

Clinical features of hemodialysis patients treated for hepatocellular carcinoma: Comparison between resection and radiofrequency ablation

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Abstract. There is no consensus regarding which therapeutic option is better and/or safer for treating hemodialysis (HD) patients with hepatocellular carcinoma (HCC). The present study compared surgical resection (Hx) and radiofrequency ablation (RFA) with regard to therapeutic efficacy in HD patients with HCC. Of 108 HD patients with naïve HCC treated at 15 institutions between 1988 and 2014 enrolled in the present study, 58 fulfilled the up-to-7 criteria [7 as the sum of the size of the largest tumor (cm) and the number of tumors] and were treated with Hx (n=23) or RFA (n=35); their clinical features, complications and prognosis were assessed. The frequency of hepatitis C virus was higher in the RFA group compared with

that in the Hx group (P=0.002), whereas there were no differences between the groups with regard to the average time from the first HD (P=0.953), tumor-nodes-metastasis (TNM) stage (Union for International Cancer Control 7th edition) (P=0.588), TNM stage (Liver Cancer Study Group of Japan 5th edition) (P=0.095), Child-Pugh classification (P=0.094), and Japan Integrated Scoring system (P=0.489). There were no significant differences in overall survival (OS) and disease-free survival (DFS) rates between the Hx and RFA groups [1-, 3- and 5-year OS rates: 81.7, 55.6 and 43.3% vs. 89.9, 67.1 and 56.3%, respectively (P=0.454); 1-, 3- and 5-year DFS rates: 71.1, 30.5 and 18.3% vs. 63.8, 31.6 and 21.1%, respectively (P=0.911)]. Complications were observed in 4 patients (11.4%) in the RFA group (2 with subcapsular hemorrhage, 1 with intraperitoneal bleeding and 1 with tardive intrahepatic hematoma) and in 4 patients (17.4%) in the Hx group (2 with postoperative infection, 1 with liver failure and 1 with pleural effusion) (P=0.700). In conclusion, Hx and RFA have a similar therapeutic efficacy in HD patients with naïve HCC who fulfilled the up-to-7 criteria.

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Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer type in males, and the ninth most common in females (1).

Although the number of hemodialysis (HD) patients with HCC remains low, the development of an effective therapeutic strategy for them is of clinical importance. It is well known that, as HD poses a risk for hepatitis C virus (HCV) infection, the HCV-positive rate is increased in HD patients, while HCV is a major risk factor for HCC (2). Ozer Etik *et al* (3) reported that the prevalence of anti-HCV seropositivity among patients receiving maintenance HD in developed countries ranges from 5-60% (3). However, the number of patients with diabetes mellitus (DM) has been increasing and diabetic nephropathy has become the primary reason for requiring HD (4). Furthermore, DM has recently been reported to be an independent risk factor for HCC (5), and thus it is expected that the number of HD patients with HCC will increase in the near future.

Hepatic resection (Hx) is a good therapeutic option for HCC (6,7), while radiofrequency ablation (RFA) has become the standard low-invasive therapy for small HCC (8,9). However, there is no consensus regarding which therapeutic option is better and/or safer for HD patients with small HCC. The aim of the present study was to retrospectively analyze clinical features, complications and prognosis of HD patients with small HCC treated with Hx or RFA.

Materials and methods

A total of 108 HD patients with naïve HCC who were treated at one of our 15 institutions (Ehime Prefectural Central Hospital, Matsuyama; Ogaki Municipal Hospital, Ogaki; Kagawa Prefectural Central Hospital, Takamatsu; Teine Keijinkai Hospital, Sapporo; Asahi General Hospital, Asahi; Isesaki Municipal Hospital, Isesaki; Ehime University Hospital, Toon; Matsuyama Red Cross Hospital, Matsuyama; Shiritsu Uwajima Hospital, Uwajima; Shiritsu Ozu Hospital, Ozu; Toyama University Hospital, Toyama; Kagawa University Hospital, Kagawa; Tokushima University Hospital, Tokushima; Saiseikai Imabari Hospital, Imabari; Okayama Saiseikai General Hospital, Okayama, Japan) between January 1988 and December 2014 were enrolled in the present study. Of these, 58 fulfilled the up-to-7-criteria [7 as the sum of the size of the largest tumor (cm) and the number of tumors] (10,11), and were treated with Hx (Hx group, n=23) or RFA (RFA group, n=35) as the curative therapy. Transcatheter arterial chemoembolization (TACE) was performed as the palliative treatment in 24 patients. All the patients had end-stage renal disease (ESRD), which requires HD or peritoneal dialysis. HCC patients within the up-to-7-criteria were regarded as having early-stage HCC. After receiving informed consent for curative treatment from each patient or their family, Hx or RFA was performed. The first HD session was performed 1 or 2 days after Hx or RFA with nafamostat mesylate (Torii Co., Ltd., Tokyo, Japan) instead of heparin.

Surveillance of HCC was mainly performed using ultrasonography (US), and diagnosis was based on an increasing course of α -fetoprotein as well as findings obtained by dynamic computed tomography (12), magnetic resonance imaging and/or contrast-enhanced US (CEUS) with perflubutane (Sonazoid®; Daiichi Sankyo Co., Ltd. Tokyo, Japan) (13). The tumor-nodes-metastasis (TNM) stage was determined according to the HCC staging systems of the Union for International Cancer Control, 7th edition (14) and the Liver Cancer Study Group of Japan (LCSGJ), 5th edition (15).

Child-Pugh classification (16) was used for evaluation of hepatic reserve function affected by liver cirrhosis. HBV and HCV positivity were determined based on positivity for the hepatitis B virus surface antigen (HBsAg) and HCsAg, respectively.

RFA was performed from 2000 onwards as a curative therapy using previously reported methods (9). Selection of therapy (Hx or RFA) was independently determined by each institution. The physicians tended to select RFA when the size and number of tumors was small (2.1 ± 0.8 cm and 1.1 ± 0.3 , respectively). When the patient or their family refused curative treatments, TACE was selected. For the TACE procedure, a microcatheter was inserted into the artery feeding the tumor in a super-selective manner after conventional hepatic angiography, followed by a segmental or subsegmental TACE procedure (17) performed by experienced radiologists and hepatologists. For embolization, epirubicin hydrochloride (Farmorubicin®; Pfizer Japan Inc., Tokyo, Japan) was used throughout January 2010, while miriplatin hydrate (MIRIPLA®; Sumitomo Dainippon Pharma Co., Ltd., Osaka, Japan), was used from February 2010, which was injected together with lipiodol in all cases, after which a gelatin sponge cut into small fragments (Gelfoam®; Upjohn, Kalamazoo, MI, USA) were used throughout August 2006, while small gelatin sponge fragments (Gelpart®; Nippon Kayaku Co., Ltd., Tokyo, Japan) were used from September 2006.

The study protocol was approved by the Institutional Ethics Committee of Ehime Prefectural Central Hospital (Matsuyama, Japan; no. 26-11).

Statistical analysis. Data are expressed as the mean \pm standard deviation. Statistical analyses were performed using Welch's t-test for unpaired data, as well as Fischer's exact test, Mann-Whitney's U-test or a log-rank test with the Kaplan-Meier method, as appropriate. All statistical analyses were performed using SPSS version 21 (IBM SPSS, Armonk, NY, USA). $P < 0.05$ was considered to indicate a statistically significant difference.

Results

The average age of all the enrolled patients (91 males, 17 females) was 67.9 ± 8.7 years. The rate of HCV-positivity, HBV-positivity and HBV + HCV-positivity was 68.5, 8.3 and 2.8%, respectively, while that of patients negative for HCV and HBV (nonBnonC) was 20.4%. Among the nonBnonC patients with HCC, DM was the primary disease in 72.7% (16/22). The average time from the first HD was 4.6 ± 4.8 years (range, 0.1-27 years) (Table I). The frequency of patients within the up-to-7 criteria was 85.2% (92/108) and 64 of these underwent curative therapies; among them, 23 received Hx, 39 received ablative therapy [RFA, 35; percutaneous ethanol injection therapy (PEIT), 2; microwave coagulation therapy (MCT), 2] and 2 received combination therapy with Hx and RFA (Fig. 1).

Comparison between patients within the up-to-7 criteria treated with Hx and those treated with RFA revealed no significant differences for most parameters, apart from the etiology of HCC ($P = 0.002$), platelet count ($P = 0.013$) and prothrombin time ($P = 0.042$) (Table II). The overall survival (OS) rate and disease-free survival (DFS) rate were not significantly

Table I. Clinical features of HD patients with naïve HCC (n=108).

Parameter/characteristic	Value
Sex (male/female) (n)	91:17
Average age (years)	67.9±8.7
Etiology of HCC (HCV/HBV/HBV + HCV/nonBnonC) (n)	74:9:3:22
Performance status (0/1/2/3/4/unknown) (n)	54:35:4:3:12
Basal disease causing ESRD (n)	DM, 72; unknown, 26; nephrosclerosis, 3; chronic glomerulonephritis, 3; renal stone, 1; multiple myeloma, 1; IgA nephropathy, 1; rapidly progressive glomerulonephritis, 1
HD (machine/peritoneal) (n)	107:1
Average time from first HD, years (range)	4.6±4.8 (0.1-27)
Aspartate aminotransferase (IU/l)	28.9±20.9
Alanine aminotransferase (IU/l)	24.7±24.1
Platelets (x10 ⁴ cells/ μ l)	13.3±6.1
Total bilirubin (mg/dl)	0.49±0.25
Albumin (g/dl)	3.57±0.53
Prothrombin time (%)	90.2±17.4
Child-Pugh classification (A/B/C) (n)	89:19:0
Tumor size (<2/ \geq 2 cm, n), (average, cm)	27:81 (3.24±2.27)
Number of tumors (single/multiple) (average)	81:27 (1.45±1.06)
Extrahepatic metastasis, n (%)	2 (bone), (1.9%)
Portal vein tumor thrombosis, n (%)	6 (5.6%)
Alpha-fetoprotein (ng/ml)	1,683.2±5,879.9
Des-gamma-carboxy prothrombin (mUA/ml)	2,706.5±8,308.3
TNM stage (UICC 7th) I/II/III/IV (n)	77:22:7:2
TNM stage (LCSGJ 5th) I/II/III/IV (n)	25:57:21:5
Therapeutic method (Hx/RFA/Hx+RFA/MCT/PEIT/TACE/RT/chemotherapy/BSC) (n)	28:35:3:2:2:29:2:1:6

Values are expressed as the mean \pm standard deviation. HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HBV, hepatitis B virus; nonBnonC, negative for HBV and HCV; ESRD, end-stage renal disease; DM, diabetes mellitus; IgA, immunoglobulin A; HD, hemodialysis; TNM, tumor-nodes-metastasis; UICC 7th, Union for International Cancer Control 7th edition; LCSGJ 5th, Liver Cancer Study Group of Japan 5th edition; RFA, radiofrequency ablation; Hx, surgical resection; MCT, microwave coagulation therapy; PEIT, percutaneous ethanol injection therapy; TACE, transcatheter arterial chemoembolization; RT, radiotherapy; BSC, best supportive care.

different between the Hx and RFA groups [1-, 3- and 5-year OS rates: 81.7, 55.6 and 43.3% vs. 89.9, 67.1 and 56.3%, respectively; $P=0.454$ (Fig. 2) and 1-, 3- and 5-year DFS rates: 71.1, 30.5 and 18.3% vs. 63.8, 31.6 and 21.1%, respectively; $P=0.911$ (Fig. 3)]. Post-procedure complications were observed in 4 of the 35 patients (11.4%) treated by RFA (subcapsular hemorrhage in the liver, 2; intraperitoneal bleeding, 1; tardive intrahepatic hematoma 4 days after RFA procedure, 1) and in 4 of the 23 patients (17.4%) treated by Hx (post-operative infection, 2; liver failure, 1; pleural effusion, 1). No significant differences were identified in the frequencies of complications between the two groups ($P=0.700$). One patient died due to post-operative infection within 1 month in the Hx group, whereas no mortalities occurred in the RFA group ($P=0.397$, according to Fischer's exact test).

In HCC patients who fulfilled the up-to-7-criteria, results of the Japan Integrated Scoring (JIS) system, calculated based on the Child-Pugh classification and TNM stage according to the LCSGJ classification, 5th edition (18) did not show any significant differences between patients treated with curative treatments

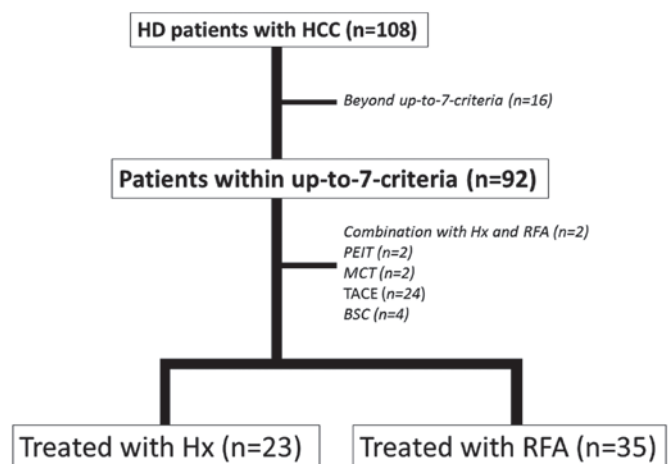


Figure 1. HD patients with naïve hepatocellular carcinoma. A total of 108 HD patients with naïve hepatocellular carcinoma were enrolled. Those within the up-to-7 criteria and treated with Hx, RFA or transcatheter arterial chemoembolization were investigated. PEIT, percutaneous ethanol injection therapy; MCT, microwave coagulation therapy; BSC, best supportive care; HD, hemodialysis; Hx, hepatic resection; RFA, radiofrequency ablation.

Table II. Comparison of clinical features between Hx and RFA groups.

Parameter/characteristic	Hx (n=23)	RFA (n=35)	P-value
Sex ^a (male:female) (n)	21:2	25:10	0.070
Average age ^b (years)	68.4±9.1	66.2±8.8	0.359
Etiology of HCC ^c (n)	10:4:1:8	29:2:1:3	0.002
(HCV/HBV/HDV + HCV/nonBnonC) (n)			
Performance status ^c (0/1/2/3/4/unknown)	11:10:1:1:0:0	16:15:0:1:0:3	0.387
Basal disease causing ESRD (n)	DM, 15; IgA, 1; chronic glomerulonephritis, 1; nephrosclerosis, 1; unknown, 5	DM, 25; multiple myeloma, 1; nephrosclerosis, 1; chronic glomerulonephritis, 1; unknown, 7	-
HD (machine/peritoneal) (n)	23:0	35:0	-
Average period after introducing HD ^b (years)	5.3±5.7	5.4±5.7	0.953
Aspartate aminotransferase ^b (IU/l)	23.0±12.1	34.4±30.7	0.057
Alanine aminotransferase ^b (IU/l)	20.3±10.6	30.4±35.2	0.123
Platelets ^b (x10 ⁴ cells/ μ l)	15.1±6.3	11.2±5.1	0.013
Total bilirubin ^b (mg/dl)	0.42±0.22	0.56±0.27	0.055
Albumin ^b (g/dl)	3.76±0.51	3.63±0.50	0.350
Prothrombin time ^b (%)	96.0±13.0	87.4±16.7	0.042
Child-Pugh classification ^c (A/B/C) (n)	22:1:0	28:7:0	0.094
Tumor size ^a (<2/ \geq 2 cm, n) (average, cm)	4:19 (2.8±1.0)	14:21 (2.1±0.8)	0.071
Tumor number ^a (single/multiple)	20:3 (1.1±0.3)	32:3 (1.1±0.3)	0.612
Alpha-fetoprotein ^b (ng/ml)	681.9±2,110.9	831.5±4,147.0	0.877
Des-gamma-carboxy prothrombin ^b (mUA/ml)	2,035.4±6,265.8	1,173.7±3,565.4	0.522
TNM stage ^c (UICC 7th) I/II/III/IV (n)	20:3:0:0	32:3:0:0	0.588
TNM stage ^c (LCSGJ 5th) I/II/III/IV (n)	3:18:2:0	13:19:3:0	0.095
JIS score ^c 0/1/2/3 (n)	3:17:3:0	11:17:6:1	0.489
Complications ^{a,d} (n)	Postoperative infection, 2 (1 died within 1 month), liver failure, 1; pleural effusion, 1 ^d	Intra-hepatic hematoma after 4 days of RFA, 1; subcapsular hemorrhage of liver, 2; intraperitoneal bleeding, 1	0.700
Cause of mortality (n)	HCC, 2; infection, 3; liver failure, 2; acute subdural hematoma, 1; cardiac failure, 1; arrhythmia, 1; others/unknown, 4	HCC, 6; infection, 1; liver failure, 1; cerebral hemorrhage, 2; suffocation by accidental ingestion, 1; acute respiratory distress syndrome, 1; general prostration, 1; others/unknown, 2	-

Values are expressed as the mean \pm standard deviation. Statistics were performed according to ^aFischer's exact test; ^bWelch's t-test; and ^cMann-Whitney's U-test. ^dComplications arose in 4/23 (17.4%) and 4/35 (11.4%) of the patients in Hx and the RFA groups, respectively. RFA, radiofrequency ablation; Hx, surgical resection; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HBV, hepatitis B virus; nonBnonC, both negative for HBV and HCV; ESRD, end-stage renal disease; IgA, immunoglobulin A; DM, diabetes mellitus; HD, hemodialysis; TNM, tumor-nodes-metastasis; UICC, Union for International Cancer Control; LCSGJ, Liver Cancer Study Group of Japan; JIS system, Japan Integrated Scoring System.

(Hx or RFA, n=58) and those who underwent palliative treatment (TACE, n=24) (P=0.071). The OS rate for those who received curative treatments revealed a better prognosis compared

with those who received TACE (n=24) [1-, 3- and 5-year OS rates: 90.6, 62.3 and 50.4% vs. 86.5, 45.9 and 0.0%, respectively; P=0.010, according to the log-rank test (data not shown)].

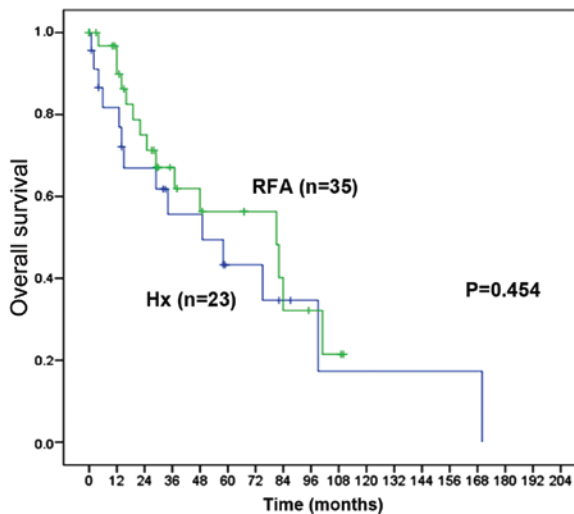


Figure 2. OSR for patients treated with hepatic resection or RFA. The overall survival rate for the Hx and RFA groups was not significantly different (1-, 3- and 5-year OSR: 81.7, 55.6 and 43.3% vs. 89.9, 67.1 and 56.3%, respectively; $P=0.454$). OSR, overall survival rate; RFA, radiofrequency ablation; Hx, surgical resection.

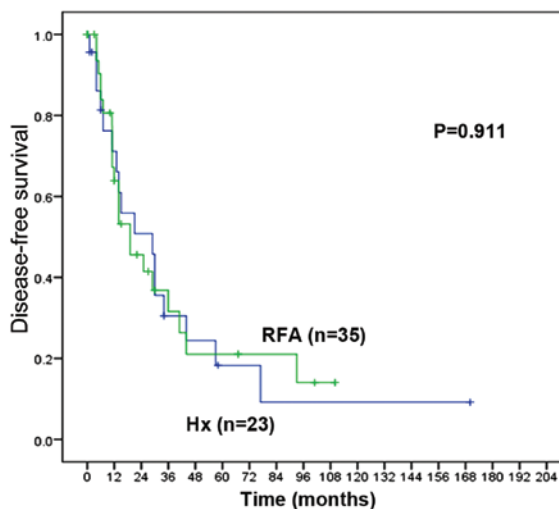


Figure 3. DFS for patients treated with Hx or RFA. The DFS rate was not significantly different between patients treated with Hx and RFA (1-, 3- and 5-year DFS rates: 71.1, 30.5 and 18.3% vs. 63.8, 31.6 and 21.1%, respectively; $P=0.911$). DFS, disease-free survival. RFA, radiofrequency ablation; Hx, surgical resection.

Discussion

Although the number of HD patients with HCC is low, such cases are at times encountered in the clinic. A previous study published in 1996 found that the frequency of HCV-positive HD patients was as high as 18.9% (409/2,164), while HCC was observed in only 2.4% (10/409) of HD patients with HCV infection (19). Factors associated with HCC in HCV-positive HD patients have remained elusive. However, positivity for DM was considered to have an important role for the occurrence of HCC in HD patients with HCV infection. In the present study, diabetic nephropathy was the most common primary disease leading to the requirement for HD, while Henderson *et al* (20) noted that HCC was 1.3 times more likely to occur in HCV-positive HD

patients with DM. Furthermore, the number of DM patients worldwide has been increasing recently. On the other hand, in patients without chronic viral hepatitis, DM increases the risk of chronic liver disease and HCC, with incidences of chronic non-alcoholic liver disease in patients with and without DM of 18.13 and 9.55, respectively, per 10,000 individuals per year, and an incidence of HCC of 2.39 and 0.87, respectively (21). Furthermore, that study found that DM is associated with an increased risk of chronic non-alcoholic liver disease and HCC [hazard ratio (HR), 1.98 and 2.16, respectively]. Noto *et al* (22) also reported that DM was associated with an increased risk for HCC (HR, 3.64; 95% confidence interval, 2.61-5.07) in Japanese patients. DM and aging, particularly in patients with a high fibrosis-4 index, were found to be associated with an increased risk of HCC in a previous study by our group (23). In the present study, at least 72.7% (16/22) of the patients without viral hepatitis had DM. Cases of HCC among HD patients without chronic viral hepatitis infection may increase in the near future in association with the increase in patients with DM and diabetic nephropathy. In the present study, numerous HCC patients without viral hepatitis had DM and establishment of a surveillance strategy for HCC in HD patients with DM nephropathy is therefore required to detect HCC in as early a stage as possible. Furthermore, screening for HCC should also be performed in HD patients with chronic hepatitis, particularly those with HCV. Although interferon and ribavirin treatment is difficult in HD patients, the effectiveness and safety of HCV-NS5A-inhibitor (daclatasvir) and protease inhibitor (asunaprevir) combination therapy for HD patients with HCV has been reported recently (24,25). Further progression in the development of direct-acting antiviral drugs will reduce the chronic hepatic diseases, HCV and HCC, in HD patients.

Although Hx and RFA are routinely performed as curative treatments for HCC, few studies have compared their efficacy and safety in HD patients. Generally, HX is performed as a curative treatment for HCC patients with good hepatic function (6,26), while treatment with RFA is regarded as a curative local therapy for small HCC (27). Although Tung *et al* (28) reported that the prognosis of HD patients with HCC who were treated with Hx was not significantly different from that of those who received best supportive care, Hx has recently been established as an acceptable procedure for HD patients with HCC (29-32). In patients with good liver function and early-stage HCC (within up-to-7 criteria), curative treatments are expected to prolong survival. However, HD has been reported to be a risk factor in cases that undergo surgical resection due to a tendency to bleed arising from platelet dysfunction and heparin usage (33), susceptibility to infection (34) and impaired wound healing (35). In the present study, complications were observed in 17.4% (4/23) of patients in the Hx group (infection, 2; liver failure, 1; pleural effusion, 1), while complications occurred in 11.4% (4/35) of patients in the RFA group, each of which was based on bleeding (subcapsular hemorrhage in the liver, 2; intraperitoneal bleeding, 1; tardive intrahepatic hematoma, 1). However, no statistical difference in the complication rates was observed between the two groups ($P=0.700$). The characteristics of the patients who showed complications of bleeding could not be determined in the present cohort. The rate of complications associated with curative treatments in patients with HD is thought to be higher compared with that seen in those without

HD. Few studies have noted that HCC patients with HD had a higher rate of complications compared with those without HD, although the rates of post-operative infection after Hx (4.03 vs. 1.17%; $P=0.0175$) (31) and bleeding after RFA (13.3 vs. 0.79%; $P=0.0002$) (36) have been reported. When a curative treatment for HCC (Hx or RFA) is applied in a patient with HD, it is important to keep in mind that the risk of complications is greater compared with that in patients without HD; thus, detailed information must be given and informed consent must be obtained.

Although RFA has been gaining in importance in terms of prolonging the survival of HCC patients, particularly those with small tumors, there are few reports on RFA as a treatment for HCC in patients with HD (37). With increasing detection of small HCC due to the progression of imaging modalities [e.g., CEUS with Sonazoid (38)], the clinical significance of RFA in the treatment of small HCC for improving the prognosis of affected patients is expected to increase. In the present study, no significant differences in the OS and DFS rates were observed between the Hx and RFA groups, and no differences with regard to the JIS score were obtained (18). Lee *et al* (32) reported that, with regard to predicting the prognosis of HCC, the JIS score is a more accurate model for patients undergoing HD and is suitable for comparing the efficacy of therapies. The present study has demonstrated that the JIS scores and the therapeutic outcome were not different between the Hx and RFA groups, indicating equally important roles for the two modalities in HD patients with HCC.

In conclusion, the present study has determined that there were no significant differences between Hx and RFA with regard to the therapeutic outcome when applied for the treatment of HCC in HD patients within the up-to-7-criteria. As the present study was retrospective in nature and the number of patients was small, there were several limitations in terms of drawing firm conclusions. Accumulation of a greater number of cases and further analysis is therefore required.

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