의학박사 학위논문

A Prospective Randomized Study Comparing Radiofrequency Ablation and Hepatic Resection for Hepatocellular Carcinoma

전향적 무작위 대조연구: 간세포암에 대한 간절제술과 고주파 열치료의 치료 성적 비교

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이 해 원

A thesis of the Degree of Doctor of Philosophy

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A Prospective Randomized Study Comparing Radiofrequency Ablation and Hepatic Resection for Hepatocellular Carcinoma

by

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A thesis submitted to the Department of Surgery in partial fulfillment of the requirement of the Degree of Doctor of Philosophy in Surgery at Seoul National University College of Medicine

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지도 교수 서 경 석

이 논문을 의학박사 학위논문으로 제출함

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이 해 원 의 의학박사 학위논문을 인준함

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본인의 학위논문에 대하여 서울대학교가 아래와 같이 학위논문 저작물을 제공하는 것에 동의합니다.

1. 동의사항

① 본인의 논문을 보존이나 인터넷 등을 통한 온라인 서비스 목적으로 복제할 경우 저작물의 내용을 변경하지 않는 범위 내에서의 복제를 허용합니다.

② 본인의 논문을 디지털화하여 인터넷 등 정보통신망을 통한 논문의 일부 또는 전부의 복제·배포 및 전송 시 무료로 제공하는 것에 동의합니다.

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① 서울대학교는 본 논문을 외부에 제공할 경우 저작권 보호장치(DRM)를 사용하여야 합니다.

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논문제목 : A Prospective Randomized Study Comparing Radiofrequency Ablation and Hepatic Resection for Hepatocellular Carcinoma

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ABSTRACT

Introduction: Some local ablative therapies are known to be effective and safe to treat small hepatocellular carcinomas (HCCs) and of them, radiofrequency ablation (RFA) has been considered the most promising one. However, it is still unclear whether RFA is as effective as hepatic resection (HR), a traditional standard treatment modality, for small HCCs.

Methods: Patients who were newly diagnosed with a solitary HCC between July 2005 and September 2009 were randomized to the HR and RFA groups. Inclusion criteria were as follows; age ≥ 20 years, ≤ 70 years, Child-Pugh A, a maximal diameter of the tumor ≥ 2m, ≤ 4cm, no previous treatment history, and platelet count > 80,000/mm^3.

Results: Twenty-nine and thirty-four patients were enrolled and prospectively followed in the HR and RFA groups, respectively, on intention-to-treat (ITT) basis. The 5-year overall survival rate was 96.6% and 86.6% in the HR and RFA group, not a statistically significant difference (P=0.669). HCC recurrence developed in 38 patients:15 patients in the HR and 23 in the RFA group. The 3- and 5-year disease-free survival rates for the HR group were significantly superior to those for the RFA group (65.4%, 38.6% vs. 43.9%, 31.4%, P=0.0353). Intrahepatic local recurrence tended to develop more frequently in the RFA group (P=0.079), while the frequency of intrahepatic distant

and extrahepatic recurrence was similar between two groups. A total of 28 complications developed in 20 patients (31.7%) after treatment:11 patients in the HR and 9 in the RFA group. However, there was no significant difference in the frequency and severity of complication between two groups.

Conclusions: HR was significantly superior to RFA in terms of disease-free survival. However, the overall survival was not different between the two treatment modalities. Further studies are needed to validate the results of the present study.

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Key words: Hepatocelluar carcinoma, hepatic resection, radiofrequency ablation, prospective randomized study, disease-free survival, recurrence

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LIST of ABBREVIATIONS

HCC: hepatocellular carcinoma

RFA: Radiofreqency ablation

HR: hepatic resection

ITT: intention-to-treat

PP: per-protocol

PT: per-treatment

AFP: alpha-fetoprotein

CT: computed tomography

MRI: magnetic resonance imaging

HBV: hepaitis B virus

HCV: hepatitis C virus

PEIT: percutaneous ethanol injection therapy

TACE: transcatheter hepatic arterial chemoembolization

PIVKA-II: protein induced by vitamin K absence or antagonist-II

INTRODUCTION

Hepatocellular carcinoma (HCC) is the sixth most common malignant tumor on earth (1). It is common in Asia and Africa, and increasing in the United States and Europe (2, 3). Korea has a high prevalence and incidence of HCC. According to the data of National Cancer Control Institute, reported in 2010, primary liver cancer was the fifth most frequent malignancy in Korea, following stomach, thyroid, colorectal and lung cancers. Moreover, the crude death rate of primary liver cancer was 22.6 per 100,000 persons, second only to lung cancer. The prognosis of HCC is generally poor. For HCC conforming to the Milan criteria, theoretically the best treatment is liver transplantation, but the scarcity of donors limits this treatment. Thus, hepatic resection (HR) is still considered useful and effective (4, 5). However, hepatic resection is suitable for only 9 to 27% of patients (6, 7). The presence of significant background cirrhosis often precludes HR in patients with HCC. In addition, recurrence of tumor within the liver remnant is also common even in patients who have undergone curative HR.

Today, small HCCs are easily detected thanks to wide utilization of screening tests. Local ablative therapies have become safe and effective for treating small HCCs, and of them, radiofrequency ablation (RFA) has been considered the most promising one (8). RFA shows encouraging results in treating HCC, with less invasiveness, shorter hospitalization,

and lower expense. Cohort studies have shown RFA givesencouraging results in terms of tumor control, with complete tumor ablation rates of 90% to 95%, and low local recurrence rate of 5% to 10% (9-12). The treatment has also been shown to be safe, with a 3-year survival rate of 62% to 68% (9, 12). On the other hands, a less than 2% treatment-related mortality and 5-year survival of 40-70% has recently been achieved with HRs for HCC by experienced surgeons (5). Therefore, it is unclear which modality is superior for small HCCs.

There are some recent reports comparing RFA and HR for smallHCCs. Chen et al. (7) claimed that percutaneous local ablative therapy might be as effective as surgical resection in the treatment of solitary and small HCCs. Four year later, however, Huang et al. (5) showed that surgical resection provided better survival and lower recurrence rates than RFA for patients with HCC to the Milan criteria. Although both of those studies are prospective randomized trials, they drew quite opposite conclusions. It may be because patients enrolled in those studies were too heterogeneous to directly compare two treatment modalities. Therefore, to compare the efficacy and safety of RFA and HR, I performed a prospective randomized study for HCC patients with very homogeneous underlying conditions.

PATIENTS AND METHODS

1) Diagnostic Criteria, Inclusion and Exclusion Criteria

Among patients who were newly diagnosed with a solitary HCC, those who met inclusion and exclusion criteria were enrolled in this clinical study. HCC diagnosis was clinically made by presence of risk factors, serum *a*-fetoprotein (AFP) level, and typical imaging appearance on dynamic imaging studies including computed tomography (CT), magnetic resonance imaging (MRI), or hepatic artery angiography. Patients were diagnosed with HCC when they met the following criteria:

1. Patients with HCC risk factors such as Hepatitis B virus (HBV), hepatitis C virus (HCV) or cirrhosis.
2. Serum AFP ≥ 400 ng/mL + typical appearance on one dynamic imaging study or AFP < 400 ng/mL + typical appearance on two dynamic imaging studies

Inclusion criteria were as follows:

1. Age between 20 and 70 years
2. Child-Pugh A (score 5-6, serum albumin level ≥ 3.2 g/dL)
3. Single HCC
4. Maximal diameter of the tumor 2 to 4 cm when measured on MRI or CT

(The diameter on MRI was prior to that on CT)

5. No previous treatment
6. Platelet count > 80,000/mm^3

Patients with HCC expected to be poorly controlled by RFA were excluded.

1. HCC abutting main hepatic veins or the first branches of the main portal vein
2. HCC abutting to vessels ≥ 0.5 cm

2) Study Design

The purpose of this study was to ascertain the null hypothesis that the effect of RFA was not different to that of HR for treatment of small HCCs. The patient's death was the primary end point. Thus, the primary goal of this study was to compare the overall survival between two treatment groups. In addition, HCC recurrence was considered the secondary end point. Disease-free survival of the two groups was also investigated. Based on the Clavien classification system forcomplications (13), the frequency and severity of adverse events after primary treatment was compared. Because of the nature of the interventions, the double-blind technique was not used. This clinical study followed the ethical guidelines of the 1975 Declaration of Helsinki,and the protocol was approved by Institutional Review Board of each center participating in this study.

3) Sample Size

A 5-year overall survival rate after treatment was used as the outcome measurement to estimate the sample size. According to the previous data, the 5-year overall survival rate was expected to be 60% for HR and 40% for RFA. By the Freedman Equation, a sample size of at least 217 patients was calculated to be needed to detect a difference at 5% type-I error and 80% power for a 2-tailed test with 10% of patients estimated to be lost to follow-up.

4) Enrollment and Assignment

Three hospital participated in this clinical study; Seoul National University Hospital, National Cancer Center, and Asan Medical Center. All patients diagnosed with a single HCC were candidates for enrollment. Once a patient met the inclusion criteria, information about this study was given by the physicians. Written informed consent was required before the patient was recruited into the study. Patients were recruited between July 2005 and September 2009. They were assigned to twogroups (the RFA and HR group) by a stratified randomization method beforehand developed by Medical Research Collaborating Center of Seoul National University Hospital. The registry numbers for patients were printed on envelopes in order, and the corresponding group name was sealed in each envelope. Research nurses opened the envelope for each patient in the registry sequence after informed consents were obtained. Patients were then informed

about the specific intervention. Patients could freely withdraw consent after they were notified of the assigned treatment modality and even after the treatment has been performed.

5) Radiofrequency Ablation

Patients assigned to the RFA group were treated by using a commercially available radiofrequency generator (Radionics, Burlington, MA USA) and a single needle electrode (Cool-tip) (tumor < 3cm) or clustered electrode composed of three needles (tumor ≥3cm), ground pads, a pump for internal cooling and a ultrasound equipment. The percutaneous RFA procedure was as follows: grounding was achieved by 2 pads attached to the patient's thighs. The electrode was inserted through the tumor under ultrasound or CT guidance after local anesthesia given. When the electrode was in position, the system was switched to the impedance mode. After measurement of the baseline impedance, generator output power was gradually increased with a pump infusing cold saline into the electrode lumen to cool the tip temperature. The target area was heated to 90-100℃ and kept at that level for 10-30 minutes. When HCC was located on the surface and close to adjacent organs such as duodenum, colon or diaphragm, saline was injected between the liver and adjacent organs before ablation to prevent thermal injuries. During the treatment, a hyperechoic, necrotic area was observed around the electrode tip on ultrasonic monitoring. The aim of the treatment was to have this necrotic area

covering a larger area than the tumor. The total ablative area was required to be 0.5 - 1 cm over the tumor edge. Occasionally, the electrode needed to be inserted in different sites, and the ablation was performed repeatedly to make a satisfactory ablative area. An enhanced CT was performed 24 hours after treatment. If any possible undestroyed lesions remained, the RFA was repeated. Without serious complications, patients with satisfactory ablation were discharged 24 - 48 hours after treatment.

6) Hepatic Resection

Surgical resection was carried out under general anesthesia. Systematic resection (segmentectomy, sectionectomy or hemihepatectomy) was performed after intraoperative ultrasound examination. Intraoperative ultrasonography was routinely performed to estimate the location and feeding vessels of the tumor, as well as to give an accurate vascular map of liver anatomy. The Cavitron Ultrasonic Aspirator (CUSA, Valleylab Corp, USA) was used to dissect the hepatic parenchyma. Pringle's maneuver was occasionally used with a clamp/unclamp time of 15 minutes /5 minutes to control bleeding during hepatic dissection. Hemostasis was achieved with bipolar electric coagulator, argon beam coagulator, titanium clips, tie or suturing and some commercially manufactured hemostats. Patients remained hospitalized until liver functions approached normal and serious complications had disappeared.

7) Follow-up

Basic patient information wascollected after enrollment, including age, sex, past medical histories, physical examinations, vital signs, the results of radiological and laboratory tests, and Child-Pugh score. All post-treatment complications were also investigated. Patients were required to come back to the out-patient clinic one month after treatment and then every 3 months for 24 months. They were followed-up every 4 months 2 years after treatment. Additional visits were allowed when there were some problems. At every visit, serum AFP, protein induced by vitamin K absence or antagonist-II (PIVKA-II), complete blood cell counts, liver function test, prothrombin time and CT or MRI were checked and the results of them were recorded. Although MRI was usually performed as an alternative imaging tool when CT was intolerable because of contrast media-related hypersensitivity, it was also used as an additional workup when intrahepatic recurrence was hard to ascertain.

8) Recurrence and Secondary Treatment

When recurrence was suspected, individualized additional workups such as chest/brain CT, bone scintigraphy or positron emission tomography were performed. All confirmed recurrences were classified into three categories: intrahepatic local recurrence, intrahepatic distant recurrence, and

extrahepatic recurrence. Intrahepatic local recurrence was defined as a recurrence which developed within 2 cm from the primary treatment margin.

Once the recurrence was confirmed, the secondary treatment suggestion was proposed according to a decision of a multidisciplinary team of doctors including surgeons, internist, and radiologists. HR, RFA, percutaneous ethanol injection therapy (PEIT), transcatheter hepatic arterial chemoembolization (TACE), chemotherapy, radiotherapy (RT) or transplantation were selected as the secondary treatments.

9) Statistical Analysis

In principle, comparison of the two treatment groups was performed on intention-to-treat (ITT) basis, that is, according to the initial assigned treatment methods. However, two additional analysis methods were also used. One was per-protocol (PP) analysis and the other was per-treatment (PT) analysis. Cases with protocol violations were excluded in PP analysis and patients were regrouped according to actual treatment methods instead of initial assigned methods in PT analysis.

Differences of demographic and medical data between the 2 groups were analyzed by Student's t-test for continuous variables, and by the $\chi 2$ test or Fisher's exact test for the categorical variables. Overall survival curves and recurrence-free survival curves were generated by the Kaplan-Meier method and compared by Breslow test. All

statistical tests were 2-sided, and the null hypothesis was rejected when $P < 0.05$. The statistical analyses were performed using the SPSS 12.0 statistical software (SPSS, Inc, an IBM Company, Chicago, Illinois).

RESULTS

1) Patient Groups

Between July 2005 and September 2009, 68 patients met the criteria and were randomly assigned to each group. Five patients of the HR group withdrew their consent after randomization and were excluded in the study. Thus, 29 and 34 patients of each group were included in ITT analysis (Figure 1.1). The demographic data, vital signs, and past medical histories of the patients are given in Table 1.1. All variables except age distribution were similar between two groups. Patients were equally distributed from forties to sixties in the HR group, while approximate 60 % of patients were fifties in the RFA group. Mean age, however, was not different. Results of pre-treatment radiological and laboratory tests are shown in Table 1.2. There was no significant difference in these variables.

Median follow-up duration of all patients was 1,706 (28-2444) days. Early exit of the study occurred in 6 patients. Causes of early exit were as follows: 4 transfers to other hospitals, 1 consent withdrawal and 1 criteria violation. All these cases were included in ITT and PT analyses. However, cases with consent withdrawal or criteria violation were excluded in PP analysis.

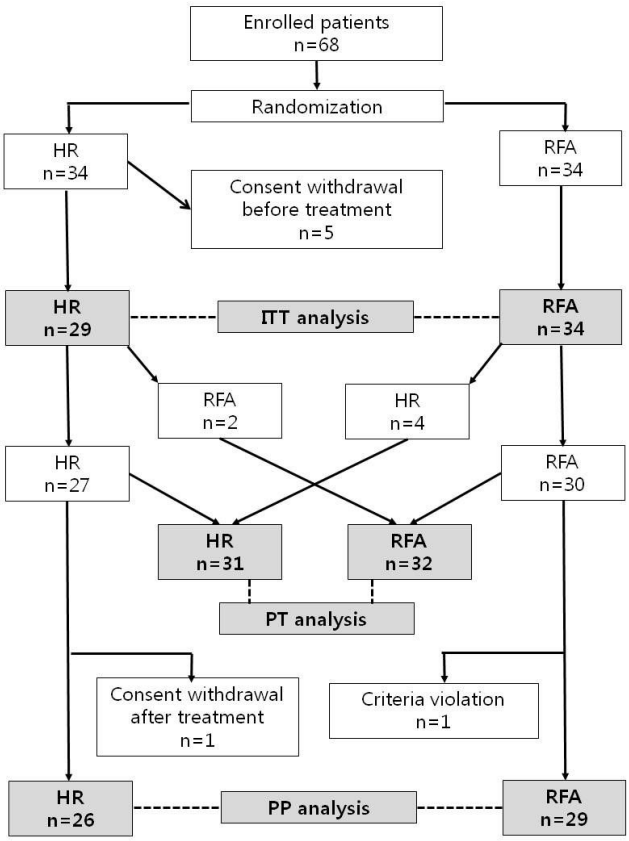

Figure 1.1 Patient numbers in ITT, PP, and PT analysis

Abbreviations: HR, hepatic resection; RFA, radiofrequency ablation; ITT, intention-to-treat; PP, per-protocol; PT, per-treatment

Excluding protocol violations, 26 and 29 patients of each group were included in the PP analysis. Final PT analysis was performed for 31 and 32 patients of each group according to actual treatment modalities, not assigned modalities.

Table 1.1 Demographic data, vital signs and past medical histories of patients

	HR (n=29)	RFA (n=34)	*P*-value
Sex (male/female)	23 (79.3) / 6 (20.7)	24 (70.6) / 10 (29.4)	0.4279
Age (years)	55.6±7.9	56.1±7.4	0.7711
Distribution of age (years)			
~39	0 (0)	1 (2.9)	**0.0341**
40~49	9 (31.0)	3 (8.8)	
50~59	9 (31.0)	20 (58.8)	
60~69	10 (34.5)	10 (29.4)	
70~	1 (3.5)	0 (0)	
Height (cm)	164.5±7.4	184.8±124.5	0.9449
Weight (kg)	67.1±10.6	88.6±141.7	0.5080
Vital signs			
SBP (mmHg)	125.4±16.2	121.9±14.9	0.3700
DBP (mmHg)	76.6±9.1	76.4±9.7	0.9533
Heart rate (/min)	73.5±9.5	74.1±10.8	0.8357
Body temperature (℃)	36.3±0.4	36.5±0.4	0.0617
Respiratory rate (/min)	21.1±12.9	18.8±1	0.8602
Past medical histories			
Diabetes (-/+)	25 (86.2) / 4 (13.8)	25 (73.5) / 9 (26.5)	0.2152
Hypertension (-/+)	19 (65.5) / 10 (34.5)	22 (64.7) / 12 (35.3)	0.9463
Tuberculosis (-/+)	28 (96.6) / 1 (3.5)	33 (97.1) / 1 (2.9)	1.0000

※ *Data was expressed as number (%) or mean±standard deviation.*

※ *Abbreviations: HR, hepatic resection; RFA, radiofrequency ablation; SBP, systolic blood pressure; DBP, diastolic blood pressure*

Table 1.2 Radiological and laboratory tests

	HR (n=29)	RFA (n=34)	*P*-value
Tumor size (cm)			
≤3	22 (75.9)	26 (76.5)	0.9549
>3, ≤4	7 (24.1)	8 (23.5)	
Child-Pugh Classification			
Total bilirubin (mg/dL)			
<2	29 (100)	34 (100)	-
2-3	0	0	
>3	0	0	
Albumin (g/dL)			
>3.5	29 (100)	31 (91.2)	0.2427
2.8-3.5	0 (0)	3 (8.8)	
<2.8	0 (0)	0 (0)	
Prothrombin time (INR)			
<1.7	29 (100)	34 (100)	-
1.7-2.3	0 (0)	0 (0)	
>2.3	0 (0)	0 (0)	
Ascites			
No ascites	29 (100)	34 (100)	-
Controlled	0 (0)	0 (0)	
Poorly controlled	0 (0)	0 (0)	
Encephalopathy			
No encephalopathy	29 (100)	34 (100)	-
Grade I/II	0 (0)	0 (0)	
Grade III/IV	0 (0)	0 (0)	
Total score			
5	29 (100)	31 (91.2)	0.2427
6	0 (0)	3 (8.8)	
AFP (ng/mL)	1671.6±5887.5	158.7±286.9	0.4269
PIVKA-II (AU/mL)	279.4±1148.5	197.2±438	0.8884
Platelet (x10^3/mm^3)	165.6±45.6	147.1±40.9	0.1636
Alkaline phosphatase (IU/L)	81.2±22.6	80.9±24.3	0.7563
AST (IU/L)	37.6±15.7	43.5±32.4	0.8039
ALT (IU/L)	41.8±21.3	44.4±34.9	0.5810
γ-GT (IU/L)	67.3±43.1	66.8±57.3	0.7468
HBsAg (-/+)	9 (31.0) / 20 (68.9)	7 (21.9) / 23 (71.9)	0.4979
Anti-HBc (IgG) (-/+)	1 (4.2) / 23 (95.8)	2 (7.1) / 26 (92.9)	1.0000
Anti-HCV (-/+)	26 (89.7) / 3 (10.3)	26 (86.7) / 4 (13.3)	1.0000
Anti-HIV (-/+)	27 (100) / 0 (0)	29 (100) / 0 (0)	-

※ *Data was expressed as number (%) or mean±standard deviation.*

※ *Abbreviations: HR, hepatic resection; RFA, radiofrequency ablation; AFP, α-fetoprotein; PIVKA-II, protein induced by vitamin K absence or antagonist-II; AST, aspartate transaminase; ALT, alanine transaminase; γ-GT, gamma-glutamyl transpeptidase; HBsAg, hepatitis B virus surface antigen; anti-HBc, anti hepatitis B virus core antibody; anti-HCV, anti hepatitis C virus antibody; anti-HIV, anti human immunodeficiency virus antibody*

2) Protocol Violations

A total of 8 patients had protocol violationsafter randomization. There were 3 protocol violations in the HR group. Two patients requested a change of a treatment modality to RFA and actually received RFA as they wanted. One patient withdrew his consent after treatment. In the RFA group, 5 patients had protocol violations. Treatment modalities were actually changed to HR in 4 patients and a criteria violation was detected in one patient. Therefore, PP analysis was performed for 26 and 29 patients in the HR and RFA groups, respectively, who followed the study protocol without violations (Figure 1.1).

After randomization, 31 patients actually received HR for HCC. Twenty-seven patients were originally randomized to HR and 4 patients changed the treatment modality to HR from RFA. As the same manner, there were 32 patients who actually received RFA. Thirty patients were primarily assigned to RFA and 2 patients selected RFA against HR, the modality they preferred. According to actual treatment methods, PT analysis were also performed (Figure 1.1).

3) Overall Survival

During the follow-up, 5 patients died: 2 patients in the HR and 3 patients in the RFA groups. The 5-year overall survival rate was 96.6% in the HR group and 86.6% in the RFA group (Figure 3.1), not a statistically significant difference (P=0.669). In the HR group, one patient died of serious pulmonary

complication on postoperative 28th day and the other patient died of progressive hepatic insufficiency during the management of HCC recurrence. In the RFA group, however, two deaths resulted from intracranial or intestinal lymphoma and only one death was directly related to HCC treatment.

4) Disease-free Survival

HCC recurrence developed in 38 patients during follow-up; 15 and 23 patients in the HR and RFA groups, respectively (51.7% vs. 67.6%). On ITT basis, the disease-free survival for the HR group was significantly superior to that for the RFA group. The disease-free survival rate was 65.4% at 3 years and 38.6% at 5 years after treatment in the HR group, while it was 43.9% at 3 years and 31.4% at 5 years in the RFA group (P=0.0353) (Figure 3.2). Also in PP analysis, the 3- and 5-year disease-free survival rate were superior in the HR group (62.5% and 31.3% vs. 41.4% and 27.6% in the RFA group, P=0.0419) (Figure 3.3). On PT basis, the 3- and 5-year disease-free survival rates were 64.4% and 34.8% in the HR group and 43.8% and 31.9% in the RFA group, respectively (Figure 3.4). Although a similar difference was observed in PT analysis, it was not significant (P=0.0529).

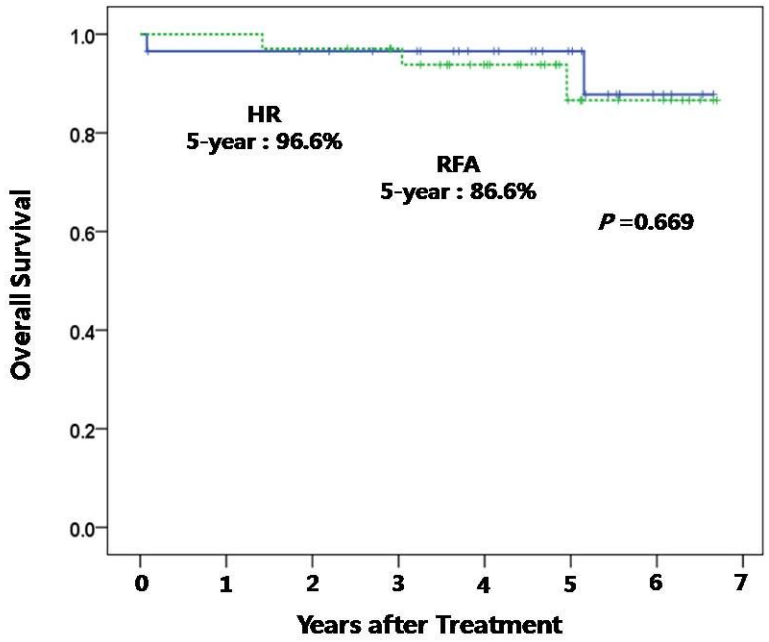

Figure 3.1 Overall survival in ITT analysis

Abbreviations: HR, hepatic resection; RFA, radiofrequency ablation; ITT, intention-to-treat

The 5-year overall survival rate was 96.6% in the HR group and 86.6% in the RFA group, respectively. This difference, however, was not statistically significant (P=0.669).

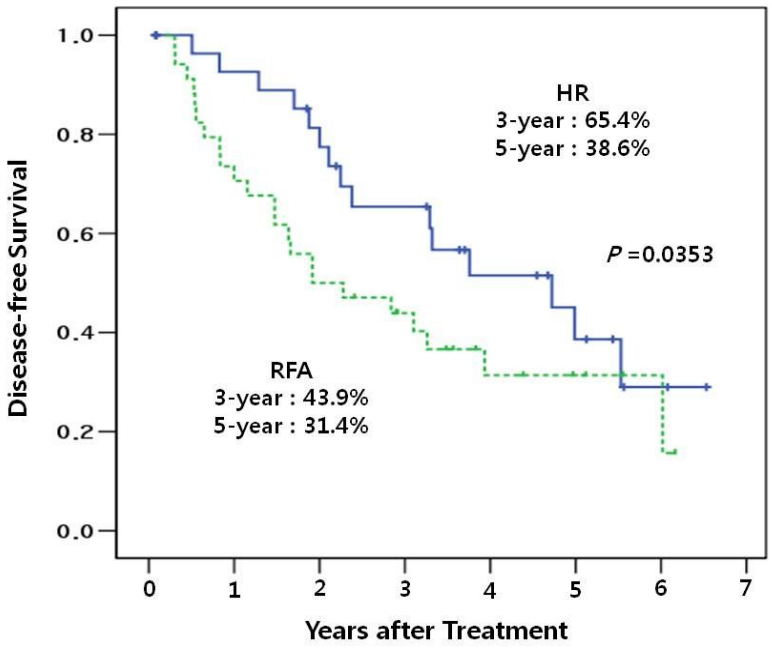

Figure 4.1 Disease-free survival in ITT analysis

Abbreviations: HR, hepatic resection; RFA, radiofrequency ablation; ITT, intention-to-treat

On ITT basis, the disease-free survival rate was 65.4% at 3 years and 38.6% at 5 years after treatment in the HR group, while it was 43.9% at 3 years and 31.4% at 5 years in the RFA group (P=0.0353).

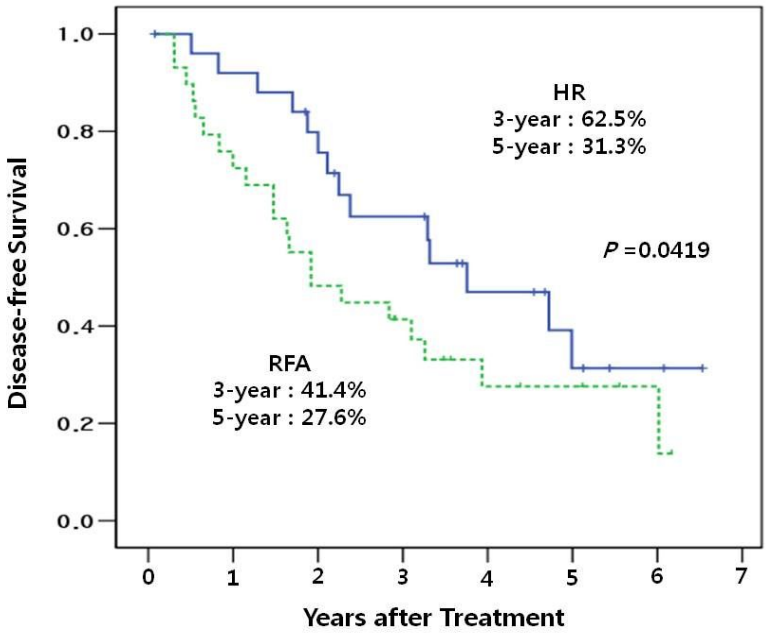

Figure 4.2 Disease-free survival in PP analysis

Abbreviations: HR, hepatic resection; RFA, radiofrequency ablation; PP, per-protocol

In PP analysis, the disease-free survival rate was 62.5% at 3 years and 31.3% at 5 years in the HR group, while it was 41.4% at 3 years and 27.6% at 5 years in the RFA group (*P*=0.0419).

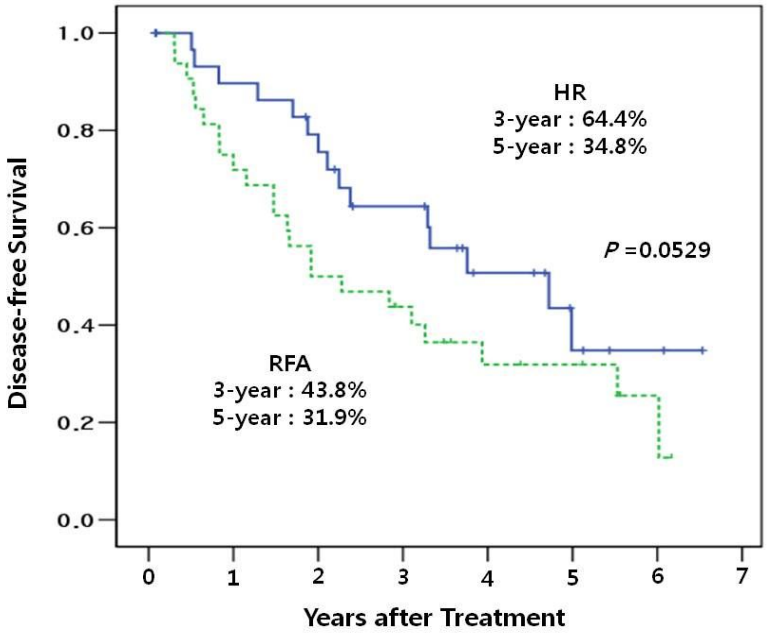

Figure 4.3 Disease-free survival in PT analysis

Abbreviations: HR, hepatic resection; RFA, radiofrequency ablation; PT, per-treatment

On PT basis, the 3- and 5-year disease-free survival rates were 64.4% and 34.8% in the HR group and 43.8% and 31.9% in the RFA group, respectively (P=0.0529).

5) Recurrence Pattern and Secondary Treatments

Recurrence pattern is given in Table 4.1. Intrahepatic local recurrence was more frequent in the RFA group, specially, with statistical significance in PT analysis (P=0.039). On the other hand, the frequency of intrahepatic distant recurrence and extrahepatic recurrence was similar between two groups.
A total of 132 secondary treatments were performed in 38 patients with HCC recurrence (Table 4.2). The most common secondary treatment was TACE not only in the HR group (61.0%) but also in the RFA group (72.5%), followed by RFA.

6) Complications

A total of 28 complications developed in 20 patients (31.7%) after primary treatment: 11 patients in the HR and 9 patients in the RFA group (37.9% vs. 26.5%). There was no significant difference in the number of patients with complications between two groups (Table 5.1).
The most common complication was pleural effusion in the HR group (24.1%) and pain in the RFA group (8.8%). According to the Clavien system, all complications but one were grade I. Only one grade IV complication developed in the HR group, a postoperative death. Therefore, there was no statistical difference in the severity of complications between two groups.

Table 5.1 Recurrence pattern

	HR	RFA	*P*-value
ITT analysis	n=29	n=34	
Intrahepatic local recurrence	8 (27.6)	17 (50.0)	0.079
Intrahepatic distant recurrence	12 (41.4)	17 (50.0)	0.614
Extrahepatic recurrence	1 (3.4)	2 (5.9)	1.000
PP analysis	n=26	n=29	
Intrahepatic local recurrence	8 (30.8)	17 (58.6)	0.058
Intrahepatic distant recurrence	11 (42.3)	15 (51.7)	0.591
Extrahepatic recurrence	1 (3.8)	2 (6.9)	1.000
PT analysis	n=31	n=32	
Intrahepatic local recurrence	8 (25.8)	17 (53.1)	0.039
Intrahepatic distant recurrence	12 (38.7)	17 (53.1)	0.315
Extrahepatic recurrence	1 (3.2)	2 (6.3)	1.000

※ *Data was expressed as number (%).*

※ *Abbreviations: HR, hepatic resection; RFA, radiofrequency ablation; ITT, intention-to-treat; PP, per-protocol; PT, per-treatment*

Table 5.2 Secondary treatments for HCC recurrence

	HR (n=15)	RFA (n=23)
HR	2 (4.9)	1 (1.1)
RFA	9 (22.0)	13 (14.3)
PEIT	2 (4.9)	10 (11.0)
TACE	25 (61.0)	66 (72.5)
Chemotherapy	1 (2.4)	0 (0)
Transplantation	0 (0)	1 (1.1)
RT	2 (4.9)	0 (0)
Total	41 (100)	91 (100)

※ *Data was expressed as number (%).*

※ *Abbreviations: HR, hepatic resection; RFA, radiofrequency ablation; PEIT, percutaneous ethanol injection therapy; TACE, transcatheter hepatic arterial chemoembolization*

Table 6.1 Patients with complications after treatment

Complications	HR (n=29)	RFA (n=34)	*P*-value
+	11 (37.9)	9 (26.5)	0.3301
-	18 (62.1)	25 (73.5)	

※ *Data was expressed as number (%).*

※ *Abbreviations: HR, hepatic resection; RFA, radiofrequency ablation;*

DISCUSSION

Partial hepatectomy is nowadays still considered the "gold standard" of treatment with an aim of providing a cure in patients with resectable HCC, good liver function, and good general condition (7). Recent improvements in perioperative management have made partial hepatectomy safer. The postoperative mortality is approaching 0% in noncirrhotic liver resection, and it is below 5% in cirrhotic liver resection (14). A recent advance of RFA, however, brought its results close to those of surgical resection. When nonrandomized and randomized comparative studies showed that outcomes of RFA were similar to those of HR (15-17), a plea was made that a prospective randomized study should be conducted between RFA and surgical resection on patients with resectable and small HCC (8).

The first prospective randomized trial comparing local ablative therapy and partial hepatectomy for HCC was performed by Chen and colleagues (7). In their study, the 1-, 2-, 3-, and 4-year overall survival rates for the local ablative therapy group and the surgical resection group were 94.4%, 79.8%, 68.6%, 65.9% and 93.3%, 82.3%, 73.4%, 64.0%, respectively. The corresponding disease-free survival rates for the 2 groups were 90.8%, 68.6%, 59.8%, 48.2% and 86.6%, 76.8%, 69.0%, 51.6%, respectively. There were no significant differences between groups in the overall survival and disease-free survival rates. Their results opposite those

of the present study. Some points should be considered in comparing two studies.

First, the most remarkable difference is the disease-freesurvival rate of the local ablative therapy group. On ITT basis, the 3- and 5-year disease-free survival rate of the present study was just 43.9% and 31.4%, while it was much higher in their study. For recurrence pattern, intrahepatic local recurrence was remarkable in the RFA group compared to the HR group (Table 3). Therefore, the low recurrence rates of their study might result from effective local control of the tumor, possibly by adding PEIT or TACE to RFA. Hence, their study cannot directly compare RFA to HR as a single treatment modality. Second, the overall survival rates of the resection group were lower compared to the present study. The 5-year overall survival rate for the HR group was 96.6% in the present study, while the 4-yearoverall survival rate for the HR group was just 64.0% in their study. This low survival was likely to result from hepatic insufficiency as well as HCC recurrence. Even if only patients with good liver function of Child-Pugh A were enrolled in their study, patients with a low platelet count (down to 40,000 /mm^3) or high indocyanine green retention rate at 15 minutes (ICG-R15) (up to 30%) were allowed to participate in the clinical study. Some patients with moderate to severe portal hypertension and cirrhosis, which are well-known prognostic factors of patients with HCC, might be enrolled in their study and could be responsible for the low

overall survival rates. This may be inferred from a high complication rate after HR in their study. At last, also in their study, the difference of the disease-free survival rates between two groups waslarger at 2- and 3-years than at 4-years. It means that recurrence developed earlier in the RFA group than in the HR group. According to their results, however, these low short-term disease-free survival rates did not have an effect on long-term survival rates, especially on overall survival rates. It is still unclear whether the timing of recurrence has an effect on long term outcomes.

Another prospective randomized trial performed by Huang and colleagues reported the superiority of HR for HCC treatment (5). According to their study, the overall as well as recurrence-free survival rates were higher in the HR group and HCC recurrence was the main reason for death in both groups. That is, tumor recurrence was directly associated with the overall survival. Their results were similar to those of the present study. Therefore, considering Huang and colleagues' study, the insignificant difference in overall survival of the present study might result from a small sample size.

Huang and colleagues (5) mentioned that the difference of recurrence rates could be explained by the difference between the tumor clearances of the 2 therapies.HCC mainly disseminates through portal and hepatic veins. The microdissemination can invade the tributaries of the portal branches and shed tumor emboli in the neighboring branches

of the same liver segment (18-21). Segment-based anatomic partial hepatectomy systematically removes normal liver parenchyma together with the original tumor and thus can eradicates both the primary tumor and venous tumor thrombi (22, 23). In the RFA procedure, when treating tumors larger than a single session ablative area, repeated insertions and ablations are needed. It is hard to overlay every ablative area precisely in the 3-dimensional liver with guidance of 2-dimensional imaging. That may explain why it has been reported that intact nests of viable tumor cells can be found within an extensively necrotic HCC specimen after RFA (24). Moreover, it remains unclear whether RFA induces tumor dissemination (25, 26). In the present study, intrahepatic local recurrence developed more frequently in the RFA group although intrahepatic distant and extrahepatic recurrence was similar between two groups. This result correspondswith the findings of Huang and colleagues.

In the present study, the frequency and severity of complications was not different between groups. In general, RFA's superiority for adverse events is obvious because of its micro-invasive characteristics. The unexpected results of the present study might result from the assessing methods foradverse events. Many subjective adverse symptoms such as nausea and pain, were assessed only by the patients' complaint. Moreover, the pain was classified only to absence or presence, not assessed according to pain rating scale. Therefore, this study had a limitation in comparison of safety

between two treatments. According to Huang and colleagues' study (5), the hospitalization length was significantly shorter and risk of adverse events was also lower in the RFA. However, it is clear that serious complications were very rare in the HR group as well as in the RFA group.

The present study could be criticized on some points. First, a small number of patients were recruited. Because of very strict inclusion criteria, only 31.3% of the initially planned sample size was achieved. The initial sample size was estimated based on the primary end point, that is to say, a 5-year overall survival rate. However, the overall survival rates were excellent for both treatment modalities and did not show significant differences. Actually, the disease-free survival rates were better in the present stud. Therefore, a disease-free survival can be used instead of a overall survival for sample size estimation. If the 5-year disease-free survival rate had been assumed as 65% for the HR group and 30% for the RFA group according to previous studies, 75 patients would have been calculated as the required sample size and the number of patients enrolled in the present study had reached 90.7% of target sample size. The actual sample size of the present study, thus, was not too small to assess the differences ofthe disease-free survival between two groups.

Second, the effectiveness of treatment methods, especially RFA, depends on the operator's experience and skill. In the present study, treatments were performed by several

surgeons and radiologists in three centers. Hence, the results of the present study may not be reproducible. This problem is a common limitation to many clinical studies.

The present clinical study, however, could be considered very worthwhile in spite of aforementioned minor faults. There are few comparable clinical studies that have been performed with strictly homogeneous patients as the present study. The condition of enrolled patients was so uniform that the tumors could be treated safely and effectively by either HR or RFA. The comparison between two treatment modalities was equitably made, minimizing confounding factors such as patients' liver function and tumor location. Therefore, the result of the present study could be considered highly valid and unbiased.

In addition, compared to the results from previous reports, the survival after RFA for a small HCC was much better although HR was superior to RFA for small HCCs in terms of disease-free survival. It might suggest that RFA could be performed as a less-invasive treatment modality for small HCCs with suitable conditions, not reducing the chance of survival. Definitely, because intrahepatic local recurrence develop more frequently after RFA, further follow-up would be necessary to investigate the long-term effectsof local recurrence.

In conclusion, HR was significantly superior to RFA in terms of disease-free survivals. However, the overall survival was excellent in both groups and not significantly different.

Further studies would be necessary to validate the results of the present study.

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초 록

서론 : 최근 선별검사의 보급으로 소간세포암의 발견 빈도가 늘고 있으며, 이에 대한 치료로 다양한 국소치료법을 적용하는 시도도 점점 많아지고 있다. 특히, 가장 효과적인 국소치료법으로 알려진 고주파 열치료(radiofrequency ablation)는 매우 우수한 치료 성적이 보고되면서, 소간세포암의 근치적, 일차 치료로 인정받고 있다. 하지만, 고주파 열치료의 소간세포암 치료 성적이 전통적인 표준 치료법인 간절제술(hepatic resection)과 동일한 지에 대해서는 아직 잘 알려져 있지 않다.

방법 : 본 임상 연구는 2005년 7월부터 2009년 9월 사이에 단일 간세포암으로 새로이 진단받은 환자들을, 간절제군과 고주파 열치료군으로 나누어 치료를 시행하고, 그 성적을 추적 관찰한 전향적 무작위 대조 연구였다. 본 연구에 참여 가능한 환자는 Child-Pugh 등급 A이면서, 혈소판 수치가 80,000/mm^3 이상인, 20세 이상 70세 이하의 간세포암 환자로, 간세포암의 크기가 2cm 이상, 4cm 이하이며, 이전에 다른 치료를 받은 적 없는 경우로 제한되었다.

결과 : 각 치료군에 34명씩의 환자가 무작위 배정되었고, 간절제군에 배정된 환자들 중 5명의 환자가 치료 전 동의를 철회함으로써, 최종적으로 29명이 간절제술을 받았고, 34명이 고주파 열치료를 받았다. 그리고, 그 결과에 대해 의향치료(intention-to-treat, ITT)분석이 이루어졌다. 인구학적 정보 및 치료 전 의학적 조건에 있어서는 두 치료군간 차이가 발견되지 않았다. 5년 전체생존율은 간절제군에서 96.6%, 고주파 열치료군에서 86.6%였으나, 통계적 유의성은 없었다. 간세포암의 재발은 간절제군에서 15명(51.7%), 고주파 열치료군에서 23명(67.6%), 총 38명에서 발생하였다. 간절제군의 3년, 5년 무병생존율은 65.4%, 38.6%로 고주파 열치료군의 43.9%,

31.4%보다 통계학적으로 의미 있게 높았다(P=0.0353). 재발 양상에 있어서는 간내 국소 재발이 고주파 열치료군에서 더 빈번한 경향을 보였지만(P=0.079), 간내 원격 재발이나 간외 재발의 빈도는 두 치료군간 차이가 없었다. 20명의 환자(31.7%)에서 총 28 건의 합병증이 발생하였는데, 간절제군에서 11명(37.9%)이, 고주파 열치료군에서 9명(26.5%)이 합병증을 경험함으로써, 합병증을 경험한 환자의 빈도에서는 유의한 차이가 없었다. Clavien 체계에 따라 합병증의 경중을 비교해 보았을 때, 간절제 후 수술 합병증으로 사망한 1 예(4등급)가 있었지만, 이를 제외하고는 모두 1등급 합병증이었기 때문에 합병증의 중증도 면에서도 두 치료군간 뚜렷한 차이점이 발견되지 않았다.

결론 : 본 연구의 결과에 따르면 간절제술이 무병생존율 측면에서 고주파 열치료보다 의미 있게 우수한 성적을 보였다. 하지만, 환자의 누적 생존율에 있어서는 두 치료군간 차이가 발견되지 않았다. 향후 추가적인 연구를 통해 본 연구의 결과가 검증 및 확인되어야 할 것이다.

중요어 : 간세포암, 간절제, 고주파 열치료, 전향적 무작위 연구, 무병생존율, 재발

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