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Comparison of outcome between liver resection, radiofrequency ablation, and transarterial therapy for multiple small hepatocellular carcinoma within the Milan criteria

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Purpose: Although surgical resection is usually considered for a single tumor, several reports have suggested that resection can be considered for multiple tumors. The objective of this study was to determine whether resection could provide better long-term outcome for patients with multiple hepatocellular carcinomas (HCCs) within Milan criteria.
Methods: A total of 276 patients with multiple HCCs within Milan criteria with liver function preserved who underwent resection, radiofrequency ablation (RFA), or transarterial chemoembolization (TACE) between 2009 and 2013 were analyzed. Propensity-score (PS) matching was conducted.
Results: Five-year overall survival (OS) and recurrence-free survival (RFS) were better in the resection group than that in the RFA or TACE group. Patients who underwent resection had more preserved liver function and different tumor characteristics compared to those received RFA or TACE. With similar baseline characteristics generated in the PS model, there was no difference in 5-year OS among 3 groups (79.5% *vs*. 72.3% or 62.0%, P = 0.232), but the 5-year RFS was better for patients who received resection than those who received RFA or TACE (51.9% *vs*. 22.0% or 0.0%, P < 0.001). Although the major complication rate was slightly higher than RFA or TACE, there was no significant difference between the 3 groups before and after PS matching.
Conclusion: Resection was associated with better RFS than RFA or TACE and showed comparable OS in multiple HCC patients within the Milan criteria, but at a cost of slightly increased risk of complication. Resection can be considered as a first-line option if selected appropriately.
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Key Words: Chemoembolization, Hepatectomy, Hepatocellular carcinoma, Propensity score, Radiofrequency ablation

INTRODUCTION

Liver resection has been a mainstay of treatment for hepatocellular carcinoma (HCC). It provides a chance of long-term outcome, with 5-year survival rate of more than 50% [1]. However, only 30%–40% of patients with HCC undergo liver

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resection as the initial treatment [2] either due to decreased liver function or advanced tumor stage. For patients presenting with multiple tumors, liver resection is not recommended as the best option by European Association for Study of the Liver [3], American Association for the Study of Liver Diseases [4], and Korean Association for the Study of the Liver guidelines [5] even if patient has preserved liver function. High chance of recurrence after liver resection and concern for small future liver volume are reasons for not considering liver resection as the best option. However, with recent advances in surgical techniques and perioperative care, surgical mortality for HCC resection has been reduced to less than 1% [6]. Several previous reports have also suggested that liver resection can be an option for multiple HCCs as it may provide better outcome than other treatment modalities [7,8].

For multiple HCCs, radiofrequency ablation (RFA) can also be considered if tumor number is 2–3 nodules and tumor size is less than 3 cm which can be defined as a tumor within the Milan criteria. For those presenting multiple HCCs within the Milan criteria (small but multiple tumors), resection, RFA, or TACE can be considered. Several previous studies have reported outcomes according to treatment modality for HCC patients diagnosed within the Milan criteria. Some studies have reported that resection can provide more favorable outcomes in survival and recurrence than RFA [9-12]. On the other hand, other studies have reported similar outcomes between resection and RFA [13-16]. Similarly, when RFA is compared to transarterial chemoembolization (TACE), some studies have reported better outcome in RFA while others have reported similar outcome between RFA and TACE [17,18]. Although the subjects in these studies were diagnosed within the Milan criteria, these studies included the patients with a single tumor less than 5 cm or included those with impaired liver function. As the risk of recurrence can be different between single and multiple tumors [8,19,20], HCC patients diagnosed within the Milan criteria need to be separately analyzed for single and multiple tumors. To date, few data have focused on the outcome between treatment modality for multifocal small tumors (2–3 nodules, less than 3 cm).

Therefore, the objective of this study was to compare long-term outcome according to the initial treatment modality (resection, RFA, or TACE) for multifocal small HCCs within Milan criteria to determine whether resection could be considered as the best option.

METHODS

Study design, setting, and participants

This was a single-center retrospective cohort study conducted at Samsung Medical Center (SMC), Seoul, Korea. A total of 4,089 consecutive HCC patients who were registered at SMC HCC registry between 2009 and 2013 were screened. SMC HCC registry is a prospective registry that collects baseline characteristics and initial treatment modality for newly-diagnosed HCC patients managed at SMC. Among them, 406 HCC patients were diagnosed within the Milan criteria defined by 2–3 nodules and tumor size ≤3 cm without vascular invasion, bile duct invasion, or extrahepatic metastasis. Of them, we excluded 130 patients who had Child-Pugh class B or C and patients who received treatment other than resection, RFA, or TACE were excluded. Finally, a total of 276 patients with multiple HCCs diagnosed within the Milan criteria with preserved liver function defined by Child-Pugh class A and received resection (n = 48), RFA (n = 87), or TACE (n = 141) as initial treatment were analyzed (Fig. 1). We also generated propensity-score (PS) matching cohort in a 1:1:1 ratio based on age, platelet count, albumin-bilirubin (ALBI) grade, number of tumors, alpha-fetoprotein (AFP), and protein induced by vitamin K absence-II (PIVKA-II). Matching variables were composed of factors which differed in the baseline characteristics between treatment arms or factors that were associated with outcomes. The PS matching resulted in 93 patients who received hepatic

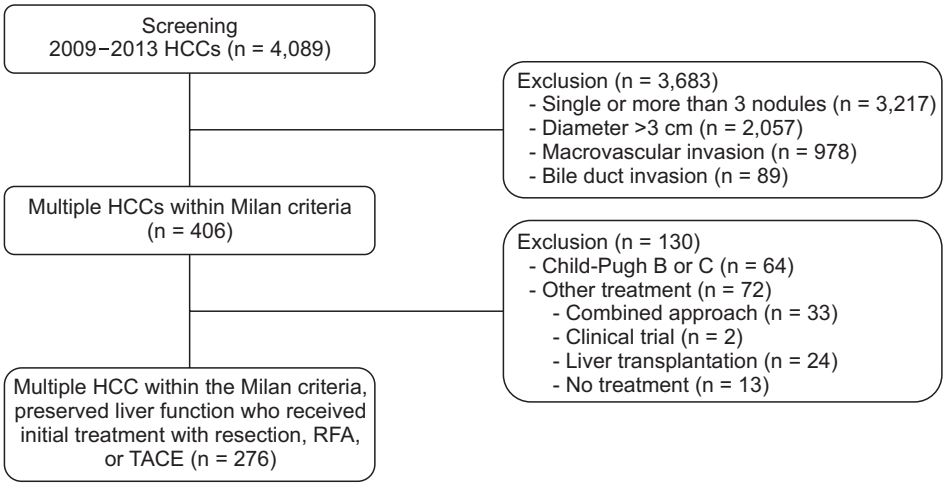

Fig. 1. Flowchart for participants' enrollment (overall cohort). HCC, hepatocellular carcinoma; RFA, radiofrequency ablation; TACE, transarterial chemoembolization.

resection (n = 31), RFA (n = 31), or TACE (n = 31).

Diagnosis of HCC was based on regional HCC guidelines during study period. The diagnosis of HCC is based on pathology or noninvasive criteria in high-risk groups. In the high-risk group, HCC can be diagnosed for nodules ≥1 cm in diameter if 1 or 2 of dynamic contrast-enhanced CT/MRI or liver-specific contrast-enhanced MRI show typical features of HCC. Typical features of HCC included arterial phase enhancement with washout in the portal or delayed phase [5]. All patients underwent staging workup including enhanced CT scan and/or gadolinium-enhanced MRI. Treatment selection was determined by physician in charge of the patient. After treatment, CT scan or MRI was conducted every 3–4 months for the first 1–2 year and every 4–6 months thereafter during the follow-up period, until March 2019. Liver function, serum AFP, and PIVKA-II levels were also monitored.

The study protocol was reviewed and approved by the Institutional Review Board at Samsung Medical Center (2018-04-044). As the study used only de-identified data routinely collected during hospital visits, the requirement to obtain informed patient consent was waived.

Variables

The primary outcome of the study was overall survival (OS). OS was measured from the date of diagnosis to the date of death or the last follow-up. Secondary outcome was recurrence-free survival (RFS). RFS was defined as the interval between the date of diagnosis and the date of the first recurrence, last follow-up, or death.

Exposure was initial treatment modality which was either resection, RFA, or TACE. Liver resection included single or multiple segmentectomies aiming to remove all macroscopic tumors. Minor resection, defined as the resection of 2 or fewer liver segment. Resection of 3 or more segments was considered a major hepatic resection. For possible confounders or mediators, the following variables were used: age, sex, etiology of liver disease, Child-Pugh score, platelet count, ALBI grade, tumor size, tumor number, and serum AFP and PIVKA level at the time of HCC diagnosis. ALBI grade was calculated using albumin and bilirubin levels as described in a previous study [21]. We also reviewed treatment response after initial treatment. Complete response (CR) was defined when complete resection was done for resection, complete ablation at immediate follow-up CT after RFA, and CR by modified response evaluation criteria in solid tumors (mRECIST) criteria after TACE (either by 1 or after 2 sessions of TACE). Recurrence was also collected for those who had CR after initial treatment. During follow-up, patients with recurrence were treated with reresection, RFA, TACE, radiation therapy, sorafenib, liver transplantation (LT) or conservative treatment depending on the liver function, and general condition of the patient.

Table 1. Baseline characteristics of overall and propensity-score matched cohort

Characteristic	Overall cohort (n = 276)				Propensity-score matched cohort (n = 93)			
	Resection (n = 48)	RFA (n = 87)	TACE (n = 141)	P-value	Resection (n = 31)	RFA (n = 31)	TACE (n = 31)	P-value
Age (yr)	54.5 (50.2–61.7)	59.0 (51.0–68.0)	62.0 (54.5–67.0)	0.007	56.0 (52.0–66.0)	57.0 (50.0–66.0)	57.0 (51.0–66.0)	0.720
Male sex	37 (77.1)	72 (82.8)	112 (79.4)	0.700	23 (74.2)	26 (83.9)	29 (93.5)	0.100
Hepatitis B[a]	41 (85.4)	67 (77.0)	98 (69.5)	0.070	27 (87.1)	25 (80.6)	23 (74.2)	0.430
Child-Pugh score, 5	43 (89.6)	75 (86.2)	118 (83.7)	0.590	29 (93.5)	29 (93.5)	28 (90.3)	0.860
Platelet (×10^3/μL)	140.0 (115.5–167.0)	116.0 (87.0–157.0)	107.0 (82.0–143.0)	0.001	137.0 (104.0–150.0)	142.0 (106.0–179.0)	120 (89.0–162.0)	0.490
ALBI grade 1	46 (95.8)	63 (72.4)	92 (65.2)	0.013	29 (93.5)	29 (93.5)	30 (96.8)	0.570
Tumor size (cm)				0.130				
≤2	21 (43.8)	52 (59.8)	84 (59.6)		14 (45.2)	18 (58.1)	17 (54.8)	0.570
2–3	27 (56.3)	35 (40.2)	57 (40.4)		17 (54.8)	13 (41.9)	14 (45.2)	
Tumor number				<0.001				0.720
2	44 (91.7)	77 (88.5)	85 (60.3)		27 (87.1)	27 (87.7)	25 (80.6)	
3	4 (8.3)	10 (11.5)	56 (39.7)		4 (12.9)	4 (12.9)	6 (19.4)	
AFP (ng/mL)	13.8 (6.1–109.5)	11.8 (5.4–55.7)	13.1 (6.3–51.9)	0.830	12.7 (6.9–63.4)	16.1 (6.3–127.4)	9.2 (4.7–17.7)	0.170
PIVKA-II (mAU/mL)	39.5 (24.5–143.2)	25.0 (17.0–54.0)	26.0 (17.0–57.0)	0.005	35.0 (20.0–64.0)	28.0 (21.0–73.0)	27.0 (16.0–71.0)	0.350
Complete response	46 (95.8)	87 (100)	127 (90.1)	0.007	29 (93.5)	31 (100)	27 (87.1)	0.110

Values were presented as median (interquartile range) or number (%).
RFA, radiofrequency ablation; TACE, transarterial chemoembolization; ALBI, albumin-bilirubin; AFP, alpha-fetoprotein; PIVKA-II, protein induced by vitamin K absence-II.
[a]Included 3 patients with HBV and HCV coinfection.

Treatment-related complications were stratified according to the Clavien-Dindo classification [22], and complication grade III or higher were collected.

Statistical analysis

Values are expressed as median (interquartile range) or number (%). Student t-test or analysis of variance (ANOVA) was used to compare continuous variables while chi-square test or Fisher exact test was used to compare categorical variables. Unadjusted hazard ratio (HR) and adjusted HR analysis were performed using Cox-regression analysis. OS and RFS curves were estimated with the Kaplan-Meier method and compared using Log-rank test. Discrete variables were computed directly whereas continuous variables were classified into binary categorical data. Cut-off points for ALBI grade was determined according to a previous study [21]. Age, platelet count, AFP, and PIVKA-II were determined according to receiver operating characteristic curve: low platelet ($\leq 100 \times 10^3/\mu L$) and high platelet ($>100 \times 10^3/\mu L$), low AFP (≤10 ng/mL) and high AFP (>10 ng/mL), low PIVKA-II (≤40 mAU/mL) and high PIVKA-II (>40 mAU/mL). PS matching cohort was generated to balance baseline characteristics and control potential selection bias due to nonrandom treatment assignment. The 1:1:1 PS model was constructed [23] with the use of multivariable logistic regression. The 3 exposures of resection, RFA, and TACE yield 3 possible matches: resection *vs.* RFA, RFA *vs.* TACE, and TACE *vs.* resection. We began with pairwise approach and produced 3 PS-matched populations. We considered resection to be the referent treatment. Using the resection *vs.* RFA and the TACE *vs.* resection PS-matched populations from the prior step, we extracted patients treated with RFA or TACE who had a common match of a patient who was treated with resection. Then, a single cohort of these patients and their resection matches were created. All statistical analyses were performed using IBM SPSS Statistics ver. 24.0 (IBM Corp, New York, NY, USA). Statistical significance was considered at $P < 0.05$.

RESULTS

Baseline characteristics

Clinical characteristics of patients with multiple HCCs within Milan criteria are shown in Table 1. Their median age was 59.0 years (range, 53.0–66.0 years). Patients who received resection were younger than those in other groups ($P = 0.007$). Although all patients belonged to Child-Pugh class A, liver resection group had more preserved liver function assessed by ALBI grade and platelet count ($P = 0.013$ and $P = 0.001$, respectively). Surgical resection group also showed different tumor characteristics. This group had more patients with 2 tumors and higher PIVKA-II levels compared to RFA or TACE group. Resection was rarely performed for those with ALBI grade 2 (n = 2). Among patients who received resection, 41.6% of patients received major resections and 58.4% of patients received minor resections.

The 1:1:1 PS-matched analysis generated 31 pairs, and the baseline characteristics of the 3 groups were described in Table 1. The median age of resection group, RFA group, and TACE group was 56.0, 57.0, and 57.0 respectively ($P = 0.720$). Among the patients, 29 (93.5%) of resection group, 29 (93.5%) of RFA group, and 30 (96.8%) of TACE group showed ALBI grade 1. Most patients had 2 tumors and half of the patients had tumors less than 2 cm.

Overall survival according to treatment modality

During a median of 5.2 years (range, 3.1–7.0 years) of follow-up, mortality was observed in 104 patients (37.7%). The OS was 81.7% at 3-year and 63.0% at 5-year. OS rates were different according to treatment modality. Resection group showed significantly better OS than RFA or TACE group. Three-year and

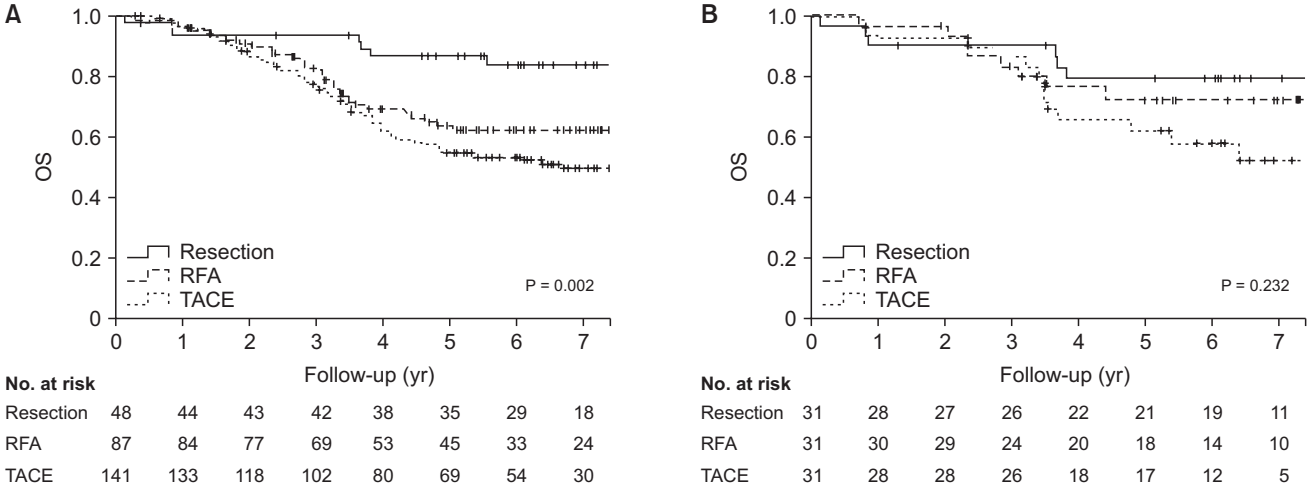

Fig. 2. (A) Overall survival (OS) by initial treatment modality in overall cohort. (B) OS by initial treatment modality in propensity-score matching cohort. RFA, radiofrequency ablation; TACE, transarterial chemoembolization.

Table 2. Factors associated with overall survival in overall and propensity-score matched cohort

Factor	Overall cohort (n = 276)				Propensity-score matched cohort (n = 93)	
	Unadjusted HR (95% CI)	P-value	Adjusted HR (95% CI)	P-value	Unadjusted HR (95% CI)	P-value
Age, >60 yr (*vs*. ≤60 yr)	1.84 (1.25–2.71)	0.002	1.53 (1.02–2.31)	0.038	1.96 (0.93–4.11)	0.070
Male sex (*vs*. female sex)	0.82 (0.51–1.32)	0.420			1.08 (0.37–3.11)	0.880
HBV (*vs*. others)	0.58 (0.21–1.58)	0.290			074 (0.30–1.83)	0.510
Platelet, >100,000 (*vs*. ≤100,000)	0.68 (0.46–1.01)	0.060			0.35 (0.16–0.77)	0.009
ALBI grade 1 (*vs*. 2)	0.46 (0.31–0.68)	<0.001	0.54 (0.35–0.82)	0.004	0.36 (0.10–1.20)	0.090
Tumor size, 2–3 cm (*vs*. ≤2 cm)	1.08 (0.73–1.59)	0.670			1.38 (0.65–2.90)	0.390
Tumor number, 3 (*vs*. 2)	1.01 (0.65–1.56)	0.950			1.54 (0.62–3.80)	0.340
AFP, >10 (*vs*. ≤10)	1.64 (1.09–2.47)	0.017	1.31 (0.86–2.00)	0.200	1.96 (0.88–4.35)	0.090
PIVKA-II, >40 (*vs*. ≤40)	1.62 (1.10–2.38)	0.014	1.79 (1.19–2.69)	0.005	1.75 (0.83–3.69)	0.130
Initial treatment modality						
Resection	Reference		Reference		Reference	
RFA	2.46 (1.13–5.36)	0.023	2.37 (1.06–5.32)	0.036	1.26 (0.45–3.50)	0.640
TACE	3.39 (1.62–7.07)	0.001	2.39 (1.08–5.26)	0.030	2.09 (0.11–5.26)	0.110
LT during follow-up	0.54 (0.24–1.24)	0.150			0.38 (0.05–2.84)	0.350
Recurrence						
None	Reference		Reference		Reference	
Recurrence[a)]	1.88 (1.00–3.53)	0.049	1.34 (0.69–2.60)	0.370	3.05 (0.72–12.96)	0.130

HR, hazard ratio; CI, confidence interval; ALBI, albumin-bilirubin; AFP, alpha-fetoprotein; PIVKA-II, protein induced by vitamin K absence-II; RFA, radiofrequency ablation; TACE, transarterial chemoembolization; LT, liver transplantation.

[a)]Included 16 patients without complete response after resection, RFA, or TACE.

5-year OS rates were 93.7% and 86.8% in the resection group, 82.5% and 63.6% in the RFA group, and 77.1% and 54.7% in the TACE group, respectively (Fig. 2A, P = 0.002). By multivariate analysis, resection was independently associated with a significantly lower risk of death.

In PS matching cohort, the median follow-up period was 5.8 years (range, 3.4–7.1 years). Five-year OS rates were 79.5%, 72.3%, and 62.0% for resection, RFA, and TACE groups, respectively (Fig. 2B). Compared to those who received RFA or TACE, the difference of OS was not statistically significant in PS cohort (P = 0.232). Multivariate analysis also showed that initial treatment modality was not an independent factor for OS (Table 2).

Recurrence-free survival according to treatment modality

Among 260 patients who achieved CR after initial treatment, 205 patients (78.8%) experienced HCC recurrence during a median of 1.2 years of follow-up (range, 0.7–3.3 years). The number of intrahepatic recurrences was 197 (75.8%), extrahepatic recurrence was 7 (2.7%), and vascular recurrence was 12 (4.6%). Eight patients (3.1%) were retreated with resection, 53 patients (20.4%) were retreated with RFA, and 109 patients (41.9%) were retreated with TACE. Five patients (1.9%) underwent LT and 30 patients (11.5%) were retreated with other treatments (Supplementary Table 1). RFS was different according to initial treatment modality. Resection group showed significantly better RFS than RFA or TACE group. RFS rates at 3-year and 5-year were 65.7% and 56.0% for those who received resection, 36.5% and 18.9% for those who received RFA, and 11.6% and 4.5% for those who received TACE, respectively (Fig. 3A, P < 0.001). By multivariate analysis, resection was independently associated with a significantly better RFS.

In PS matching cohort, 93 patients who achieved CR after initial treatment, recurrence was observed in 67 patients (72.0%) during a median 1.5 years of follow-up (range, 0.8–4.0 years). Five-year RFS rate were 51.9%, 22.0%, and 3.4% for patients who received resection, RFA, and TACE, respectively (Fig. 3B, P < 0.001). By multivariate analysis, initial treatment modality was independent factor associated with RFS (Table 3).

Major complications according to treatment modality

In overall, 7 patients experienced a major complication, defined as more than Clavien-Dindo grade III complication; 3 (6.3%) in resection group, 2 (2.3%) in RFA group, and 2 (1.4%) in TACE group (P = 0.170). In resection group, one patient experienced hepatic encephalopathy, requiring lactulose enema, and 2 patients experienced hepatic failures, which required subsequent LT. All of the 3 patients underwent major hepatectomy. In RFA group, 2 patients experienced 3rd-degree atrioventricular block and dyspnea due to large amount of pleural effusion, requiring thoracentesis. In TACE group, 1 patient experienced contrast anaphylaxis, and 1 patient experienced acute cholecystitis and ischemic colitis, requiring diagnostic endoscopy. After PS matching, major complication remained in 5 patients (3 in resection group, 2 in RFA group, and zero in TACE group; P = 0.360).

DISCUSSION

This study focused on the long-term outcome after treatment for those who had multiple small HCCs (2–3 nodules and ≤3 cm) with preserved liver function. In the present study, liver resection was associated with better OS than RFA or TACE for patients with multiple small HCCs. Since the resection group

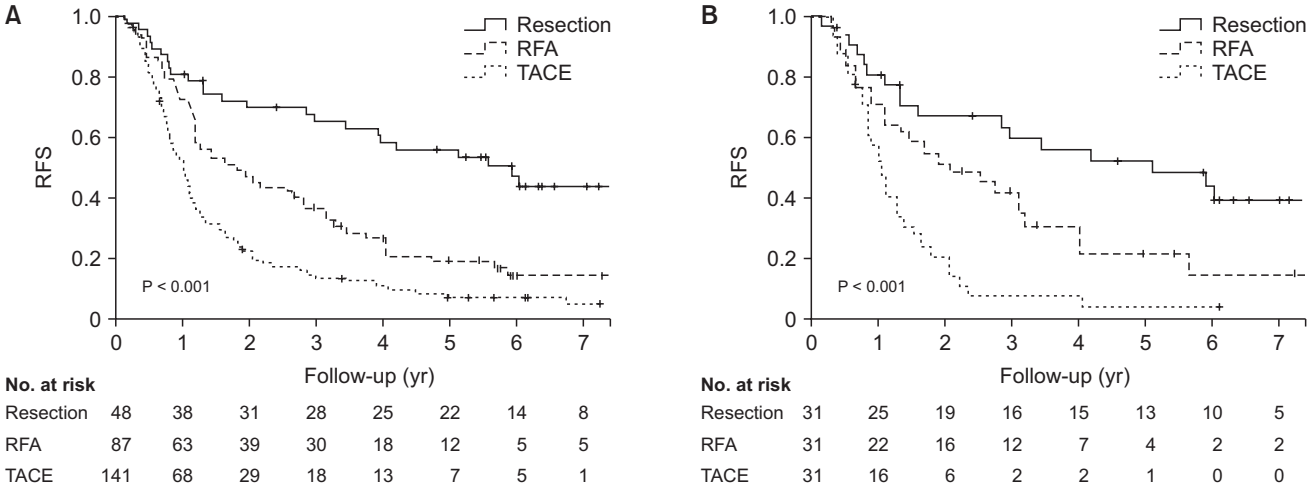

Fig. 3. (A) Recurrence-free survival (RFS) by initial treatment modality in overall cohort. (B) RFS by initial treatment modality in propensity-score matching cohort. RFA, radiofrequency ablation; TACE, transarterial chemoembolization.

Table 3. Factors associated with recurrence-free survival in overall cohort propensity-score matched cohort

Factor	Overall cohort (n = 276)				Propensity-score matched cohort (n = 93)			
	Unadjusted HR (95% CI)	P-value	Adjusted HR (95% CI)	P-value	Unadjusted HR (95% CI)	P-value	Adjusted HR (95% CI)	P-value
Age, >60 yr (*vs.* ≤60 yr)	1.58 (1.21–2.07)	0.001	1.42 (1.08–1.86)	0.011	1.30 (0.79–2.13)	0.280		
Male sex (*vs.* female sex)	1.07 (0.75–1.51)	0.700			1.44 (0.69–3.02)	0.320		
HBV (*vs.* others)	0.79 (0.35–1.80)	0.580			0.94 (0.50–1.65)	0.760		
Platelet, >100,000 (*vs.* ≤100,000)	0.70 (0.53–0.93)	0.015	0.92 (0.68–1.23)	0.590	0.76 (0.42–1.38)	0.370		
ALBI grade 1 (*vs.* 2)	0.64 (0.48–0.87)	0.004	0.96 (0.71–1.32)	0.840	0.65 (0.23–1.82)	0.420		
Tumor size, 2–3 cm (*vs.* ≤2 cm)	1.08 (0.82–1.41)	0.560			1.36 (0.84–2.20)	0.200		
Tumor number, 3 (*vs.* 2)	1.67 (1.23–2.26)	0.001	1.04 (0.76–1.43)	0.760	1.89 (1.02–3.49)	0.040	1.26 (0.65–2.42)	0.480
AFP, >10 (*vs.* ≤10)	1.25 (0.95–1.64)	0.100			1.23 (0.76–1.99)	0.380		
PIVKA-II, >40 (*vs.* ≤40)	0.96 (0.72–1.27)	0.780			1.03 (0.63–1.69)	0.880		
Initial treatment modality								
Resection	Reference		Reference		Reference		Reference	
RFA	2.29 (1.44–3.66)	<0.001	2.08 (1.30–3.33)	0.002	1.94 (1.03–3.68)	0.040	1.96 (1.03–3.71)	0.038
TACE	4.55 (2.90–7.15)	<0.001	3.54 (2.19–5.72)	<0.001	5.18 (2.63–10.18)	<0.001	4.86 (2.42–9.76)	<0.001

Excluded 16 patients without complete response after resection, RFA, or TACE.

HR, hazard ratio; CI, confidence interval; ALBI, albumin-bilirubin; AFP, alpha-fetoprotein; PIVKA-II, protein induced by vitamin K absence-II; RFA, radiofrequency ablation; TACE, transarterial chemoembolization.

was demographically favorable, we used PS matching to balance baseline features. After matching, the difference in OS was not statistically significant. In the aspect of RFS, however, resection group showed consistently better RFS than the RFA or TACE group before and after PS matching. Although the difference was not statistically significant before and after PS matching, major complications were more frequent in the resection group than RFA group or TACE group.

Five meta-analysis studies and 3 randomized controlled trials (RCT) [9-16] have compared outcomes in multiple HCCs within Milan criteria between resection and RFA. One RCT [11] and 3 meta-analysis studies [9,10,12] have concluded that resection is superior to RFA in terms of survival and recurrence. However, in these studies, resection was performed on population with a high proportion of single tumor, multiple tumors larger than 3 cm, or with unknown ALBI grade. Another 2 RCTs [14,15] and 2 meta-analysis studies [13,16] showed no significant difference in OS between RFA and resection groups, although RFA was associated with lower RFS. Three studies have compared resection to TACE and reported favorable survival in those who received resection [24-26]. In this present study, we focused on multiple HCCs within Milan criteria characterized as small but multiple tumors (2–3 nodules and ≤3 cm). In multivariate and PS-matched analyses, there was no statistically significant difference between the 3 groups in OS. However, RFS was better for the resection group than that for the RFA or TACE group. Our findings suggest that RFA and TACE are more likely to be incomplete for treatment and resection can be justified as the first-line treatment for small but multiple HCCs.

One of the reasons why liver resection has been avoided in patients with multiple HCCs is the high chance of *de-novo* recurrence or concern of hidden intrahepatic metastasis which has been estimated to exceed 70% at 5 years, higher than that of single HCC (56%–60%) [8,19,20]. In this study, we also observed high recurrence rate for those who received resection. Nevertheless, the recurrence rate in the resection group was lower than that in the RFA or TACE group in this study. The advantage of hepatic resection can be from removing not only macroscopic tumor but also potential tissues of microscopic tumor with suitable margin [27]. This might explain the better RFS in those who received resection. Another concern of resection is small future liver volume which may decrease liver function after resection. In this study, hepatic failures leading to LT were infrequent but were present only in the resection group. Special attention is required as complication rate can be higher in the resection group. Notably, almost all patients who received resection showed ALBI grade 1, indicating they were highly selected population with well-preserved liver function. These results suggest that liver resection should be very carefully considered for highly selected population with preserved liver function, but can results in better RFS and OS if

selected appropriately.

Our data warrants careful interpretation as this is an observational study. The better outcome of resection might be due to careful selection of patients. Resection can only be considered when remnant volume is adequate, and when multiple tumors are located in right or left liver (unilobal tumors). Also, in this study, we noticed that almost all patients who received resection showed ALBI grade 1. ALBI grade offers a simple, evidence-based, and objective method for assessing liver function in HCC [28]. It has shown low mortality rate after resection among patients with preserved liver function assessed by ALBI grade [28,29]. Hence, better outcome in resection group might not be from treatment modality itself, but from selection of better patients. Other limitations of this study include its retrospective design and analysis of patients in a single center. In this study, OS was better in overall cohort, not in PS-matched cohort. We used PS matching to minimize heterogeneity between groups. However, PS matching cannot completely remove heterogeneity between groups, and PS-matched cohort became small (n = 93) to make definite conclusion. All cases in the resection group were histologically confirmed cases, while tumors treated by TACE or RFA were not histologically confirmed cases. This study did not assess subsequent quality of life after treatment which might be another important issue in choosing treatment option. In addition, following treatment after recurrence can influence OS, which we could not adjust in the study, due to relatively small number of patients with recurrence (n = 23) in the resection group. Despite these limitations, the present data may have some advantages in terms that we can provide evident results compared to other studies where heterogeneous population included.

In summary, resection was associated with a significantly lower risk of recurrence compared with RFA or TACE and showed better or comparable OS in multiple HCC patients within the Milan criteria. These findings suggest that surgical resection can be considered as a first-line option for multiple small HCCs if patients are selected appropriately. However, considering retrospective nature of the study, prospective studies are warranted to see the risks and benefits of each treatment option, in order to find out patients who may best benefit from resection of multiple, small HCCs.

SUPPLEMENTARY MATERIAL

Supplementary Table 1 can be found via https://doi.org/10.4174/astr.2020.99.4.238.

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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