after RFA using dynamic CT scanning. Recurrence that occurred distantly from the ablated area in the same segment was included as distant recurrence. Extrahepatic recurrence was determined using chest CT scan, whole abdominal CT scan and bone scintigraphy. LTP, distant recurrence and extrahepatic recurrence were determined by the same three radiologists mentioned above.

RFA procedure

The details of our RFA procedure have been described previously [34]. Briefly, we routinely used a cool-tip needle (Radionics Corp., Burlington, MA, USA) while performing RFA. Using the intercostal or subcostal approach a 17-gauge, 2 or 3 cm long cooled-tip electrode was inserted under real-time ultrasound guidance. The duration of a single ablation session using RFA was 12 min for the 3-cm electrode and 6 min for the 2-cm electrode. All procedures were performed under ultrasound guidance by one of five operators who had at least 3 years of experience performing RFA. We used the artificial ascites technique to prevent collateral thermal injury when the anticipated RFA zone was in contact with a critical organ, such as the hepatic flexure of the colon. We also used this technique to improve visibility when the index tumor was located in the hepatic dome area.

Complete ablation of HCC was defined as hypoattenuation of the lesion, including the surrounding liver parenchyma. Therefore, we routinely performed additional RFA treatment until we had confirmed that the ablative margin surrounded the entire circumference of the tumor (R grade: Grade A or B), provided that patient consent had been obtained. The reasons for not attempting to perform additional RFA in patients with R grading scores of Grade C or D have been detailed elsewhere [34].

Comorbid diseases

The presence of hypertension, cardiovascular diseases, respiratory diseases, cerebrovascular diseases, diabetes mellitus and renal dysfunction, all of which with potential impact on the prognosis, were recorded.

Follow up

Follow-up after initial RFA consisted of periodic blood tests and monitoring of tumor markers, including alpha-fetoprotein (AFP) and des-γ-carboxy prothrombin (DCP), which was measured using a chemiluminescent enzyme immunoassay (Lumipulse PIVKAII Eisai, Eisai, Tokyo, Japan). Dynamic CT scans and/or magnetic resonance imaging (MRI) were obtained every 3-4 months after RFA.

Statistical analysis

Data were expressed as the mean ± standard deviation (SD). Differences between the two groups were analyzed using the unpaired *t* test for continuous variables, and categorical variables were analyzed using Fisher's exact test. Data were analyzed using univariate and multivariate analysis. Time to recurrence was defined as the interval between initial RFA and first confirmed recurrence. For analysis of OS, follow-up ended at the time of death from any cause, censoring the remaining patients at the last follow-up visit. For analysis of RFS and LTP, follow-up was terminated at the time of first recurrence; other patients were censored at their last follow-up visit and at the time of death from any cause without recurrence. The cumulative OS rate, RFS rate and LTP rate between the two groups were calculated using the Kaplan-Meier method, and tested using the log-rank test. The Cox proportional hazard model was used for multivariate analysis of factors that were considered significant by univariate analysis. These statistical methods were used to estimate the interval from initial RFA treatment. Values of $P<0.05$ were considered to be statistically significant.

Results

Clinical characteristics

The baseline clinical characteristics of the two groups are shown in Table I. The mean tumor diameter and the mean observation period between the elderly group and the control group were 2.13 ± 0.86 cm and 1.92 ± 0.63 cm, respectively, and 2.5 ± 1.8 years and 3.2 ± 2.0 years, respectively. There was a significantly higher proportion of female patients, a lower positivity rate for hepatitis B surface antigen, larger tumor size, a greater number of RFA sessions, a lower body mass index and lower levels of hepatobiliary enzymes such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma glutamyl transpeptidase (GGT) and total bilirubin in the elderly group.

Comorbid diseases

The prevalence of hypertension, cardiovascular disease, respiratory disease, cerebrovascular disease was significantly higher in the elderly group than in the control group. Serum creatinine levels were significantly higher in the elderly group than in the control group (Table I).

Treatment efficacy in the two groups

In the elderly group using the proposed R grading system, 18 (13.8%) patients were classified as Grade A, 50 (38.5%) as Grade B, 40 (30.8%) as Grade C and 22 (16.9%) as Grade D. In the control group, 52 (21.8%) patients were classified as Grade A, 112 (47.1%) as Grade B, 60 (25.2%) as Grade C and 14 (5.9%) as Grade D. In terms of treatment efficacy, there was a significant difference between the two groups (P=0.001) (Table I).

Overall survival rates in the two groups

The 1, 3 and 5 year OS rates after initial RFA therapy were 90.0%, 64.1% and 44.8%, respectively, in the elderly group and 97.6%, 83.7% and 64.0%, respectively, in the control group. In terms of OS, there was a significant difference between the two groups (P=0.001) (Fig. 1).

Recurrence free survival rates in the two groups

The 1, 3 and 5 year RFS rates after initial RFA were 66.9%, 21.3% and 19.0%, respectively, in the elderly group and 80.5%, 40.0% and 19.5%, respectively, in the control group. In terms of RFS, there was a significant difference between the two groups (P=0.001) (Fig. 2).

Local tumor progression rates in the two groups

The 1, 2 and 3 year LTP rates after initial RFA were 15.0%, 29.0% and 43.0%, respectively, in the elderly group and 8.3%, 15.5% and 26.3%, respectively, in the control group. In terms of LTP, there was a significant difference between the two groups (P=0.002) (Fig. 3).

Univariate and multivariate analyses of factors contributing to OS

In the univariate analysis, age >75 years, tumor size >2 cm, Child-Pugh classification, cause of liver disease, serum albumin >3.5 g/dL, total bilirubin >1.0 mg/dL, prothrombin time >70 %, platelet count $>10\times10^4/mm^3$, post-RFA antiviral therapy, serum creatinine >1 mg/dL, HCC recurrence within 1 year after RFA and R grade A or B were significant factors contributing to OS (Table II). In the multivariate analysis involving 12 factors that were found to be significant in the univariate analyses, age >75 years, prothrombin time >70 %, platelet count $>10\times10^4/mm^3$ and serum creatinine >1 mg/dL were significant factors contributing to OS. The hazard ratios (HRs) and 95% confidence interval (CI) for these factors are detailed in Table III.

Univariate and multivariate analyses of factors contributing to RFS

In the univariate analysis, age >75 years, Child-Pugh classification, cause of liver disease, AST >40 IU/L, GGT >80 IU/L, serum albumin >3.5 g/dL, total bilirubin >1 mg/dL, platelet count $>10\times10^4/mm^3$, presence of cardiovascular disease and R grade A or B were significant factors contributing to RFS (Table II).

Table I. Baseline characteristics between the elderly group and the control group

Variables	Elderly group (n=130)	Control group (n=238)	P value
Age (years)	78.6 ± 3.3	65.2 ± 7.5	<0.001[a]
Gender, male/female	67 / 63	150 / 88	0.036[b]
Tumor size (cm)	2.13 ± 0.86	1.92 ± 0.63	0.008[a]
Child-Pugh classification			
Chronic hepatitis / Child-Pugh A / B / C	27 / 87 / 16 / 0	53 / 145 / 36 / 4	0.358[b]
Causes of liver disease			
Hepatitis B/hepatitis C/non B non C	2 / 113 / 15	27 / 176 / 35	0.002[b]
Session number of RFA	1.32 ± 0.56	1.21 ± 0.43	0.025[a]
R grading			
Grade A/B/C/D	18 / 50 / 40 / 22	52 / 112 / 60 /14	0.001[b]
AST (IU/L)	52.2 ± 24.2	60.5 ± 32.8	0.012[a]
ALT (IU/L)	42.1 ± 24.3	54.1 ± 46.2	0.007[a]
ALP (IU/L)	317.1 ± 112.6	380.1 ± 233.9	0.004[a]
GGT (IU/L)	59.5 ± 44.1	80.7 ± 81.5	0.006[a]
Serum albumin (g/dL)	3.74 ± 0.47	3.82 ± 0.53	0.123[a]
Total bilirubin (mg/dL)	0.78 ± 0.36	1.04 ± 0.60	<0.001[a]
Prothrombin time (%)	86.5 ± 14.5	84.6 ± 16.2	0.280[a]
Platelets ($\times 10^4/mm^3$)	11.3 ± 4.4	10.8 ± 5.3	0.301[a]
AFP (ng/mL)	159.9 ± 572.7	145.3 ± 942.2	0.872[a]
DCP (mAU/mL)	587.8 ± 3668.2	227.0 ± 1216.9	0.167[a]
Duration of hospitalization (days)	13.7 ± 5.6	13.5 ± 6.6	0.807[a]
Body mass index (kg/m^2)	22.8 ± 3.4	23.8 ± 3.6	0.013[a]
Comorbid diseases			
Hypertension, yes/no	92 / 38	131 / 107	0.004[b]
Cardiovascular disease, yes/no	45 / 85	36 / 202	<0.001[b]
Respiratory disease, yes/no	33 / 97	33 / 205	0.007[b]
Cerebrovascular disease, yes/no	23 / 107	23 / 215	0.032[b]
Diabetes mellitus, yes/no	37 / 97	83 / 155	0.245[b]
Serum creatinine (mg/dL)	1.03 ± 0.82	0.84 ± 0.43	0.004[a]

Data are expressed as number or mean ± standard deviation. RFA; radiofrequency thermal ablation, R; radicality, AST; aspartate aminotransferase, ALT; alanine aminotransferase, ALP; alkaline phosphatase, GGT; gamma glutamyl transpeptidase, AFP; alpha-fetoprotein, DCP; des-γ-carboxy prothrombin, a; unpaired *t* test, b; Fisher's exact test

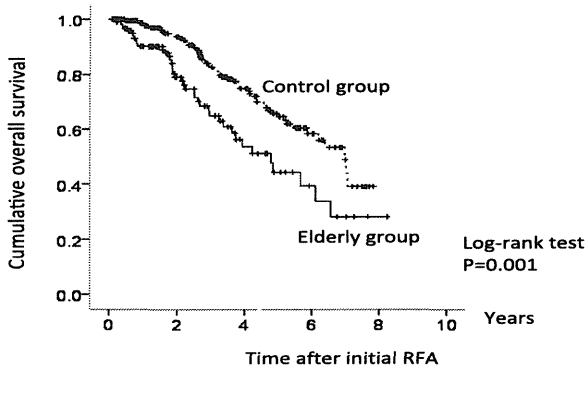

Fig 1. Cumulative overall survival (OS) rates in the elderly group (n=130) and the control group (n=238). The 1, 3 and 5 year OS rates after initial radiofrequency ablation (RFA) were 90.0%, 64.1% and 44.8%, respectively, in the elderly group and 97.6%, 83.7% and 64.0%, respectively, in the control group..

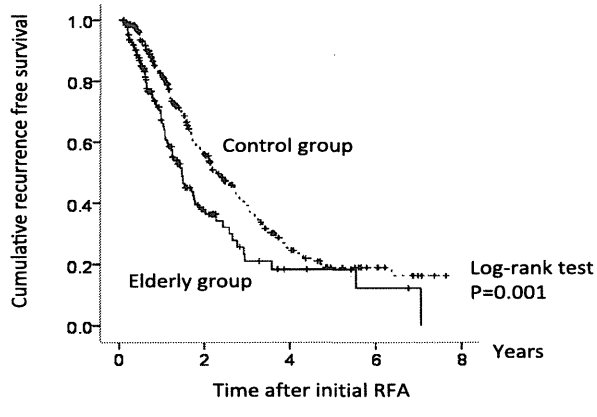

Fig 2. Cumulative recurrence free survival (RFS) rates in the elderly group (n=130) and the control group (n=238). The 1, 3 and 5 year RFS rates after initial radiofrequency ablation (RFA) were 66.9%, 21.3% and 19.0%, respectively, in the elderly group and 80.5%, 40.0% and 19.5%, respectively, in the control group.

Table II. Univariate analysis of factors contributing to overall survival and recurrence free survival after initial RFA

Variables	n	Overall survival P value[a]	Recurrence free survival P value[a]
Age (>75 years), yes/no	130 / 238	0.001	0.001
Gender (male), yes/no	217 / 151	0.786	0.884
Tumor size (>2 cm), yes/no	139 / 229	0.040	0.065
Child-Pugh classification			
Chronic hepatitis/C-P A/C-P B or C-P C	89 / 223 / 56	<0.001	0.049
Cause of liver disease			
Hepatitis B/hepatitis C/nonB nonC	29 / 289 / 50	0.010	0.032
AST (>40 IU/L), yes/no	256 / 112	0.103	0.013
ALT (>40 IU/L), yes/no	185 / 183	0.200	0.695
ALP (>340 IU/L), yes/no	146 / 222	0.863	0.124
GGT (>80 IU/L), yes/no	106 / 262	0.920	0.019
Serum albumin (>3.5 g/dL), yes/no	215 / 154	< 0.001	0.004
Total bilirubin (>1 mg/dL), yes/no	107 / 261	0.046	0.019
Prothrombin time (>70 %), yes/no	307 / 61	< 0.001	0.059
Platelets (>10×10^4/mm^3), yes/no	192 / 176	< 0.001	< 0.001
AFP (>100ng/mL), yes/no	64 / 304	0.720	0.635
DCP (>200mAU/mL), yes/no	46 / 322	0.127	0.296
Post-RFA antiviral therapy, yes/no	48 / 320	0.014	0.689
Body mass index (>25 kg/m^2), yes/no	111 / 257	0.616	0.604
Diabetes mellitus, yes/no	119 / 249	0.261	0.155
Hypertension, yes/no	223 / 145	0.924	0.249
Cardiovascular disease, yes/no	81 / 287	0.111	0.005
Respiratory disease, yes/no	66 / 302	0.760	0.519
Cerebrovascular disease, yes/no	46 / 322	0.741	0.307
Serum creatinine >1mg/dL, yes/no	90 / 278	0.004	0.239
HCC recurrence within 1 year after RFA, yes/no	76 / 292	< 0.001	
R grade, A or B/C or D	232 / 136	0.009	< 0.001

RFA, radiofrequency thermal ablation; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; GGT, gamma glutamyl transpeptidase; AFP, alpha-fetoprotein; DCP, des-γ-carboxy prothrombin; HCC, hepatocellular carcinoma; R, radicality; a, log-rank test

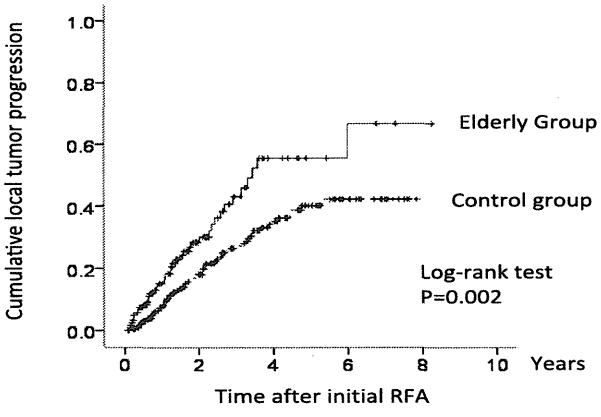

Fig 3. Cumulative local tumor progression (LTP) rates in the elderly group (n=130) and the control group (n=238). The 1, 2 and 3 year LTP rates after initial radiofrequency ablation (RFA) were 15.0%, 29.0% and 43.0%, respectively, in the elderly group and 8.3%, 15.5% and 26.3%, respectively, in the control group.

Table III. Significant factors for OS in the multivariate analysis

Variable	Hazard ratio	95% CI	P value[a]
Age (years)			
≥ 75 years	0.646	0.425-0.982	0.041
< 75 years	1.000		
Prothrombin time			
> 70%	2.196	1.045-4.614	0.038
≤ 70%	1.000		
Platelets count			
>10×10^4/mm^3	1.795	1.086-2.966	0.023
≤ 10×10^4/mm^3	1.000		
Serum creatinine			
≥ 1 mg/dL	0.530	0.338-0.831	0.006
< 1mg/dL	1.000		

95% CI, 95% confidence interval; a, Cox proportional hazard model

In the multivariate analysis involving the 10 factors that were significant in the univariate analysis, age >75 years, platelet count $>10\times10^4/mm^3$ and R grading A or B were significant factors contributing to RFS. The HRs and 95%CI for these factors are detailed in Table IV.

Table IV. Significant factors for recurrence free survival in the multivariate analysis

Variables	Hazard ratio	95% CI	P value[a]
Age (years)			
≥ 75 years	0.674	0.494-0.921	0.013
< 75 years	1.000		
Platelets count			
$> 10\times10^4/mm^3$	2.003	1.406-2.853	<0.001
$\leq 10\times10^4/mm^3$	1.000		
R grading			
Grade A or B	2.232	1.684-2.958	<0.001
Grade C or D	1.000		

R, radicality; 95% CI, 95% confidence interval; a, Cox proportional hazard model

HCC recurrence

In the present study, during the follow-up period, 71 (54.6%) patients in the elderly group and 143 (60.1%) patients in the control group had HCC recurrence. In the elderly group, LTP alone was found in five patients, LTP with distant recurrence in 35 patients and distant recurrence alone in the other 31 patients. In the control group, LTP alone was found in 7 patients, LTP with distant recurrence in 57 patients and distant recurrence alone in the other 79 patients.

The patterns of HCC recurrence after the initial RFA in the elderly group were as follows: single HCC recurrence in the liver (43 patients); multiple HCC recurrences in the liver (25 patients); multiple HCC recurrences in the liver with lung metastases (1 patient); and single lymph node metastasis (2 patients). In the control group, the patterns of HCC recurrence after the initial RFA were: single HCC recurrence in the liver (81 patients); multiple HCC recurrences in the liver (59 patients); single HCC recurrence with invasion of the inferior vena cava (1 patient); multiple HCC recurrences in the liver with lung metastases (1 patient) or peritoneal dissemination (1 patient) and single lymph node metastasis in 1 patient.

There were 36 (27.7%) patients who had HCC recurrence within 1 year after initial RFA in the elderly group and 40 (16.8%) patients in the control group. In no patient was neoplastic seeding identified. Treatment methods for the first recurrence in the elderly group were as follows: surgical resection in zero patients; RFA in 43 patients; TACE in 11 patients; PEI in 6; systemic chemotherapy in 2 patients and no specific treatment in 9 patients. In the control group, the treatment methods used were: surgical resection in 8 patients; RFA in 106 patients; TACE in 15 patients; PEI in 2 patients; systemic chemotherapy in 1 patient and no specific treatment in 11 patients.

Causes of death

Forty patients (30.8%) in the elderly group and 58 (24.4%) patients in the control group died during the follow-up period. The causes of death in the elderly group were as follows: HCC recurrence (12 patients); liver failure (15 patients); and miscellaneous (13 patients). In the control group the causes of death were: HCC recurrence (29 patients); liver failure (22 patients); and miscellaneous (seven patients). The miscellaneous causes of death in the elderly group were: myocardial infarction (2 patients); pneumonia (3); renal failure (1); lung cancer (1); cerebral hemorrhage (1); cerebral infarction in two patients and unknown causes (3) patients. The miscellaneous causes of death in the control group were: intestinal obstruction (1 patient); pneumonia (1); pulmonary hypertension (1); lung cancer (1); gastric cancer (1); rectal cancer (1); and unknown cause (1 patient).

Antiviral therapy after initial RFA

In the elderly group after initial RFA no patient received nucleotide analogue therapy for hepatitis B and only two patients received interferon (IFN) therapy for hepatitis C. In the control group after initial RFA, 23 patients received nucleotide analogue therapy for hepatitis B and 23 patients received IFN therapy for hepatitis C.

Duration of hospitalization and major adverse events related to the initial RFA

The mean duration of hospitalization was 13.7 ±5.6 days in the elderly group and 13.5 ±6.6 days in the control group. There was no significant difference between the two groups (P=0.807) (Table I). Major adverse events related to the initial RFA treatment as defined by current guidelines [35] were as follows: biloma (1 patient); refractory ascites (1 patient); and intra-abdominal bleeding (1) in the elderly group. In the control group major adverse events were: pneumothorax (1 patient); intra-abdominal bleeding (1); and liver abscess (1). There was no significant difference between the two groups (P=0.670). These serious adverse events improved during the same hospitalization. There was no needle tract seeding or deaths related to complications associated with RFA, and consequently the mortality rate was 0% in both groups.

Subgroup analyses in patients with radicality grade A and B

We performed subgroup analyses in patients with R grade A and B (n=232). There were 68 patients in the elderly group and 164 patients in the control group, respectively. In terms of OS, the difference between the two groups was significant (Fig. 4). In terms of RFS, lower RFS rate was observed in the elderly group, however, the difference did not reach significance (Fig. 5). In terms of LTP, there was no significant difference between the two groups (Fig. 6).

Discussion

In Japan, the proportion of elderly patients with HCC

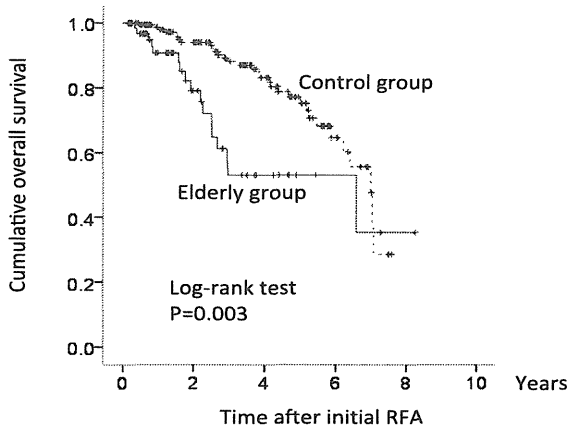

Fig 4. Subgroup analysis in patients with radicality (R) grade A and B (n=232) in terms of overall survival. The difference between the two groups was significant (P=0.003).

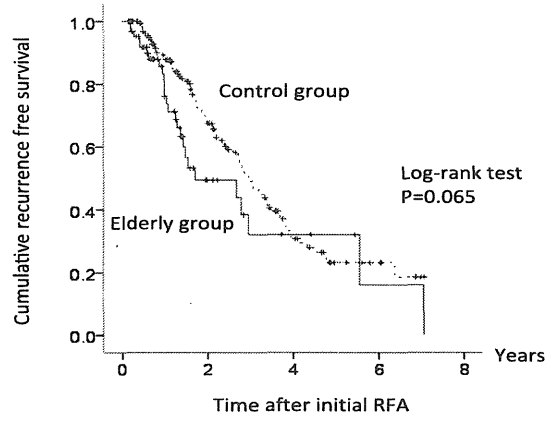

Fig 5. Subgroup analysis in patients with radicality (R) grade A and B (n=232) in terms of recurrence free survival (RFS). Although the elderly group had a lower RFS rate, the difference was not significant (P=0.065).

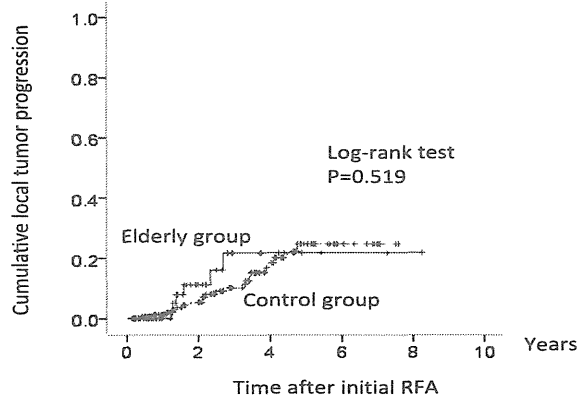

Fig 6. Subgroup analysis in patients with radicality (R) grade A and B (n=232) in terms of local tumor progression. There was no significant difference between the two groups (P=0.519).

and their average age is increasing [8]. These trends have led to a rising demand in our country for investigations related to the outcome of therapy in elderly HCC patients. Several comparative studies on clinical outcomes between elderly patients and younger patients treated with surgical resection, PEI or TACE have been reported. Most of these reports have demonstrated similar survival rates and safety in old and young patients [15-31]. However, to our knowledge, there have been few reports on the clinical outcome and safety of RFA treatment of elderly HCC patients; hence the reason for the current comparative study.

Takahashi et al reported that 3 year OS rate in elderly patients who underwent RFA was 82% and the corresponding RFS rate was 51%, while ours were 64.1% in OS and 21.3% in RFS [15]. Our results were poorer than those of their study, although the reasons for these were unclear.

In our study, in terms of OS, age >75 years was found to be a significant adverse prognostic factor using multivariate analysis. Moreover, in subgroup analysis in patients with R grade A and B, the difference was significant between the two groups in terms of OS. However, several other studies have reported that old age was not a significant factor associated with survival prognosis after RFA [15, 18]. One possible reason for this is that in the elderly patients that were analyzed in the current study there was a higher incidence of HCC recurrence than in the control group, as indicated in our analysis of RFS. Age is a well-known risk factor for HCC [36, 37]. Our results suggest that after the initial RFA therapy for HCC, old age is associated not only with hepatocarcinogenesis but also with recurrence. One of the other possible reasons is that the proportion of deaths from miscellaneous causes in the elderly group (13 out of 40 deaths; 32.5%) was higher than that in the control group (7 out of 58 deaths; 12.1%). In our study, comorbid diseases were more common in the elderly group. In order to optimize the clinical outcome of RFA, clinicians should be alert to the presence of comorbid diseases in elderly HCC patients. The other possible reason is that in 113 elderly patients with hepatitis C virus (HCV)-related HCC, only 2 (1.8%) patients had received IFN therapy after RFA, whereas in 176 patients with HCV-related HCC in the control group, 23 (13.1%) patients had received IFN therapy after RFA. IFN therapy cannot be tolerated in elderly patients owing to expected serious side effects, although it has been reported that IFN therapy after RFA can improve survival in HCV-related HCC patients treated with RFA [38, 39].

In relation to our proposed R grading system, the proportion of HCC patients with insufficient ablative margin (i.e. grade C or D) in the elderly patient group (62 out of 130 patients; 47.7%) was higher than that in the control patient group (74 out of 238 patients; 31.1%), leading to a higher LTP rate in the elderly patients [34]. In most of these patients, additional RFA therapy for obtaining a sufficient ablative margin was not performed for several reasons including the fear of potential toxicities, perceived minimal survival advantage, poor liver function, technical impossibility and physical burden. Our results seem to agree with previously reported findings regarding RFA therapy in elderly HCC patients.

In the multivariate analysis, R grade A and B was significant independent factor linked to RFS. Since poor

treatment efficacy may cause poor prognosis even in elderly patients, additional RFA therapy should be considered when it is safely feasible in elderly patients with insufficient ablative margin of RFA to optimize their clinical outcome.

In the present study, there were significantly more females than males in the elderly group. This may be related to the presence of a larger proportion of females than males in the elderly Japanese population owing to the longer life expectancy of women. Furthermore, there were significantly more hepatitis B virus (HBV)-associated HCC patients in the control group. Several investigators have reported that HBV-associated HCC was common in younger patients in Japan [40-42]. Our results are consistent with their reports.

A platelet count of $>10 \times 10^4/mm^3$ was found to be a significant favorable prognostic factor in terms of both OS and RFS. A lower platelet count reflects the progression of hepatic fibrosis, resulting in an increased risk of hepatocarcinogenesis [43]. In HCC patients treated with RFA, those with a lower platelet count should be closely monitored after RFA.

Serum creatinine level >1 mg/dL was a significant adverse factor linked to OS in the multivariate analysis. It was expected that the presence of comorbid diseases might be a poor prognostic factor. Several investigators have reported that renal insufficiency was associated with poor clinical outcomes for HCC patients [44, 45]. Our results were similar to those reported in these studies. We recommend that clinicians should notice the clinical course in HCC patients with poor renal function as well as those with low platelet count.

In the present study, there was no significant difference in terms of duration of hospitalization and serious complications related to RFA between the two groups. This was despite the fact that the number of RFA sessions in the elderly group was significantly higher than that of the control group. These results suggest that RFA is less invasive than other treatments and is safe in elderly HCC patients. Interestingly, when the first HCC recurrence after initial RFA treatment had developed, no patients in the elderly group had received surgical resection for HCC recurrence, whereas eight patients in the control group had undergone surgical resection. In general, the risks of surgical resection for HCC are higher in elderly patients than in younger patients [19-21, 24-30]. Our results in elderly HCC patients seem to support this finding.

There were several limitations to the current study. Firstly, this was a retrospective single center study. Secondly, the mean observation periods were too short to achieve optimal survival analysis. Thirdly, 27 patients lost in follow up were excluded from the current comparative study, leading to bias. Hence, a prospective comparative study with a longer observation period will be required. However, our results indicated that although RFA therapy in the elderly patients was considered to be a safe procedure, clinical outcomes in this group were poorer than those in the control group.

Conclusion

Since clinical outcomes in the elderly HCC patients treated with RFA are less favorable than those in younger patients, clinicians should observe the clinical course after RFA therapy, especially in elderly patients.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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