World J Surg (2016) 40:1709–1719
DOI 10.1007/s00268-016-3465-6

ORIGINAL SCIENTIFIC REPORT

Comparison of the Outcomes of Patients with Hepatocellular Carcinoma and Portal Hypertension After Liver Resection Versus Radiofrequency Ablation

Noboru Harada[1] · Ken Shirabe[3] · Takashi Maeda[1] · Hiroto Kayashima[1] · Shintaro Takaki[2] · Yoshihiko Maehara[3]

Published online: 24 February 2016

Abstract

Background The aim of this study was to compare the outcome of patients with hepatocellular carcinoma (HCC), Barcelona Clinic Liver Cancer (BCLC) stages 0 and A, and portal hypertension (PHT) who underwent liver resection (LR) or radiofrequency ablation (RFA).

Methods The study population consisted of 121 patients with PHT and HCC of BCLC stage 0 and A who underwent LR ($n = 81$) or RFA ($n = 40$). To reduce bias in patient selection, the different covariate distributions in two groups were adjusted using inverse probability treatment weighting (IPTW). The prognostic outcomes of LR- and RFA-treated patients were then analyzed.

Results Before IPTW adjustment, the 5-year overall survival (OS) of LR and RFA patients was comparable. Five-year recurrence-free survival (RFS) was significantly better in the LR group than in the RFA group ($P < 0.0001$). Multivariate analysis showed that RFA was an independent predictor of worse RFS ($P = 0.0004$). The local recurrence rate was higher in the RFA than in the LR group, with recurrences in each group tending to be treated with the same modality as initially. After IPTW adjustment, the OS of patients in the LR and RFA groups did not significantly differ, whereas the RFS of the LR group remained significantly better than that of the RFA group ($P = 0.00014$). However, the RFA group had fewer postoperative complication rates and a shortened length of hospital stay.

Conclusions By reducing postoperative complications, LR may be a treatment option for patients with BCLC stage 0 or A HCC and PHT.

Introduction

According to the guidelines of the Barcelona Clinic Liver Cancer (BCLC) Group [1] and the American Association for the Study of Liver Disease (AASLD) [2], patients with HCC and clinically significant portal hypertension (PHT) are candidates for radiofrequency ablation (RFA) or liver transplantation, whereas hepatectomy is contraindicated.

Clinically significant PHT, defined as a hepatic venous pressure gradient (HVPG) ≥10 mmHg, is the most powerful predictor of postoperative liver failure or poor long-term survival in patients with Child–Pugh A liver function [3]. However, this conclusion was based on a small retrospective cohort study of only 77 patients who underwent

This manuscript is not based on a previous communication to a society or meeting.

✉ Noboru Harada
nharada@surg2.med.kyushu-u.ac.jp

[1] The Department of Surgery, Hiroshima Red Cross Hospital and Atomic Bomb Survivors Hospital, Hiroshima 730-8619, Japan

[2] The Department of Gastroenterology, Hiroshima Red Cross Hospital and Atomic Bomb Survivors Hospital, Hiroshima, Japan

[3] The Department of Surgery and Medical Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

liver resection (LR). Preoperative HVPG measurement is invasive and is not performed routinely in most liver centers; instead, indirect clinical parameters, including esophageal varices (EVs) and/or splenomegaly associated with thrombocytopenia, are considered clinical signs of PHT [4]. Conversely, there are many reports that LR improves survival in patients with PHT and that PHT should not be considered as an absolute contraindication for hepatectomy in patients with cirrhosis [5–7]. Given the serious shortage of available liver transplant donor organs [8], surgical resection may be a better treatment option for some HCC patients with clinical PHT [9].

In this study, we compared the long-term outcome of patients with BCLC stages 0 and A HCC and PHT who underwent LR or RFA. Inverse probability treatment weighting (IPTW) was applied to reduce the bias in patient selection. IPTW weighs the samples using the propensity score to reduce the confounding that frequently occurs in cohort studies of the effects of treatment on outcome. In addition, IPTW enables the estimation of marginal or population-average treatment effects [10].

Materials and methods

Patients and inclusion criteria

The study population consisted of 121 consecutively enrolled patients with HCC who underwent LR or RFA at the Hiroshima Red Cross Hospital and Atomic Bomb Survivors Hospital between January 2008 and December 2013. All patients had tumors measuring <3 cm, each with a maximum of three tumors or a solitary tumor <5 cm, and had been diagnosed with PHT, defined as the presence of EVs and/or a platelet count of <100,000/μL in association with splenomegaly. EV was determined preoperatively based on upper gastrointestinal endoscopic findings. Splenomegaly was defined as spleen length exceeding 10 cm on preoperative computed tomography [5, 11]. Patients with ascites who did not respond to diuretic drugs were excluded.

Surgical procedure, RFA procedure, and treatment decision

The surgical indications were based on the patient's daily living activities, age, and fitness, the degree of tumor invasion, extent of resection, and remnant liver function [12, 13]. The type of hepatectomy was selected based on liver function and tumor extension [14–16]. Treatment modalities were mainly determined by Child-Pugh class and the results of indocyanine green retention tests at 15 min ($ICGR_{15}$). Patients with Child-Pugh class A or B and $ICGR_{15} \leq 45$ % tended to be treated with LR. Surgical procedures included hemihepatectomy or segmentectomy for patients with $ICGR_{15} < 20$ %, subsegmentectomy for patients with $ICGR_{15} < 30$ %, and partial resection for patients with $ICGR_{15} \leq 45$ %. If $ICGR_{15}$ was >45 %, 99mTc-GSA scintigraphy was performed, followed by partial resection to ensure that $ICGR_{15}$ was <45 % by scintigraphy [17]. The presence of ascites was considered an absolute contraindication for resection. The hepatectomy procedures have been described elsewhere [13, 14].

All patients scheduled for RFA underwent outpatient abdominal ultrasonography (US) to assess the feasibility of US-guided percutaneous RFA [18]. The method and therapeutic strategy of RFA were the same as described in previous studies [19]. RFA was selected for patients with Child-Pugh class A or B, $ICGR_{15} > 45$ %, and contraindications for general anesthesia, and for those requesting RFA. RFA was not performed in patients with segment 1 tumors; tumors overhanging the liver margin or near adjacent organs, including the gallbladder, stomach, or colon; or tumors located near major intrahepatic vessels.

Written informed consent was obtained from all patients for surgical treatment and RFA therapy according to the guidelines of our hospital. Decisions regarding treatment modalities were made at a meeting attended by all participating surgeons and gastroenterologists. The HCC patients were then divided accordingly into those to be treated with LR (LR group) and those to be treated with RFA (RFA group).

The selection criteria for the treatment of recurrent HCC were identical to those for primary tumors. TACE, microwave coagulation therapy, radiation, or best supportive therapy was chosen based on liver function, number of tumors, and patient choice. The study protocol conformed with the updated ethical guidelines of the 2013 Declaration of Helsinki and was approved by our Institutional Review Board.

Definitions

HCCs were diagnosed in the LR group by pathological methods and in the RFA group by pretreatment imaging modalities, including abdominal contrast-enhanced dynamic CT and Gd-EOB-DTPA enhanced MRI. On contrast-enhanced dynamic CT, HCCs appeared as early enhancement during the arterial phase and hypoattenuation during the portal venous or equilibrium phase. On Gd-EOB-DTPA enhanced MRI, HCC was defined as a nodular lesion with enhancement in the arterial phase and washout in the late phase or decreased uptake in the hepatobiliary phase. If a nodule did not completely fulfill the above criteria, a pretreatment biopsy was performed.

Table 1 Characteristics of the patients with BCLC stage 0 and A HCC and portal hypertension who underwent LR or RFA

Variables	LR group ($n = 81$)	RFA group ($n = 40$)	P value
Age (years) at enrollment	70.4 (53–85)	71.9 (58–87)	0.357
Sex			
Male	45 (55.6 %)	23 (57.5 %)	0.839
Female	36 (44.4 %)	17 (42.5 %)	
Etiology of hepatopathy			
HBsAg positive	8 (9.9 %)	2 (5.0 %)	0.340
Anti-HCVAb positive	61 (75.3 %)	29 (72.5 %)	0.740
Alcohol	9 (11.2 %)	4 (10.0 %)	0.852
NASH 1	(1.2 %)	2 (5 %)	0.229
Others	2 (2.4 %)	3 (7.5 %)	0.208
Esophageal varices	68 (84.0 %)	30 (75.0 %)	0.245
ASA status <3	73 (90.1 %)	36 (90.0 %)	0.983
Serum biochemistry			
Albumin (g/dL)	3.8 (2.7–4.7)	3.7 (2.7–4.7)	0.090
Total bilirubin (mg/dL)	0.8 (0.2–2.3)	1.1 (0.4–2.4)	0.027
AST (U/L)	47 (16–150)	45 (19–80)	0.956
ALT (U/L)	43 (14–245)	39 (14–105)	0.733
Creatinine (mg/dL)	0.8 (0.34–2.0)	0.9 (0.35–4.3)	0.735
Prothrombin activity (%)	85.9 (61–117)	82.5 (60–118)	0.126
Platelet count ($\times 10^4/\mu L$)	10.3 (4.6–24)	9.7 (3.8–33)	0.229
$ICGR_{15}$ (range %)	25.6 (5.6–68.7)	32.2 (9.5–83.4)	0.021
Splenomegaly with platelet count			
<10,0000/μL	34 (42.0 %)	21 (52.5 %)	0.275
Child-pugh score (points)	5.5 (5–8)	5.7 (5–9)	0.737
AFP (ng/mL)	132 (2.8–2340)	61 (3.3–283)	0.493
Maximum tumor diameter (cm)	2.1 (0.7–5)	1.4 (0.7–2.4)	<0.0001
Number of tumors	1.3 (1–3)	1.2 (1–3)	0.659
Intrahepatic tumor location			
S1/2/3/4/5/6/7/8 (n)	4/4/13/15/13/17/13/17	0/3/1/3/13/4/8/12	–
BCLC stage			
Stage 0	35 (43.2 %)	28 (70.0 %)	0.005
Stage A	46 (56.8 %)	12 (30.0 %)	

Values are expressed as percent, mean (range), or number

BCLC Barcelona clinic liver cancer, *HCC* hepatocellular carcinoma, *LR* liver resection, *RFA* radiofrequency ablation, *HBsAg* hepatitis B surface antigen *HCVAb* hepatitis C virus antibody, *ASA* American Society of Anesthesiologists physical status score, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, $ICGR_{15}$ indocyanine green retention test at 15 min, *AFP* alpha-fetoprotein

Major hepatectomy was defined as the resection of at least one subsegment. Minor resection, including partial resection, involved less than one subsegment. EVs were preoperatively classified according to the general rules based on endoscopic findings [20]. Serious postoperative complications were defined as Clavien–Dindo grade III or higher [21, 22].

Survival and recurrence

Patients underwent blood tests and CT every 3 months after LR or RFA. Recurrence was diagnosed based on imaging findings. Patients with intrahepatic distant recurrence or local recurrence were managed with ablative therapy, transcatheter arterial chemoembolization (TACE), surgery, microwave coagulation therapy under laparotomy, radiation, or best supportive care. In case of death, survival time after surgery and cause of death were recorded.

Statistical analysis

For continuous variables, the Wilcoxon rank-sum test was used for nonparametric analyses. Categorical variables were compared using the χ^2 test. The Kaplan–Meier

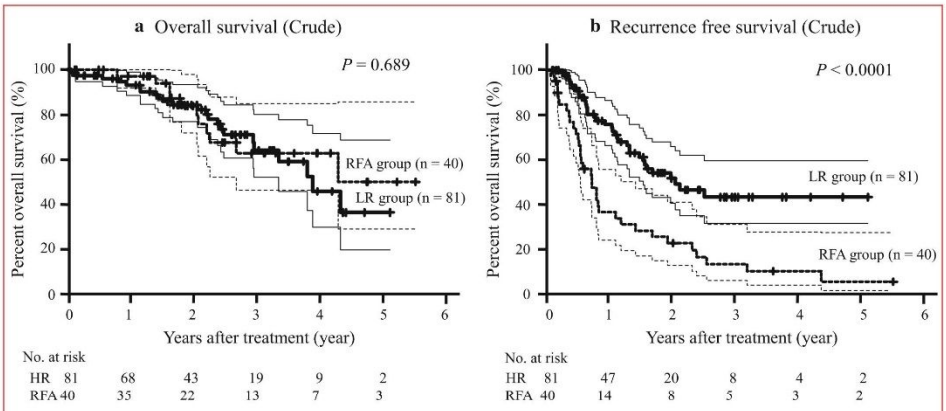

Fig. 1 Prognosis of 121 patients with BCLC stage 0 and A HCC and portal hypertension who underwent liver resection (LR group; $n = 81$) or radiofrequency ablation (RFA group; $n = 40$) therapy. **a** Unweighted (crude) Kaplan–Meier curve showing the percent overall survival (OS) after treatment. The OS of the LR group (*bold black line*) was comparable to that of the RFA group (*bold dotted line*, $P = 0.689$). **b** Unweighted (crude) Kaplan–Meier curve of recurrence-free survival (RFS) after treatment. The RFS of the LR group (*bold black line*) was significantly better than that of the RFA group (*bold dotted line* $P < 0.0001$). Each confidence interval of the OS and RFS were displayed using normal *black* and *dotted line*

method was used to construct overall survival (OS) and recurrence-free survival (RFS) curves. All survival curves were compared using log-rank tests. To identify independent factors of OS and RFS, the factors resulting in P values <0.2 on univariate analysis were subjected to multivariate analysis using a Cox proportional hazards model.

IPTW analysis was used to overcome possible bias in the different distributions of the covariates among the LR and RFA groups. Propensity scores from the IPTW analysis were calculated using a logistic regression model to predict the probability of each patient receiving LR or RFA on the basis of clinicopathological variables. After IPTW balancing of the two groups, the differences in the OS and RFS rates were tested by Cox regression analyses. Statistical significance was defined as a P value <0.05. Statistical analyses were performed using the R statistical programming environment and JMP 9.0 software (SAS Institute, Cary, NC, USA) [10].

Results

HCC diagnosis

All 104 nodules in the LR group (80 patients) were diagnosed as HCC by pathological methods. In the RFA group, 44 nodules in 36 patients were diagnosed as HCC based on contrast-enhanced dynamic CT and/or Gd-EOB-DTPA enhanced MRI, and eight nodules in five patients were diagnosed as HCC by pathological examination of pretreatment biopsy specimens.

Clinicopathological characteristics of patients with BCLC stage 0 and A HCC and PHT who underwent LR or RFA.

The preoperative background characteristics of the patients with HCC and PHT who underwent LR or RFA are summarized in Table 1. Compared with the RFA group, the LR group had a lower mean serum total bilirubin (0.8 vs. 1.1 mg/dL, $P = 0.027$), lower mean $ICGR_{15}$ (25.6 vs. 32.2 %, $P = 0.021$), and greater maximum tumor diameter (2.1 vs. 1.4 %, $P < 0.0001$). In the RFA group, in addition to the absence of tumors in S1, the proportion of right lobe tumors (S5, 6, 7, and 8; 84.1 %) was significantly higher than in the LR group (63.5 %; $P = 0.023$). Sixty-two patients underwent partial resection, 11 underwent subsegmentectomy, and four each underwent segmentectomy and lobectomy. Thus, 23.5 % of patients underwent major resection and 76.5 % underwent minor resection.

Crude OS and RFS (before IPTW adjustment)

The median follow-up after surgery was 24.6 months (range 0.8–65.7 months). There were no significant differences in the OS of LR and RFA patients ($P = 0.689$). The percentages at 1, 3, and 5 years were 93.4, 84.5, and 37.1 %, respectively, for the LR group and 97.2, 84.1, and

Table 2 Univariate and multivariate analyses of overall survival in all HCC patients with portal hypertension

Variables	Univariate analysis		Multivariate analysis	
	HR (95 % CI)	*P* value	HR (95 % CI)	*P* value
Age (per 1 year)	1.03 (0.99–1.08)	0.174	1.05 (1.00–1.10)	0.053
Sex: male/female	2.12 (1.02–4.82)	0.042	3.27 (1.48–7.84)	0.003
Treatment (RFA/LR)	0.86 (0.58–1.74)	0.687		
HBsAg positive	0.59 (0.10–1.97)	0.444		
Anti-HCVAb positive	1.76 (0.81–4.41)	0.219		
Esophageal varices (yes/no)	1.52 (0.64–4.50)	0.368		
ASA status <3 (yes/no)	1.33 (0.40–8.25)	0.679		
Serum biochemistry				
Albumin (g/dL)	0.45 (0.23–0.87)	0.017	4.97 (1.79–14.3)	0.003
Total bilirubin (mg/dL)	1.26 (0.62–2.37)	0.498		
AST (U/L)	1.00 (0.98–1.01)	0.806		
ALT (U/L)	0.99 (0.97–1.00)	0.124	0.99 (0.97–1.01)	0.314
Creatinine (mg/dL)	1.35 (0.39–2.74)	0.572		
Prothrombin activity (%)	0.99 (0.97–1.02)	0.654		
Platelet count ($\times 10^4/\mu L$)	0.94 (0.86–1.03)	0.205		
$ICGR_{15}$	1.01 (0.99–1.03)	0.250		
Child-Pugh score (points)	1.35 (0.91–1.94)	0.133	0.74 (0.40–1.32)	0.311
AFP (ng/mL)	1.00 (1.00–1.00)	0.067	1.00 (1.00–1.00)	0.066
Maximum tumor diameter (cm)	1.16 (0.78–1.64)	0.441		
Number of tumors	1.64 (0.82–2.92)	0.149	2.33 (1.15–4.26)	0.022
Postoperative serious complications				
(Clavien–Dindo ≥ III) yes/no	1.46 (0.43–3.76)	0.501		

HCC hepatocellular carcinoma, *HR* hazard ratio, *CI* confidence interval, *RFA* radiofrequency ablation, *LR* liver resection, *HBsAg* hepatitis B surface antigen *HCVAb* hepatitis C virus antibody, *ASA* American Society of Anesthesiologists physical status score, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, $ICGR_{15}$ indocyanine green retention test at 15 min, *AFP* alpha-fetoprotein

50.6 %, respectively, for the RFA group (Fig. 1a). By contrast, RFS at 1, 3, and 5 years was significantly better in the LR group than in the RFA group ($P < 0.0001$): 74.1, 48.8, and 42.9 % versus 36.1, 22.2, and 4.8 %, respectively (Fig. 1b).

The clinicopathological factors were evaluated to identify those associated with worse OS (Table 2). In univariate analyses, the *P* values for age, sex, serum albumin, serum ALT, Child–Pugh score, AFP, and number of tumors were <0.20. The inclusion of these seven variables in a multivariate Cox proportional hazards analysis showed that male sex [$P = 0.003$; hazard ratio (HR) 3.27; 95 % confidence interval (CI) 1.48–7.84], serum albumin value ($P = 0.003$; HR 24.7; 95 % CI 1.72–15.2), and number of tumors ($P = 0.022$; HR 2.33; 95 % CI 1.15–4.26) were independent predictors of worse OS.

The clinicopathological factors were also evaluated to identify those associated with worse RFS (Table 3). In univariate analyses, the P values for male sex, LR, anti-HCV antibody positivity, serum total bilirubin, serum ALT, $ICGR_{15}$, and number of tumors were <0.20. The inclusion of these seven variables in a multivariate Cox proportional hazards analysis showed that RFA ($P = 0.0004$; HR 2.56; 95 % CI 1.53–4.29) and number of tumors ($P = 0.019$; HR 1.93; 95 % CI 1.12–3.17) were independent predictors of worse RFS.

Postoperative complications and hospital stay

The 30-day postoperative complication rates in the LR and RFA groups were 46.9 and 12.5 % ($P < 0.0001$), respectively. In the LR group, one in-hospital death occurred secondary to sepsis. This group had a significantly higher rate of postoperative complications than the RFA group (46.9 vs. 12.5 %; $P < 0.0001$, Table 4) as well as a significantly higher rate of serious postoperative complications (Clavien–Dindo grade III or higher; 16.1 vs. 2.5 %; $P = 0.025$). Patients in the LR also had a significantly longer postoperative hospital stay (median 15 days; range 7–80 days) than the RFA group (median 8 days; range 2–29 days, $P < 0.0001$).

Table 3 Univariate and multivariate analyses of recurrence-free survival in all HCC patients with portal hypertension

Variables	Univariate analysis		Multivariate analysis	*P* value
	HR (95 % CI)	*P* value	HR (95 % CI)	
Age (per 1 year)	0.99 (0.96–1.02)	0.547		
Sex: male/female	1.39 (0.85–2.29)	0.188	1.46 (0.86–2.51)	0.161
Treatment (RFA/LR)	2.74 (1.70–4.43)	<0.0001	2.56 (1.53–4.29)	0.0004
HBsAg positive	0.88 (0.31–1.99)	0.780		
Anti-HCVAb positive	0.69 (0.42–1.19)	0.179	0.71 (0.41–1.27)	0.240
Esophageal varices (yes/no)	1.11 (0.62–2.13)	0.732		
ASA status <3 (yes/no)	1.17 (0.55–3.05)	0.699		
Serum biochemistry				
Albumin (g/dL)	1.07 (0.65–1.77)	0.791		
Total bilirubin (mg/dL)	1.44 (0.84–2.35)	0.177	0.76 (0.40–1.40)	0.378
AST (U/L)	0.99 (0.98–1.00)	0.223		
ALT (U/L)	0.99 (0.98–1.00)	0.062	0.99 (0.98–1.00)	0.080
Creatinine (mg/dL)	1.09 (0.62–1.61)	0.713		
Prothrombin activity (%)	1.01 (0.99–1.03)	0.498		
Platelet count ($\times 10^4/\mu L$)	1.01 (0.94–1.06)	0.821		
$ICGR_{15}$	1.01 (1.00–1.03)	0.113	1.01 (0.99–1.04)	0.209
Child-Pugh score (points)	0.96 (0.69–1.29)	0.791		
AFP (ng/mL)	1.00 (1.00–1.00)	0.222		
Maximum tumor diameter (cm)	0.93 (0.69–1.21)	0.613		
Number of tumors	1.65 (0.99–2.60)	0.054	1.93 (1.12–3.17)	0.019
Postoperative serious complications (Clavien–Dindo ≥ III) yes/no	0.93 (0.36–1.99)	0.869		

HCC hepatocellular carcinoma, *HR* hazard ratio, *CI* confidence interval, *LR* liver resection, *RFA* radiofrequency ablation, *HBsAg* hepatitis B surface antigen, *HCVAb* hepatitis C virus antibody, *ASA* American Society of Anesthesiologists physical status score, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, $ICGR_{15}$ indocyanine green retention test at 15 min, *AFP* alpha-fetoprotein

Recurrence pattern and treatment modalities after recurrence

At the time of data collection, tumor recurrence had developed in 34 of the 81 patients in the LR group: 33 (40.7 %) intrahepatic distant recurrences and 1 (1.2 %) local recurrence. In the RFA group, tumor recurrence had developed in 34 of the 40 patients: 27 (67.5 %) intrahepatic distant recurrences and 7 (17.5 %) local recurrences. The differences in intrahepatic distant recurrence and local recurrence were significant ($P = 0.0056$ and $P = 0.0007$, respectively).

Table 5 shows the treatment modalities after tumor recurrence in both groups of HCC patients with PHT. The most frequent treatment modality for patients in the LR and RFA groups with recurrent disease was TACE. Within the recurrence cohort, hepatic resection was significantly more frequent in the LR group than in the RFA group ($P = 0.031$), while the RFA group had a significantly higher frequency of repeat RFA (including RFA plus TACE) ($P = 0.0006$).

OS and RFS after IPTW adjustment

Among the 18 clinicopathological variables (age, sex, HBsAg, anti-HCV antibody, EVs, ASA status, albumin, total bilirubin, AST, ALT, creatinine, prothrombin activity, platelet count, $ICGR_{15}$, Child-Pugh score, AFP levels, maximum tumor diameter, and number of tumors), the distributive covariates that differed between the LR and RFA groups were total bilirubin, $ICGR_{15}$, and maximum tumor diameter (Table 1). After IPTW adjustment of these covariates, the weighted OS of the LR group was not significantly lower than that of the RFA group ($P = 0.485$, adjusted HR 1.35; 95 % CI 0.57–3.21; Fig. 2a). By contrast, the weighted RFS of the LR group remained significantly lower than that of the RFA group ($P = 0.00014$, adjusted HR 0.37; 95 % CI 0.22–0.61; Fig. 2b).

Subgroup analyses

As >70 % of patients in the original cohort were anti-HCV positive, subgroup analysis was performed. The 5-year OS

Table 4 Complications and mortality of early HCC patients with portal hypertension receiving LR or RFA

Variables	LR group (n = 81)	RFA group (n = 40)	*P* value
Complications	38 (46.9 %)	5 (12.5 %)	<0.0001
Clavien–Dindo classification			
Grade I			
Shoulder pain	0 (0.0 %)	1 (2.5 %)	
Ascites (treated with diuretics)	6 (7.4 %)	0 (0.0 %)	
Grade II			
Superficial surgical site infection	6 (7.4 %)	0 (0.0 %)	
Colitis	3 (3.7 %)	0 (0.0 %)	
Cholangitis	1 (1.2 %)	3 (7.5 %)	
Delirium	2 (2.5 %)	0 (0.0 %)	
Bile leakage (treated with antibiotics)	2 (2.5 %)	0 (0.0 %)	
Pneumonia 2	(2.5 %)	0 (0.0 %)	
Atrial fibrillation	1 (1.2 %)	0 (0.0 %)	
Deep vein thrombosis	1 (1.2 %)	0 (0.0 %)	
Urinary tract infection	1 (1.2 %)	0 (0.0 %)	
Grade IIIa			
Pleural effusion (requiring drainage)	1 (1.2 %)	1 (2.5 %)	
Deep surgical site infection	5 (6.0 %)	0 (0.0 %)	
Bile leakage (requiring drainage)	3 (3.7 %)	0 (0.0 %)	
Grade IVa			
Liver failure	2 (2.5 %)	0 (0.0 %)	
Grade V			
Sepsis	1 (1.2 %)	0 (0.0 %)	
Postoperative serious complications			
(Clavien–Dindo grade III or higher)	13 (16.1 %)	1 (2.5 %)	0.025
Mortality	1 (1.2 %)	0 (0.0 %)	

HCC hepatocellular carcinoma, *LR* liver resection, *RFA* radiofrequency ablation

rates in anti-HCV patients who underwent LR (29.6 %) and RFA (56.1 %) were comparable, whereas the 5-year RFS rate was significantly higher in the LR than in the RFA group (46.2 vs. 0 %, $P < 0.0001$). IPTW analysis showed that OS did not differ significantly in the LR and RFA groups ($P = 0.7258$, adjusted hazard ratio [aHR] 1.182; 95 % confidence interval [CI] 0.45–3.1), whereas RFS was significantly higher in the LR than in the RFA group ($P < 0.0001$, aHR 0.32; 95 % CI 0.18–0.56).

The LR and RFA groups also differed significantly in the percentages with BCLC stages 0 and A (Table 1). Crude analyses showed that 5-year RFS was significantly higher in BCLC 0 ($P = 0.0002$, Fig. 3a) and A ($P = 0.036$, Fig. 3b) patients who underwent LR than RFA. IPTW analyses of the BCLC 0 and A groups also showed that 5-year RFS was significantly higher with LR than with RFA in BCLC stage 0 ($P = 0.0017$, aHR 0.25; 95 % CI 0.12–0.51; Fig. 4a). RFS was also significantly better in the LR than in the RFA group in BCLC stage A ($P = 0.040$, aHR 0.45; 95 % CI 0.22–0.93; Fig. 4b).

Discussion

Neither the BCLC nor the AASLD Group guidelines recommend LR for patients with BCLC stage 0 or A HCC and PHT; however, for these patients the guidelines do recommend RFA or liver transplantation. In patients with cirrhosis and/or PHT and disease extent within the Milan criteria, liver transplantation is clearly the best option [23]. But given the serious shortage of available liver transplant donor organs [8], surgical resection may be the next best option for the treatment of some HCC patients with clinical PHT [9]. The major drawback in these recommendations is that they were formulated in the absence of a control, nonsurgical treatment group that could be compared with the group of HCC patients with PHT who underwent surgical resection.

To date, there have been only a few studies comparing the outcome of patients with BCLC stage 0 and A HCC and PHT who underwent LR vs. RFA. In a recent report, LR was shown to be a safe procedure for patients with HBV-

Table 5 Recurrence pattern and treatment modalities of HCC patients with portal hypertension who underwent LR or RFA

Variables	LR group ($n = 81$)	RFA group ($n = 40$)	P value
Recurrence	34	34	<0.001
Intrahepatic distant recurrence	33 (40.7 %)	27 (67.5 %)	0.0056
TACE	19 (23.4 %)	10 (25.0 %)	
TACE and RFA	0	2 (5.0 %)	
TACE and liver resection	0	0	
RFA	2 (2.5 %)	9 (22.5 %)	
Liver resection	10 (12.3 %)	2 (5.0 %)	
MCT under laparotomy	2 (2.5 %)	1 (2.5 %)	
Radiation	0	1	(2.5 %)
Best supportive care	0	2 (5.0 %)	
Local recurrence	1 (1.2 %)	7 (17.5 %)	0.0007
TACE	0	2 (5.0 %)	
TACE and RFA	0	0	
TACE and liver resection	0	1 (2.5 %)	
RFA	0	3(7.5 %)	
Liver resection	0	0	
MCT under laparotomy	0	0	
Radiation	0	0	
Best supportive care	1 (1.2 %)	1 (2.5 %)	

HCC hepatocellular carcinoma, *LR* liver resection, *RFA* radiofrequency ablation, *TACE* transarterial chemoembolization, *MCT* microwave coagulation therapy

related PHT and it conferred a survival advantage over ablation. Thus, LR may be recommended as an optimal form of treatment for these patients [24].

In the present study, LR resulted in a significantly better RFS than achieved with RFA for patients with BCLC stage 0 or A HCC and PHT. However, in clinical studies, bias often arises in the selection of patients with BCLC stage 0 and A HCC, because those with PHT may prefer minimally invasive treatment, and thus RFA rather than LR. To reduce the potential for bias in patient selection, an IPTW analysis was conducted. A comparison of the background characteristics of the two group showed that the RFA group had significantly higher serum total bilirubin level and $ICGR_{15}$ and a smaller maximum tumor diameter than the LR group. These results implied that our BCLC stage 0 or A HCC patients with PHT who underwent RFA had more severe liver dysfunction than the patients in the LR group. Patients in the latter had a greater maximum tumor diameter than those in the RFA group. Thus, some patients with slightly better liver function [25] and a greater maximum tumor diameter [19, 26] may be candidates for LR. Using data from the BRIDGE study, Roayaie et al. clearly demonstrated that safe hepatic resection with excellent outcomes is possible for patients with moderate PHT or for those with slightly elevated bilirubin, but not both [27].

The reason for the better RFS of the LR group than the RFA group is unclear; however, at least in theory, LR has the advantage of offering better local control of HCC, whereas RFA carries with it the potential risk of local recurrence associated with insufficient ablation [26]. Moreover, about one-fourth of the patients in the LR group underwent anatomical resection to remove minute tumor satellites [28], which might have decreased the intrahepatic recurrence rate compared with the RFA group. Based on the tumor location data, no patients with S1 tumors underwent RFA, which suggests that LR, but not RFA, can be performed regardless of tumor location.

Despite significant differences in recurrence rates, survival rates were similar in the LR and RFA groups. Patients were followed-up every 3 months after RFA treatment, enabling the early detection of recurrence and more rapid and appropriate treatment with surgical or interventional methods. As a result, the high HCC recurrence rate in the RFA group did not markedly increase the death rate.

In addition, there are several limitations to the use of RFA based on the location of the tumor(s). Specifically, in patients with tumors overhanging the liver margin and approaching adjacent organs such as the gallbladder, stomach, or colon, or tumors located near major intrahepatic vessels, RFA may be technically unfeasible owing to the risk of thermal injuries to these structures [29]. In our study, all ablation procedures were performed in our hospital by one of the two experienced hepatologists, each

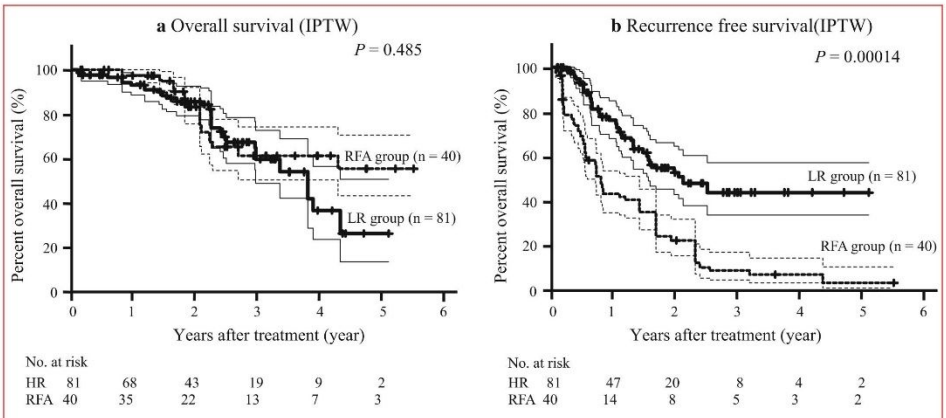

Fig. 2 **a** Kaplan–Meier curve after inverse probability treatment weighting (IPTW) showing OS after treatment. The percent OS of the LR group (*bold black line*) was comparable to that of the RFA group (*bold dotted line*, $P = 0.485$). **b** Kaplan–Meier curve after IPTW showing RFS after treatment. The RFS of the LR group (*bold black line*) was significantly better than that of the RFA group (*bold dotted line*, $P = 0.00014$). Each confidence interval of the OS and RFS were displayed using normal *black* and *dotted line*

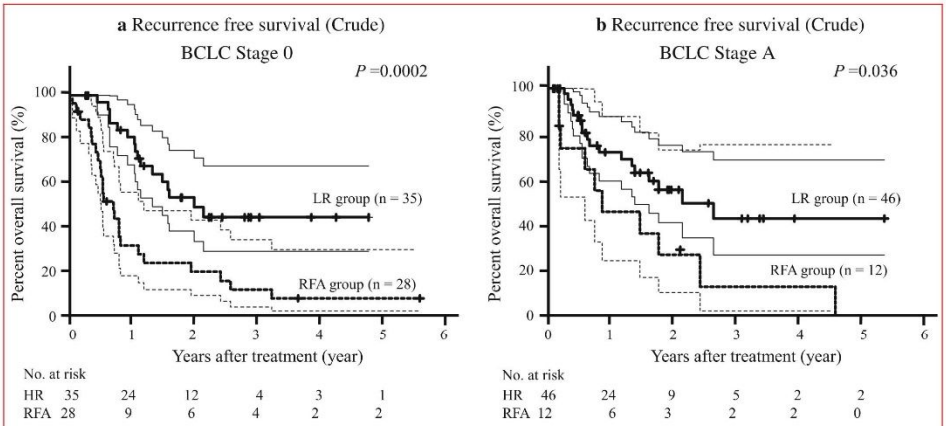

Fig. 3 Prognosis of patients with BCLC stage 0 ($n = 63$) and A ($n = 58$) HCC and portal hypertension who underwent liver resection or radiofrequency ablation therapy. **a** Unweighted (crude) Kaplan–Meier curve showing the percent RFS after treatment. The RFS of the LR group ($n = 35$; *bolded black line*) was significantly better than that of the RFA group ($n = 28$, *bold dotted line*, $P = 0.0002$) in BCLC stage 0. **b** Unweighted (crude) Kaplan–Meier curve of RFS after treatment. The RFS of the LR group ($n = 46$; *bold black line*) was significantly better than that of the RFA group ($n = 12$; *bold dotted line*, $P = 0.036$) in BCLC stage A. Each confidence interval of the RFS were displayed using normal *black* and *dotted line*

with at least 10 years of experience in RFA. Nonetheless, the local recurrence rate was 17.5 %. In a previous study, local recurrence rates ranged from 0.9 to 33.3 %; in cirrhotic patients, they were as high as 46.2 % [30]. Thus, local recurrence remains a challenging issue in cirrhotic patients with PHT who have been treated with RFA.

Our study showed that RFA was associated with fewer postoperative complications and shorter hospital stays

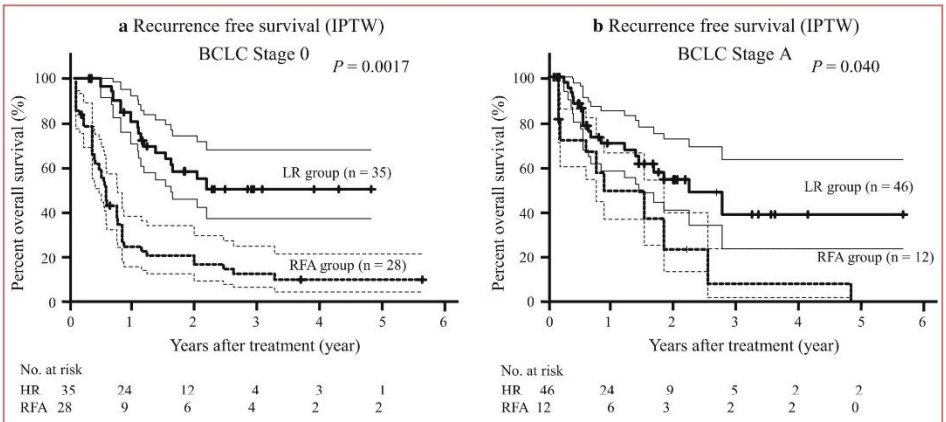

Fig. 4 a Kaplan–Meier curve after inverse probability treatment weighting (IPTW) showing RFA after treatment. The percent RFA of the LR group ($n = 35$; *bold black line*) was significantly better than that of the RFA group ($n = 28$; *bold dotted line*, $P = 0.0017$) in BCLC stage 0. b Kaplan–Meier curve after IPTW showing RFS after treatment. The RFS of the LR group (n = 46; *bold black line*) was significantly better than that of the RFA group ($n = 12$; *bold dotted line*, $P = 0.040$) in BCLC stage A. Each confidence interval of the OS and RFS were displayed using normal *black* and *dotted line*

after treatment. These results are in agreement with those of a previous meta-analysis comparing RFA and LR [31]. LR is a more invasive treatment than RFA and requires careful intraoperative management of hemostasis and the endoscopic treatment of EVs [9]. Similarly, HCC patients with PHT require meticulous postoperative management and treatment should be carried out only in specialized high-volume centers [5].

There were several limitations to our study. First, the sample size was relatively small, which made it difficult to evaluate the outcome of HCC patients with BCLC stage 0 and A disease and PHT who underwent LR or RFA. However, unlike in other studies, tumor location, surgical procedure, postoperative complications, and treatment after recurrence were evaluated in detail. Second, our study results might not be applicable in other centers because ours was a single-center study and our study was not an randomized controlled trial.

Despite these limitations, our findings contribute to validating the current BCLC and AASLD criteria by providing additional clinical evidence subjected to IPTW analysis to compare LR and RFA. In the study by Roayaie et al. [27], only one-third of the 2342 patients undergoing LR fulfilled the criteria for this procedure.

In conclusions, our results suggest that, by caring for postoperative complications, LR is an appropriate treatment option for patients with BCLC stage 0 or A HCC and PHT.

Acknowledgments The authors thank Dr. M. Fujiwara at the Hiroshima Red Cross Hospital and Atomic Bomb Survivor Hospital for diagnosing the pathological characteristics of HCC.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Forner A, Reig ME, Bruix J et al (2010) Current strategy for staging and treatment: the BCLC update and future prospects. Semin Liver Dis 30(1):61–74
2. Bruix J, Sherman M, American Association for the Study of Liver Diseases (2011) Management of hepatocellular carcinoma: an update. Hepatology 53(3):1020–1022
3. Bruix J, Castells A, Rodés J et al (1996) Surgical resection of hepatocellular carcinoma in cirrhotic patients: prognostic value of preoperative portal pressure. Gastroenterology 111(4):1018–1022
4. Llovet JM, Brú C, Bruix J (1996) Prognosis of hepatocellular carcinoma: the BCLC staging classification. Semin Liver Dis 19(3):329–338
5. Ishizawa T, Kokudo N, Makuuchi M et al (2008) Neither multiple tumors nor portal hypertension are surgical contraindications for hepatocellular carcinoma. Gastroenterology 134(7):1908–1916
6. Cucchetti A, Ercolani G, Pinna AD et al (2009) Is portal hypertension a contraindication to hepatic resection? Ann Surg 250(6):922–928
7. Capussotti L, Ferrero A, Bouzari H et al (2006) Portal hypertension: contraindication to liver surgery? World J Surg 30(6):992–999. doi:10.1007/s00268-005-0524-9

8. Dutkowski P, Müllhaupt B, Clavien PA et al (2014) Challenges to liver transplantation and strategies to improve outcomes. Gastroenterology 148:307–323
9. Harada N, Shirabe K, Maehara Y et al (2015) Surgical resection for hepatocellular carcinoma with concomitant esophageal varices. World J Surg 39:2510–2518. doi:10.1007/s00268-015-3110-9
10. Austin PC (2012) The performance of different propensity score methods for estimating marginal hazard ratios. Stat Med 32:2837–2849
11. Bezerra AS, D'Ippolito G, Ahmed M et al (2005) Determination of splenomegaly by CT: is there a place for a single measurement? AJR Am J Roentgenol 184(5):1510–1513
12. Shirabe K, Takeishi K, Maehara Y et al (2011) Improvement of long-term outcomes in hepatitis C virus antibody-positive patients with hepatocellular carcinoma after hepatectomy in the modern era. World J Surg 35:1072–1084. doi:10.1007/s00268-011-1013-y
13. Yamashita YI, Shirabe K, Maehara Y et al (2014) Trends in surgical results of hepatic resection for hepatocellular carcinoma: 1,000 consecutive cases over 20 years in a single institution. Am J Surg 13:522–529
14. Takeishi K, Shirabe K, Maehara Y et al (2011) Clinicopathological features and outcomes of young patients with hepatocellular carcinoma after hepatectomy. World J Surg 35(5):1063–1071. doi:10.1007/s00268-011-1017-7
15. Pugh RN, Pietroni MC, Williams R et al (1973) Transection of the oesophagus for bleeding oesophageal varices. Br J Surg 60(8):646–649
16. Chau GY, King KL, Wu CW et al (2005) Evaluation of effect of hemihepatic vascular occlusion and the Pringle maneuver during hepatic resection for patients with hepatocellular carcinoma and impaired liver function. World J Surg 29(11):1374–1383. doi:10.1007/s00268-005-7766-4
17. Kawamura H, Kamiyama T, Todo S et al (2008) Preoperative evaluation of hepatic functional reserve by converted ICGR15 calculated from Tc-GSA scintigraphy. J Gastroenterol Hepatol 23(8 Pt 1):1235–1241
18. Rhim H, Lim HK, Choe BK et al (2010) Ultrasonography-guided percutaneous radiofrequency ablation of hepatocellular carcinomas: a feasibility scoring system for planning sonography. Eur J Radiol 75(2):253–258
19. Waki K, Aikata H, Chayama K et al (2010) Percutaneous radiofrequency ablation as first-line treatment for small hepatocellular carcinoma: results and prognostic factors on long-term follow up. J Gastroenterol Hepatol 25(3):597–604
20. Tajiri T, Yoshida H, Idezuki Y et al (2010) General rules for recording endoscopic findings of esophagogastric varices (2nd edition). Dig Endosc 22(1):1–9
21. Dindo D, Demartines N, Clavien PA (2004) Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 240(2):205–213
22. Rahbari NN, Garden OJ, Weitz J et al (2011) Posthepatectomy liver failure: a definition and grading by the International Study Group of Liver Surgery (ISGLS). Surgery 149(5):713–724
23. Jarnagin WR (2010) Management of small hepatocellular carcinoma: a review of transplantation, resection, and ablation. Ann Surg Oncol 17(5):1226–1233
24. Qiu J, Zheng Y, Yuan Y et al (2015) Resection versus ablation in hepatitis B virus-related hepatocellular carcinoma patients with portal hypertension: A propensity score matching study. Surgery 158:1235–1243
25. Kokudo N (2015) Is it a time to modify the BCLC guidelines in terms of the role of surgery? World J Surg 39(2):469–470. doi:10.1007/s00268-014-2915-2
26. Cammà C, Di Marco V, Craxì A et al (2005) Unità Interdipartimentale Neoplasie Epatiche (U.I.N.E) Group. Treatment of hepatocellular carcinoma in compensated cirrhosis with radiofrequency thermal ablation (RFTA): a prospective study. J Hepatol 42(4):535–540
27. Roayaie S, Jibara G, Sherman M et al (2015) The role of hepatic resection in the treatment of hepatocellular cancer. Hepatology 62:440–451
28. Makuuchi M, Hasegawa H, Yamazaki S (1985) Ultrasonically guided subsegmentectomy. Surg Gynecol Obstet 161(4):346–350
29. Fonseca AZ, Santin S, Ribeiro MA Jr et al (2014) Complications of radiofrequency ablation of hepatic tumors: Frequency and risk factors. World J Hepatol 6(3):107–113
30. Bertrand J, Caillol F, Giovannini M et al (2015) Percutaneous hepatic radiofrequency for hepatocellular carcinoma: results and outcome of 46 patients. Hepat Med 7:21–27
31. Duan C, Ma K, Bie P (2013) Radiofrequency ablation versus hepatic resection for the treatment of early-stage hepatocellular carcinoma meeting Milan criteria: a systematic review and meta-analysis. World J Surg Oncol 11(1):190