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Resection or ablation versus transarterial therapy for Child-Pugh A patients with a single small hepatocellular carcinoma

Young Ju Suh, PhD[c], Young-Joo Jin, MD, PhD[a,b,*], Yujin Jeong, MS[d], Woo Young Shin, MD, PhD[e], Jeong-min Lee, MD[f], Soongu Cho, MD, PhD[f], Jung Hwan Yu, MD, PhD[a,b], Jin-Woo Lee, MD, PhD[a,b]

Abstract

Data from a direct comparison of the long-term survival outcomes of surgical resection (SR) or radiofrequency ablation (RFA) versus transarterial therapy in Child-Turcotte-Pugh (CTP)-class A patients with a single small T1/T2 stage hepatocellular carcinoma (HCC) (≤3 cm) are still lacking. This study retrospectively compared the therapeutic outcomes of these treatment types for CTP-A patients with a single small HCC.

Using a nationwide Korean registry, we identified 2314 CTP-A patients with SR (n = 722), RFA (n = 731), or transarterial therapy (n = 861) for a single (≤3 cm) T1/T2 stage HCC from 2008 to 2014. The posttreatment overall survival (OS) of transarterial therapy with either SR or RFA were compared using the Inverse Probability of treatment Weighting (IPW). The median follow-up period was 50 months (range 1–107 months).

After IPW, the cumulative OS rates after SR or RFA were significantly higher than those after transarterial therapy in all subjects (all *P* values < .05). The OS rates after SR or RFA were better than those after transarterial therapy in patients with the hepatitis B or C virus (all *P* values < .05), and in patients aged <65 years (all *P* values < .05). The cumulative OSs between RFA and transarterial therapy were statistically comparable in patients with a 2 to 3 cm HCC and aged ≥65 years, respectively. For all subjects, the weighted Cox proportional hazards model using IPW provided the adjusted hazard ratios (95% confidence interval) for the OS after SR versus transarterial therapy and after RFA versus transarterial therapy of 0.42 (0.30–0.60) (*P* < .001) and 0.78 (0.61–0.99) (*P* = .044), respectively.

In CTP-A patients with a single (≤3 cm) T1/T2 HCC, SR or RFA provides a better OS than transarterial therapy, regardless of the HCC etiology (hepatitis B virus or hepatitis C virus), especially in patients with HCC of <2 cm and aged <65 years.

Abbreviations: AFP = alpha-fetoprotein, BMI = body mass index, CI = confidence interval, CTP = Child-Turcotte-Pugh, DM = diabetes mellitus, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, HR = hazard ratio, HTN = hypertension, IPW = Inverse Probability of treatment Weighting, KCCR = Korea Central Cancer Registry, LT = liver transplantation, OS = overall survival, PS = propensity score, PT = prothrombin time, RCTs = randomized controlled trials, RFA = radiofrequency ablation, SR = surgical resection, TACE = transarterial chemoembolization, TACL = transarterial chemolipidolization.

Keywords: hepatocellular carcinoma, overall survival, radiofrequency ablation, single (≤3 cm), surgical resection, transarterial therapy

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[a] Department of Internal Medicine, Inha University Hospital, Inha University School of Medicine, Incheon, South Korea, [b] The Korean Liver Cancer Study Group, South Korea, [c] Department of Biomedical Sciences, College of Medicine, Inha University, Incheon, South Korea, [d] Department of Biostatistics, Korea University, Seoul, South Korea, [e] Department of Surgery, Inha University Hospital, Inha University School of Medicine, Incheon, South Korea, [f] Department of Radiology, Inha University Hospital, Inha University School of Medicine, Incheon, South Korea.

[*] Correspondence: Young-Joo Jin, Department of Internal Medicine, Inha University Hospital, Inha University School of Medicine, 27 Inhang-ro, Jung-gu, Incheon 22332, South Korea (e-mail: jyj412@hanmail.net).

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1. Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer globally and the second most common cause of cancer-related death.[1] Many HCCs have been diagnosed at an early stage due to advances in diagnostic imaging methods[2] or the introduction of active HCC surveillance strategies in high-risk populations.[2–5] Liver transplantation (LT), surgical resection (SR), and radiofrequency ablation (RFA) are the recommended curative treatments for early-stage HCC. On the other hand, LT is administered to a limited number of patients because of the shortage of liver donors. Thus, SR is considered the first-line treatment for early HCC in non-cirrhotic patients.[2–4,6] Nonetheless, not all patients with early HCC can undergo SR for various reasons, such as the risk of impaired liver function after SR.[7] RFA is an effective treatment for small-sized single HCC,[8–11] but can be difficult to apply in some patients when the tumor is close to the adjacent organs, main blood vessels or bile duct, or liver capsules.[2–4,12] As such, LT, SR, or RFA is sometimes ineligible even in early HCC, and transarterial chemoembolization (TACE) is administered frequently in these cases.

TACE is now the preferential treatment for intermediate-stage HCCs.[2–4] Recently, several studies have suggested that TACE may be an alternative treatment in some patients with early HCC.[13–15] On the other hand, these retrospective studies were performed on patients with multiple tumors,[13–15] a large tumor (>3 cm),[13,14] or of Child-Turcotte-Pugh (CTP)-class B.[13,14] In another retrospective study, TACE provided good survival outcomes, which were similar to those of SR or RFA in small nodular HCC,[16] but this study involved a relatively small number of patients treated at a single-center and included the CTP-class B cases. In order to more accurately evaluate the role of TACE compared to SR or RFA in early HCC, it is necessary to analyze large-scale patients under uniform criteria. Regarding the comparison of the outcomes of SR and RFA, 3 randomized controlled trials (RCTs)[17–19] and meta-analysis[20] were already conducted in early staged HCC within the Milan criteria. However, until now, direct comparison data on long-term survival outcomes of SR or RFA versus TACE are still lacking especially in CTP-class A patients with a single small T1/T2 stage HCC (≤3 cm).

Therefore, we performed a large-scale nationwide cohort study using the Inverse Probability of treatment Weighting (IPW) based on the propensity score (PS) estimates[21] to compare the long-term therapeutic outcomes between SR or RFA and transarterial therapy in CTP-class A patients with a single small (≤3 cm) T1/T2 staged HCC. In addition, this study also evaluated whether the treatment outcomes between the treatment groups can vary according to the demographic differences, such as HCC etiology (hepatitis B virus [HBV] or hepatitis C virus [HCV]) or patient age (<65 or ≥65 years).

2. Materials & methods

2.1. Study subjects

Patient data were abstracted from the nationwide Korea Central Cancer Registry (KCCR) in South Korea using C22.0 based on the International Classification of Disease 10th edition coding system. Using the random sample audit method, 83,231 patients registered in the KCCR from 2008 to 2014 were assessed, and, of these, after taking into account an additional 3% sampling error, 10,811 (13%) patients were randomly abstracted for initial data construction. Of these, 10,578 patients had clinically available data on HCC tumor status (Fig. 1).

However, of the 10,578 patients, those with no available data on T stage (n=77), CTP-class (n=465), or treatment type (n=167), or those with an age of <18 years (n=6) were excluded.

In order to compare the treatment outcomes according to the treatment method and to exclude the confounding effect by residual liver function of HCC patients, only CTP-class A patients were selected in the present study. Of the remaining 9863 patients, those with CTP-class B or C (n=2726), T3 or T4 stage (n=1652), T2 with multiple tumors (n=1239), T1/T2 HCC with a tumor size of >3 cm (n=1775), or T1/T2 HCC with a metastasis (n=25) were also excluded. In addition, 132 patients who received treatments other rather than SR, RFA, or TACE/transarterial chemolipidolization (TACL) were excluded. Finally, 2314 patients with a single small (≤3 cm) T1 or T2 staged HCC of CTP-class A and treated by SR (SR group, n=722), RFA (RFA group, n=731), or TACE(L) (transarterial group, n=861) were enrolled in this retrospective cohort study (Fig. 1). The transarterial group included 231 HCC patients who underwent TACL because posttreatment survival was similar in patients who received TACE and TACL in the present study (Figure S1, Supplemental Digital Content, http://links.lww.com/MD2/A562).

HCC was histologically proven or clinically diagnosed based on the criteria issued by the American Association for the Study for Liver Diseases guideline.[3] None of the patients recruited had been previously treated for HCC. T stage was determined using the American Joint Committee on Cancer 7th TNM staging system.[22] Tumor size was recorded as the greatest diameter of tumor lesions in at least 1 dimension on liver dynamic computed tomography or magnetic resonance images. The mortality data were obtained from the Korean National Statistics Office. The follow-up duration was defined as the time from initial treatment date to death date or to December 31, 2016. The study was approved by the Institutional Review Board of Inha University Hospital, Incheon, South Korea (Approval number: INHAUH 2020-03-041).

2.2. Statistical analyses

The primary study outcome was the overall survival (OS) differences between the SR or RFA groups and transarterial group. The secondary outcomes were the OS differences between the comparison groups in the HBV- and HCV-associated patients, respectively, and in patients aged <65 and ≥65 years, respectively.

The baseline clinical characteristics are presented as the mean (±standard deviations) or numbers (percentages). The differences in the categorical or continuous variables among the 3 groups were analyzed using the ANOVA or the chi-square test, as appropriate. We performed the post-hoc test when the overall P values were <.05 of the variable among 3 groups. For the post-hoc test, Dunnett test (SR vs transarterial groups and RFA vs transarterial groups) was used for the continuous variables, and Fisher exact test with adjustments by permutation resampling was used for the categorical variables.

To reduce possible imbalances between the distributions of baseline clinical characteristics in comparison groups, we used IPW, which is based on the PS analysis.[21] The PS scores of the 3 different treatment groups were estimated by predicting the

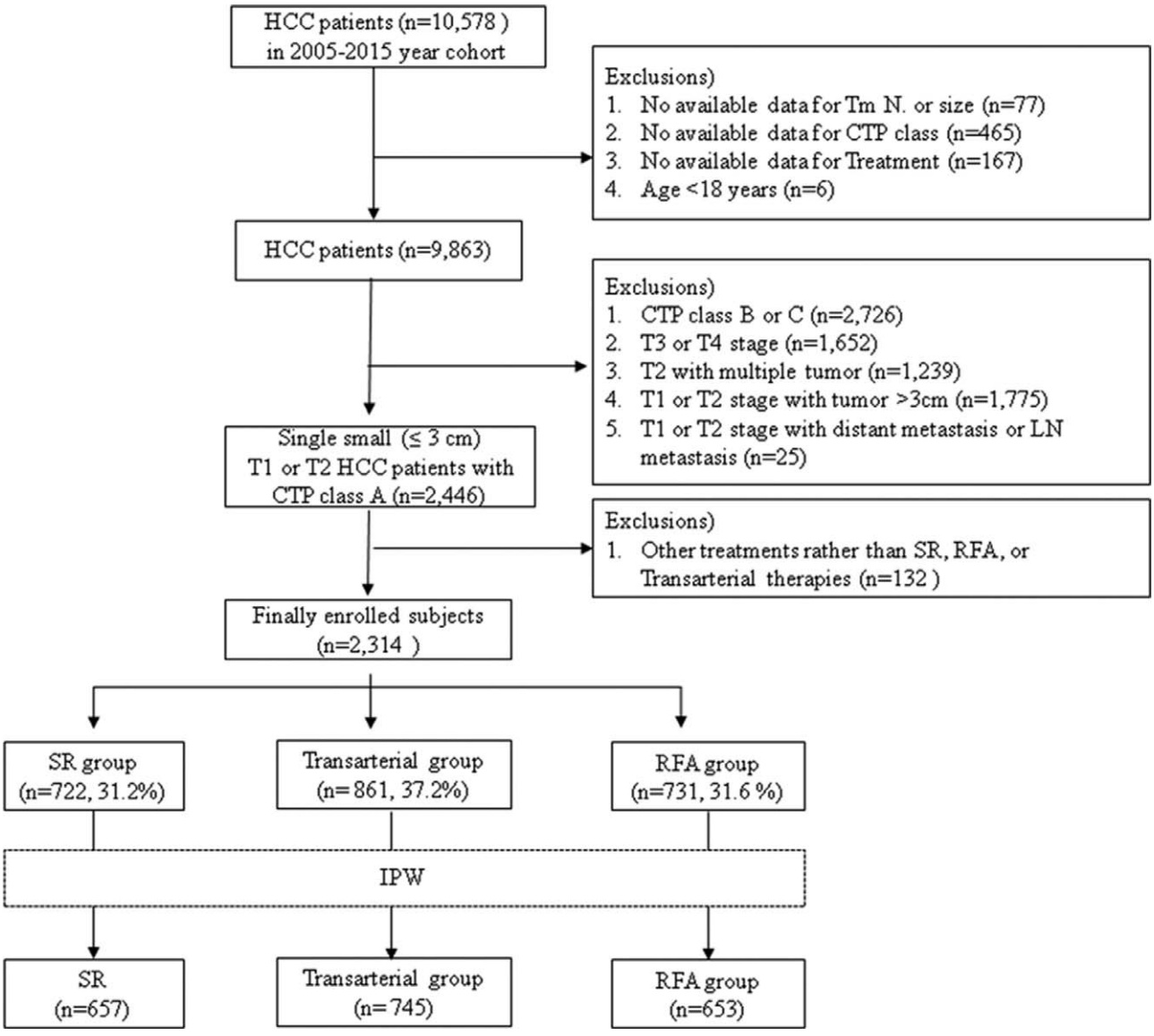

Figure 1. Flow diagram of all patients enrolled (n=2314).

probability of each subject receiving a particular treatment using a multinomial logistic regression model. In the model for the 3 groups, covariates, such as the body mass index (BMI), comorbidities of diabetes mellitus (DM) or hypertension (HTN), HCC etiology (HBV, HCV, or others), serum albumin, serum total bilirubin, PT (prothrombin time) (international normalized ratio), platelet count, alpha-fetoprotein (AFP) level, and tumor size were considered.

The IPW was calculated using the inverse of the PS score for each different treatment group. We used the stabilized IPW[23] to reduce the large variance calculated by multiplying the IPW by the marginal probability of receiving the given treatment. After considering the IPW, this study confirmed that the distribution was balanced using the absolute standardized differences between the group pairs. The balance was considered to have been achieved when the absolute standardized difference between the group pairs was ≤ 0.1. If there was a variable with an absolute standardized difference greater than 0.1, the effects of this variable were additionally adjusted when analyzing the weighted Cox proportional hazards model using IPW. This model was used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) for mortality. The posttreatment OS rates were estimated using the weighted Cox proportional hazards model with IPW. Two-tailed P values of $<.05$ were considered statistically significant. The statistical analyses were performed using SAS v 9.4 (SAS Institute Inc., Cary, NC) and SPSS v 19.0 (SPSS Inc., Chicago, IL).

3. Results

3.1. Baseline characteristics of the study subjects

The baseline clinical characteristics of all study subjects before IPW are shown in Table 1. Before IPW, 722, 731, and 861 patients were enrolled in the SR, RFA, and transarterial groups, respectively. The SR group showed a younger patient age

Table 1

Baseline clinical characteristics of all study subjects before IPW.

Variables	SR group (n = 722)	RFA group (n = 731)	Transarterial group (n = 861)	P‡
Age, category, n (%)	a	b	b	<.001
≥65 yrs	154/722 (21.3)	262/731 (35.8)	346/861 (40.2)	
<65 yrs	568/722 (78.7)	469/731 (64.2)	515/861 (70.3)	
Gender, male, n (%)	548/722 (75.9)	525/731 (71.8)	605/861 (70.3)	.160
BMI (kg/m^2)*	23.9 ± 2.8[a]	24.3 ± 3.4[b]	24.4 ± 3.3[b]	.011
HTN, presence, n (%)	220/718 (30.6)	258/729 (35.4)	309/858 (36.0)	.045
DM, presence, n (%)	148/719 (20.6)	187/730 (25.6)	226/857 (26.4)	.038
Etiology, n (%)				.884
HBV	543/722 (75.2)[a]	434/731 (59.4)[b]	514/861 (59.7)[b]	<.001
HCV	48/722 (6.6)[a]	115/731 (15.7) [b]	128/861 (14.9)[b]	<.001
Others (reference)	131/722 (18.1)	182/731 (24.9)	219/861 (25.4)	
Albumin (g/dL)*	4.2 ± 0.4[a]	4.1 ± 0.4[b]	3.9 ± 0.5[c]	<.001
Bilirubin (mg/dL)	0.9 ± 0.4[a]	0.9 ± 0.4[b]	0.9 ± 0.5[b]	<.001
PT, INR*	1.1 ± 0.1[a]	1.1 ± 0.1 [b]	1.1 ± 0.1[c]	<.001
PLT (×10^3/uL)*	150 ± 54[a]	127 ± 58[b]	122 ± 58[b]	<.001
AFP (ng/dL)*	345 ± 1212	230 ± 3219	371 ± 5006	.245
Tm size, category, n (%)	a	b	c	<.001
<2cm	226/861 (31.3)	478/731 (65.4)	431/861 (50.1)	
≤2 cm and ≤3cm	496/722 (68.7)	253/731 (34.6)	430/861 (49.9)	
FU duration (month)†	51 (1–106)	52 (3–107)	48 (1–107)	.001

AFP = alpha-fetoprotein, BMI = body mass index, DM = diabetes mellitus, FU = follow-up, HBV = hepatitis B virus, HCV = hepatitis C virus, HTN = hypertension, INR = international normalized ratio, IPW = Inverse Probability of treatment Weighting, PLT = platelet, PT = prothrombin time, RFA = radiofrequency ablation, SR = surgical resection, Tm = tumor.

* Mean (±standard deviation).

† Median (range).

‡ *P* values were calculated using the ANOVA or the chi-square test, and we performed post-hoc test when overall *P* value <.05 of variable among 3 groups. Different letters (a, b, and c) stand for significant difference between 2 groups (comparing with transarterial group) at the 0.05 level. Dunnett post-hoc test was performed for continuous variable and Fisher exact test with adjustments by permutation resampling was done for categorical variable.

(*P* < .001); lower BMI (*P* = .011), bilirubin (*P* < .001), and PT level (*P* < .001); and smaller tumor size (*P* < .001); and higher albumin level (*P* < .001) and platelet count (*P* < .001) than the RFA or transarterial groups. In addition, HTN (*P* = .045) and DM (*P* = .038) were less common in the SR group. The RFA group showed higher albumin and PT levels and smaller tumor size than the transarterial group, but age, BMI, HCC etiologies, serum bilirubin level, and platelet count were not significantly different between the RFA and transarterial groups. The frequency of males and the serum AFP levels were not significantly different among the 3 groups. The median follow-up durations of the SR, RFA, and transarterial groups were 51 months (range, 1–106 months), 52 months (3–107 months), and 48 months (range, 1–107 months), respectively (*P* = .001) (Table 1).

3.2. OS rates of all HCC patients before IPW adjustment

Before IPW, 87 (12.0%), 196 (26.8%), and 354 (41.1%) patients of the SR, RFA, and transarterial groups died respectively, during the median follow-up of 51, 52, and 48 months, respectively. The cumulative OS rates at 2, 4, 6, and 8 years were 96.7%, 89.7%, 85.7%, and 80.2%, respectively, in the SR group, 93.8%, 81.5%, 65.3%, and 57.3%, respectively, in the RFA group; and 84.6%, 68.2%, 54.6%, and 44.5%, respectively, in the transarterial group (Fig. 2A). The estimated OS was higher in the SR and RFA groups than in the transarterial group, respectively (both *P* values < .001) (Fig. 2A).

3.3. OS rates of HCC patients after IPW adjustment

We focused on a comparison between the SR or RFA group and transarterial groups, respectively. The baseline characteristics of the 3 treatment groups were balanced using IPW to evaluate the OS rates of the 3 treatment groups under the same conditions (Table 2). After IPW, 657, 653, and 745 patients were allocated to the SR, RFA, and transarterial groups, respectively. Of these patients, 75 (11.4%), 169 (25.9%), and 307 (41.2%) patients in the SR, RFA, and transarterial groups died during the median follow-up of 50, 52, and 48 months, respectively. The cumulative OS rates at 2, 4, 6, and 8 years were 95.7%, 88.2%, 78.2%, and 72.2%, respectively, in the SR group; 92.3%, 79.3%, 63.5%, and 54.8%, respectively, in the RFA group; and 90.2%, 74.2%, 55.9%, and 46.1%, respectively, in the transarterial group. The estimated OS were higher in the SR (*P* < .001) and RFA (*P* = .044) groups than that in the transarterial group, respectively (Fig. 2B). After adjusting for the HCC etiologies and serum AFP levels, the weighted Cox proportional hazards model using IPW showed the HR (95% CI) of posttreatment OS after SR versus transarterial therapy was 0.42 (0.30–0.60) (*P* < .001) and after RFA versus transarterial therapy was 0.78 (0.61–0.99) (*P* = .044) (Table 3).

Subgroup analysis was performed to analyze the results when the tumor size was subdivided further into those with HCC of <2 cm and 2 to 3 cm (Figure S2, Supplemental Digital Content, http://links.lww.com/MD2/A563). Between the SR and transarterial groups, OS in the SR group was significantly better than that in the transarterial group for HCC of <2 cm (*P* < .008) and 2 to 3 cm (*P* < .001), respectively. Between the RFA and transarterial groups, the OS in the RFA group was better than that in the transarterial group of HCC <2 cm (*P* < .001) (Figure S2A, Supplemental Digital Content, http://links.lww.com/MD2/A563), but was comparable to that in the transarterial group for HCC of 2 to 3 cm (*P* = .479) (Figure S2B, Supplemental Digital Content, http://links.lww.com/MD2/A563).

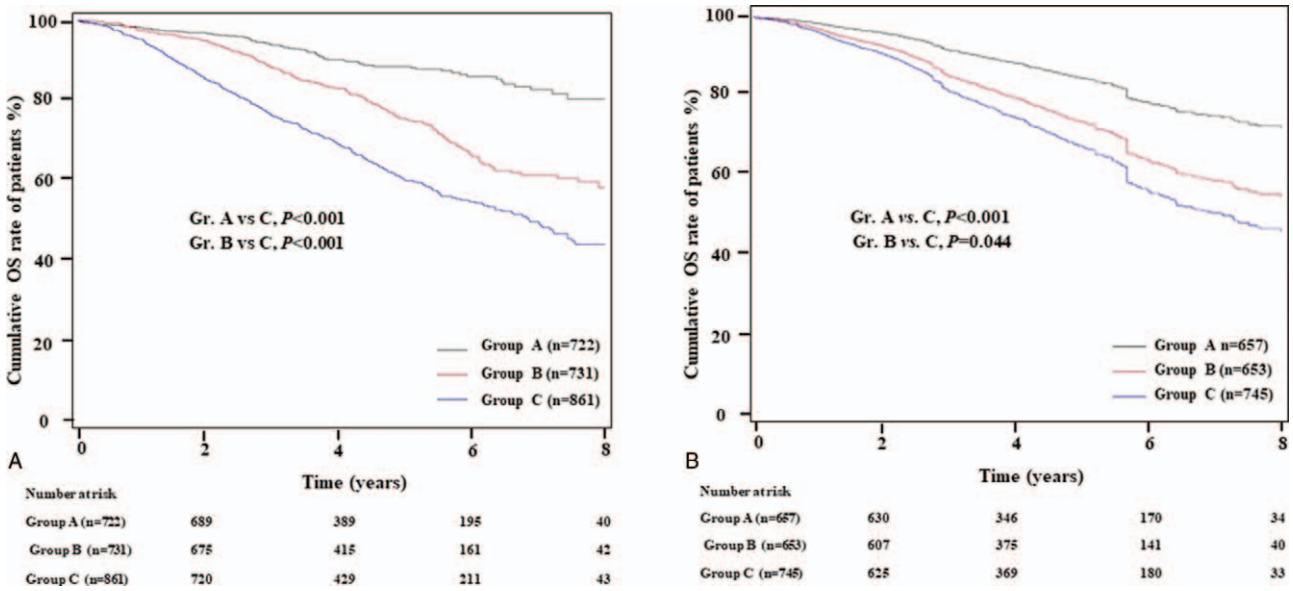

Figure 2. Cumulative overall survival rates of the HCC patients before and after IPW. (A) and (B) show the cumulative OS rates of the transarterial group compared to either the SR and RFA group before (A) and after IPW (B), respectively. Gr = group, Group A = surgical resection group, Group B = radiofrequency ablation group, Group C = transarterial group, HCC = hepatocellular carcinoma, IPW = Inverse Probability of treatment Weighting, OS = overall survival, RFA = radiofrequency ablation, SR = surgical resection.

3.4. OS rates of HCC patients with HBV or HCV after IPW adjustment

The posttreatment OS rates between treatment groups after IPW for HBV- and HCV-associated HCC patients were compared to determine if the treatment outcomes between the treatment groups differ according to the demographic difference, such as HCC etiology (HBV or HCV). For HBV-associated HCC patients, after IPW, 497, 391, and 444 patients were allocated to the SR, RFA, and transarterial groups, respectively (Table S1, Supplemental Digital Content, http://links.lww.com/MD2/

Table 2

Baseline clinical characteristics of all study subjects after IPW.

Variables	After IPW					
	SR group (n = 657)	RFA group (n = 653)	Transarterial group (n = 745)	*IPW SD*$^{+}$	*IPW SD*$^{++}$	*IPW SD*$^{+++}$
Age, n (%)				−0.0247	0.0277	0.0524
≥65 yrs	218.341 (33.59)	209.022 (31.14)	244.353 (32.43)			
<65 yrs	431.667 (66.41)	462.22 (68.86)	509.115 (67.57)			
Gender, male, n (%)	479.937 (73.84)	493.054 (73.45)	546.844 (72.58)	−0.0284	−0.0198	0.0087
BMI (kg/m^2)*	24.2 ± 2.9	24.2 ± 3.3	24.2 ± 3.3	−0.0110	0.0018	0.0128
HTN, presence, n (%)	242.147 (37.25)	248.235 (36.98)	262.128 (34.79)	−0.0513	−0.0457	0.0056
DM, presence, n (%)	151.447 (23.3)	154.005 (22.94)	181.207 (24.05)	0.0177	0.0261	0.0084
Etiology, n (%)						
HBV	410.41 (63.14)	440.4 (65.61)	489.276 (64.94)	0.0375	−0.0141	−0.0516
HCV	95.011 (14.62)	82.323 (12.26)	93.78 (12.45)	−0.0635	0.0055	0.0690
Others (reference)						
Albumin (g/dL)*	4.1 ± 0.5	4.1 ± 0.5	4.1 ± 0.5	−0.0110	−0.0818	−0.0722
Bilirubin (mg/dL)	0.9 ± 0.4	0.9 ± 0.4	0.9 ± 0.5	0.0211	−0.0009	−0.0228
PT, INR*	1.1 ± 0.1	1.1 ± 0.1	1.1 ± 0.1	−0.0213	−0.0268	−0.0067
PLT (×10^3/uL)*	138.2 ± 52.9	133.9 ± 61.5	136.7 ± 64.9	−0.0261	0.0431	0.0745
AFP (ng/dL)*	247.3 ± 928.5	632.8 ± 2374.1	268.3 ± 3271	0.0088	−0.1275	−0.2139
Tumor size, n (%)				0.0032	0.0143	0.0112
<2 cm	314.788 (48.43)	321.319 (47.87)	366.081 (48.59)			
≤2 cm and ≤3cm	335.219 (51.57)	349.923 (52.13)	387.388 (51.41)			
FU duration (month)†	50 (1–106)	52 (3–107)	48 (1–107)			

$^{+}$, $^{++}$, and $^{+++}$, SD between groups of SR vs transarterial, of RFA vs transarterial, of SR vs RFA, respectively.

AFP = alpha-fetoprotein, BMI = body mass index, DM = diabetes mellitus, FU = follow-up, HBV = hepatitis B virus, HCV = hepatitis C virus, HTN = hypertension, INR = international normalized ratio, IPW = Inverse Probability of treatment Weighting, PLT = platelet, PT = prothrombin time, RFA = radiofrequency ablation, SD = standard difference, SR = surgical resection.

* Mean (±standard deviation).

† Median (range).

Table 3

OS between groups by weighted Cox proportional hazards model using IPW.

Variables	Event, n (%)	HR (95% CI)*	*P* value*
OS between groups in all patients			
Transarterial group (reference)	307 (41.2)		
SR group	75 (11.4)	0.42 (0.30–0.60)	<.001
RFA group	169 (25.9)	0.78 (0.61–0.99)	.044
OS between groups with HCC (<2 cm)			
Transarterial group (reference)	149 (38.7)		
SR group	21 (10.6)	0.48 (0.28–0.83)	.008
RFA group	94 (21.9)	0.61 (0.47–0.80)	<.001
OS between groups with HCC (2–3 cm)			
Transarterial group (reference)	158 (43.9)		
SR group	54 (11.8)	0.36 (0.26–0.51)	<.001
RFA group	75 (33.6)	0.88 (0.64–1.24)	.479
OS between groups in pts with HBV (+)			
Transarterial group (reference)	154 (34.7)		
SR group	46 (9.3)	0.33 (0.22–0.50)	<.001
RFA group	89 (22.8)	0.73 (0.55–0.98)	.034
OS between groups in pts with HCV (+)			
Transarterial group (reference)	60 (54.5)		
SR group	14 (30.4)	0.45 (0.24–0.82)	.009
RFA group	36 (33.6)	0.61 (0.37–1.01)	.057
OS between groups in pts with <65 yrs			
Transarterial group (reference)	157 (35.3)		
SR group	52 (10.0)	0.31 (0.22–0.45)	<.001
RFA group	83 (19.6)	0.64 (0.48–0.85)	.002
OS between groups in pts with ≥65 yrs			
Transarterial group (reference)	150 (50.0)		
SR group	23 (16.5)	0.43 (0.31–0.60)	<.001
RFA group	86 (37.4)	0.84 (0.63–0.1.11)	.215

CI = confidence interval, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, HR = hazard ratio, IPW = Inverse Probability of treatment Weighting, OS = overall survival, pts = patients, RFA = radiofrequency ablation, SR = surgical resection.

* Weighted Cox proportional hazards model using IPW, Event: death during the follow-up in each group.

A564). The estimated cumulative OS rates were significantly lower in the transarterial group versus the SR ($P < .001$) and RFA ($P = .034$) groups after IPW, respectively (Fig. 3A). After adjusting for DM, PT (international normalized ratio), platelet count, and AFP, the weighted Cox proportional hazards model using IPW showed the HR (95% CI) of the posttreatment OS was 0.33 (022–0.49) ($P < .001$) after SR versus transarterial therapy, and 0.73 (0.55–0.98) ($P = .034$) after RFA versus transarterial therapy (Table 3).

In HCV-associated HCC patients, after IPW, 46, 107, and 110 patients were allocated to the transarterial, SR, and RFA groups, respectively (Table S2, Supplemental Digital Content, http://links.lww.com/MD2/A565). After IPW, the median follow-up durations in each group were relatively short; 46, 49, and 38 months, respectively; and the number of patients in each group was relatively small. Thus, we evaluated patients who were followed up for up to 60 months. The estimated cumulative OS rate of the transarterial group was significantly lower than those of the SR group ($P = .009$) and was tended to be lower than that of the RFA group ($P = .057$) (Fig. 3B). The weighted Cox proportional hazards model using IPW after adjusting for age, gender, HTN, BMI, albumin, bilirubin, PT, platelet, and AFP showed the HR (95% CI) of posttreatment was 0.45 (0.24–0.82) ($P = .009$) after SR versus transarterial therapy, and 0.61 (0.37–1.01) ($P = .057$) after RFA versus transarterial therapy (Table 3).

3.5. OS rates of HCC patients aged <65 or ≥65 years after IPW adjustment

In order to identify whether treatment outcomes between treatment groups can vary depending on the patients' age, we compared posttreatment OS rates between treatment groups after IPW in patients aged <65 and ≥65 years, respectively. In patients aged <65 years, after IPW, 518, 423, and 445 patients were allocated to the SR, RFA, and transarterial groups, respectively (Table S3, Supplemental Digital Content, http://links.lww.com/MD2/A566). The estimated cumulative OS rate of the transarterial group was significantly lower than those of the SR ($P < .001$) and RFA ($P = .002$) groups, respectively (Fig. 4A). The weighted Cox proportional hazards model using IPW after adjusting for HTN, BMI, albumin, and AFP showed the HR (95% CI) of the posttreatment OS was 0.31 (0.22–0.45) after SR versus transarterial therapy, and 0.64 (0.48–0.85) ($P = .002$) after RFA versus transarterial therapy (Table 3).

In patients aged ≥65 years, after IPW, 139, 230, and 300 patients were allocated to the SR, RFA, and transarterial groups, respectively (Table S4, Supplemental Digital Content, http://links.lww.com/MD2/A567). The estimated cumulative OS rate of the transarterial group was significantly lower than that of the SR groups ($P < .001$), but not than that of the RFA group ($P = .215$), respectively (Fig. 4B). The weighted Cox proportional hazards model using IPW after adjusting for gender, BMI, HTN,

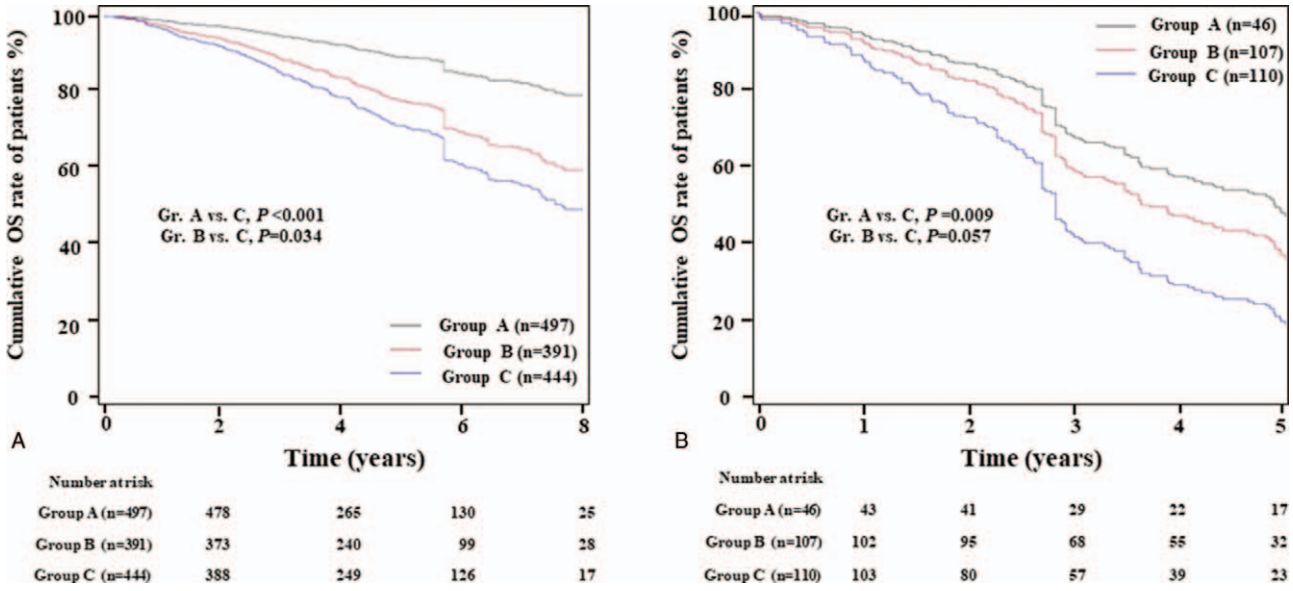

Figure 3. Cumulative overall survival rates of HBV- or HCV-associated HCC patients after IPW. (A) and (B) show the cumulative OS rates of the transarterial group compared to either the SR or RFA group in HBV- (A) and HCV-associated HCC patients (B) after IPW, respectively. Gr = group, Group A = surgical resection group, Group B = radiofrequency ablation group, Group C = transarterial group, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, IPW = Inverse Probability of treatment Weighting, OS = overall survival, RFA = radiofrequency ablation, SR = surgical resection.

HCC etiology, and tumor size showed the HR (95% CI) of posttreatment OS was 0.43 (0.31–0.59) ($P < .001$) after SR versus transarterial therapy, and 0.84 (0.63–0.1.11) ($P = .215$) after RFA versus transarterial therapy (Table 3).

4. Discussion

In this large-scale study, the long-term treatment outcomes of SR or RFA with transarterial therapy in patients with a single small (≤3 cm) T1/T2 staged HCC and well-preserved liver function (CTP-class A) were compared directly. During the median follow-up period of 50 months for all study subjects, cumulative OSs were significantly better in patients who underwent SR therapy than those who received transarterial therapy, regardless of the HCC tumor size (<2 cm or 2–3 cm), HCC etiology (HBV or HCV) or age (<65 or ≥65 years). Interestingly, the cumulative OSs between patients with RFA and transarterial therapy were

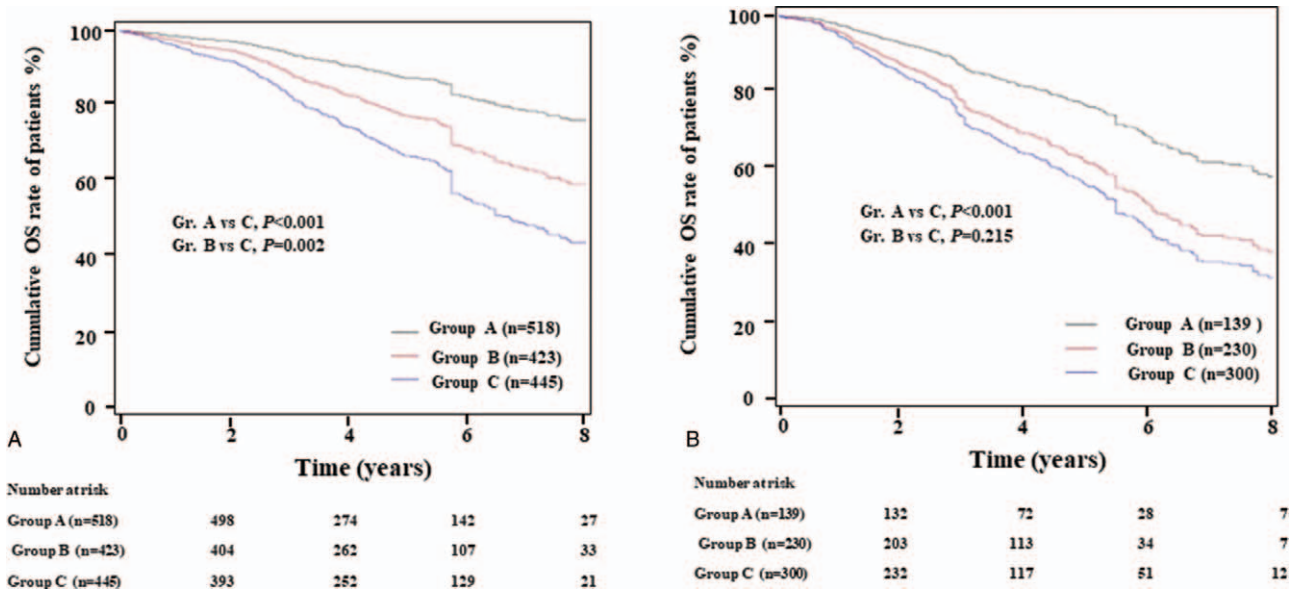

Figure 4. Cumulative overall survival rates of HCC patients aged <65 and ≥65 years after IPW. (A) and (B) show cumulative OS rates of the transarterial group compared to either the SR or RFA group in patients aged <65 years (A) and ≥65 years (B) after IPW, respectively. Gr = group, Group A = surgical resection group, Group B = radiofrequency ablation group, Group C = transarterial group, HCC = hepatocellular carcinoma, IPW = Inverse Probability of treatment Weighting, OS = overall survival, RFA = radiofrequency ablation, SR = surgical resection.

not statistically different in patients with HCC of 2 to 3 cm and with HCV infection, and in those aged ≥65 years. The present study has some strengths that deserve mention. First, this large-scale study is the first to directly compare the therapeutic effectiveness of SR or RFA therapy versus transarterial therapy in CTP-class A patients with a single small (≤3 cm) HCC in the literature. According to the current guidelines,[2–4,24] the first-line therapeutic options for CTP-class A patients with single small (≤3 cm) area is generally SR or RFA. Transarterial therapy is an alternative therapeutic option. For this reason, RCT comparing transarterial therapy with SR/RFA cannot be easily performed due to ethical issues considering their respective posttreatment survival outcomes. Thus, these results can be important clinical evidence for determining the treatment regimens for these patients. Second, we comprehensively evaluated survival outcomes between treatment groups even in HCV- as well as HBV-associated HCC patients, respectively, and in younger (<65 years) and older (≥65 years) patients, respectively. Third, we minimized selection bias as much as possible by enrolling a large number of patients by random sampling from a nationwide HCC registry. We also used IPW based on PS analysis. Generally, PS-based methods can be used to adjust for possible imbalances between the distributions of covariates that may exist between the groups in observational studies. Among them, the IPW method is deemed appropriate when 2 or more groups are compared or when the sample is small or censored.[21]

A previous retrospective study[16] reported that the weighted OS rates among SR, RFA, and TACE were not statistically different for single small HCC (85.6%, 87.6%, and 80.7%, respectively, $P = .834$). In the present study, however, the estimated OS rates of the patients were significantly better in the order of SR, RFA, and transarterial therapy. These discrepancies between studies can be explained as follows. First, the previous study was limited to a relatively small numbers of patients that received SR (n = 52), RFA (n = 79), or TACE (n = 66), performed in a single-center, and included CTP-class B patients in each group (3.8%, 13.9%, and 16.7%, respectively).[16] On the other hand, the present study was conducted on a large number of patients (SR [n = 657], RFA [n = 653], and TACE (L) [n = 745]) after IPW using a nationwide HCC registry, and enrolled only homogenous subjects with the well-preserved liver function of CTP-class A. Second, the previous study reported comparable survival outcomes in the SR and RFA groups.[16] On the other hand, this result requires a careful interpretation because 2 previous low-risk-of-bias RCTs demonstrated that OS was more favorable after SR than RFA for HCC patients within the Milan criteria,[17,18] even though the study population or statistical method was different for each study. On the other hand, in the present study, survival after SR was also significantly better than after RFA, which is in-line with the results reported in the previous 2 RCTs.[17,18] Taken together, these findings suggest that our results are more applicable to CTP-class A patients with a single small (≤3 cm) T1/T2 stage HCC and that SR or RFA should be preferentially recommended in these patients.

In a previous study that compared the survival outcomes after SR versus TACE,[25] the OSs after TACE were comparable to those after SR in The Union for International Cancer Control T1/2 HCC patients with a good liver function or in those with compact lipiodol uptake in the tumor after TACE. However, this study was performed in a single center without adjusting for potential confounders on a comparatively small number of T1/2 HCC patients who underwent SR (n = 80) or TACE (n = 61).[25] In another retrospective study,[14] the 5-year survival rate of SR was significantly higher than that of TACE (43.6% vs 25.6%, $P < .01$) in resectable HCC, but the survival rates were lower than those of the present study. These different results may be explained by the inclusion of heterogeneous study subjects in the previous study, such as CTP-class B patients in each group (9.7% in the SR group and 10.8% in the TACE group) or those with multiple tumor (≥3) cases (73% and 64% in the SR and TACE groups, respectively), and by the enrollment of a relatively small number of patients with TACE (n = 157).[14]

Regarding the treatment outcomes of RFA versus TACE in early HCC, previous studies reported conflicting results.[26,27] In 1 study,[26] the OSs after RFA and TACE were not significantly different ($P = .079$), but this study had a relatively small cohort size (n = 165 and n = 122 for RFA and TACE, respectively), included CTP-class B patients in each group (n = 33 and n = 34 for RFA and TACE, respectively), and did not adjust for potential confounders.[26] In the other study,[27] the 4-year OS after RFA was significantly better than after TACE (54.1% vs 31.5%, $P = .042$), but this study was also limited in terms of the small number of patients (n = 61 per group), included various featured tumors ≥3 cm (41% in each group), multiple nodules (23% and 31% in the RFA and TACE groups, respectively),[27] and had a short median follow-up of only 2.25 years.[27] However, this study analyzed a large number of patients, and enrolled only those with well-preserved liver function (CTP-class A). Furthermore, because T1/T2 HCC tumors have sizes up to 5 cm, we compared treatment groups under the same tumor number (single) and size (≤3 cm) criteria, in which the HCC was treated equally well by either SR or RFA. The same conditions also contributed to reducing disturbance variables in the present study. Most of all, after IPW, our results suggest that RFA should be preferred over TACE for the treatment of single small T1/T2 HCC in patients of CTP-class A, especially for single HCC of ≤2 cm. Interestingly, the posttreatment OS after transarterial therapy for 2 to 3 cm sized single HCC was statistically similar after RFA in the present study, suggesting that the effectiveness of transarterial therapy can be as hopeful as RFA in a single HCC (2–3 cm). Nevertheless, this outcome needs to be further validated, given the non-randomized design of the present study.

The clinical impacts of the demographic differences, such as the etiologic prevalence of HBV or HCV, on the survival outcomes after different therapies in CTP-class A patients with single small HCC, remain unclear. In the previous studies conducted in Asian countries, where HBV is a common cause of HCC, the survival outcome after TACE for early-stage HCC was reported to be comparable to those after SR or RFA.[16,25,26] However, another Asian study reported different results that SR is more effective than TACE for the treatment of patients with resectable HCC.[14] Unfortunately, these studies were limited by the small cohort sizes[16,25,26] or by the enrollment of only a very small number of patients, which prevented an analysis of the outcomes after SR or TACE in HCV-associated HCC patients.[14,16,25,26]

In contrast, the present study compared the survival outcomes of transarterial therapy with either SR or RFA using large study subjects in HBV- and HCV-associated HCC patients, respectively. In the present study, OS rates in HBV-associated HCC patients followed the order SR > RFA > transarterial therapy. Furthermore, the same OS rate pattern was observed in HCV-associated HCC patients. Based on these results, we could identify that SR or RFA therapy is more effective than transarterial therapy in CTP-class A patients with single small T1/T2 HCC, regardless of the

demographic differences between in Asia, where HBV is highly common cause of HCC and Europe or America, where HCV is highly prevalent cause of HCC. On the other hand, there was a marginally significant difference between patients with RFA and transarterial therapy in HCV-associated HCC patients. We think that this outcome may be resulted by the relatively small number of patients in each treatment group, suggesting that further studies will be required to confirm these results. Nonetheless, we expect that our results may provide useful information for researchers contemplating an RCT on this topic in HCV-endemic countries.

In a previous study,[28] elderly (≥70 years) and non-elderly (<70 years) patients who underwent the same treatments showed similar posttreatment survival outcome without being affected by their age. On the other hand, the survival outcomes of transarterial therapy with either SR or RFA for single small HCC were not compared in each patient age group.[28] Other studies have also reported that elderly and non-elderly HCC patients had similar survival rates after a treatment for HCC,[29–31] but these studies did not compare the posttreatment survival rates by age group in CTP-class A patients with a single small HCC.[29–31] However, in the present study, we identified that OS rates after SR were better than those after transarterial therapy in these patients, regardless of patients age (<65 and ≥65 years). Interestingly, in the present study, the OS rates of older patients in the RFA group were not statistically different with those of older patients in the transarterial group. These findings suggest that in older patients in whom SR cannot be applied for HCC treatment, transarterial therapy can be an effective treatment option comparable to RFA.

The present study has some limitations. First, the study was inherently limited by its retrospective design. However, we minimized the effects of potential confounders by IPW based on PS analysis, by comparing patients under homogenous conditions, such as single small (≤3 cm) T1/T2 staged HCC and CTP-class A, and by extracting the study subjects randomly from a large-scale KCCR database by random sampling. Second, data were unavailable on the presence of cirrhosis or the severity of portal HTN. Although these factors are consideration when determining the resectability of HCC, all study subjects were of uniformly well-preserved liver function (CTP-class A), and platelet count was adjusted using IPW in the 3 treatment groups. Third, the effect of antiviral treatment on the survivals of HBV- or HCV-associated HCC patients could not be assessed. Considering the potential effects of antivirals on posttreatment recurrence and mortality, the results of the present study should be augmented by studies on antiviral treatments. Forth, it was unfortunate that the data on the tumor location could not be obtained from the study cohort. Hence, the difference between the treatment groups could not be analyzed. Fifth, the high percentage of censored cases in survival analysis of the present study may affect the reliability of the survival outcomes. On the other hand, these results could not be avoided considering the feature of the study subjects, who had well-reserved liver function of CTP-class A and the very early or early staged HCC with a single small (≤3 cm) HCC. Given that these featured HCC shows good 5-year OS ranging 70 to 90%,[2] a very long follow-up period may be required for the reduction of censored events.

In conclusion, in CTP-class A patients with a single small (≤3 cm) T1/T2 HCC, the OS of SR was better than that of transarterial therapy, regardless of the HCC tumor size (<2 cm or 2–3 cm), HCC etiology (HBV or HCV), or age (<65 or ≥65 years). Moreover, the cumulative OSs were significantly better in those who underwent RFA than those who received transarterial therapy, but not in those with HCC of 2 to 3 cm and in those aged ≥65 years. Therefore, SR or RFA should be preferentially applied to improve the survival outcomes in these patients. On the other hand, if these patients are ineligible for SR, transarterial therapy can be an effective treatment option comparable to RFA. Furthermore, current practice guidelines[2–4,24] make it ethically difficult to perform RCTs that compare the treatment results of transarterial therapy with either SR or RFA therapy in a single small (≤3 cm) T1/T2 staged HCC patients of CTP-class A. Thus, we believe these results can be important evidence for determining the therapeutic effectiveness of transarterial therapy compared to either SR or RFA in these patients.

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Author contributions

YJ Jin was responsible for the concept and design of the study, the acquisition, analysis and interpretation of data, and drafting of the manuscript. **YJ Suh** was responsible for the design of the study, analysis, and interpretation of data. **Y Jeong** helped with the statistical analysis and data interpretation. **WY Shin, JM Lee, S Cho, JH Yu, and JW Lee** helped with data acquisition and interpretation and with critical revision of the manuscript for intellectual content.

Conceptualization: Young-Joo Jin, Young Ju Suh.
Data curation: Young-Joo Jin, Yujin Jeong Jeong, Woo Young Shin, Jeong-min Lee, Soongu Cho.
Formal analysis: Young-Joo Jin, Young Ju Suh.
Investigation: Young-Joo Jin.
Methodology: Young-Joo Jin, Young Ju Suh, Yujin Jeong Jeong, Woo Young Shin, Jeong-min Lee, Soongu Cho.
Supervision: Woo Young Shin, Jeong-min Lee, Soongu Cho, Jung Hwan Yu, Jin-Woo Lee.
Writing – original draft: Young-Joo Jin, Young Ju Suh.

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