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Comparison of initial treatments for resectable hepatocellular carcinoma within Milan criteria: an observational study based on a nationwide survey

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Purpose: Treatment options for hepatocellular carcinoma (HCC) vary according to known guidelines among liver resection (LR), liver transplantation (LT), radiofrequency ablation (RFA), and transarterial chemoembolization (TACE). This study aimed to compare the outcomes of initial treatment for patients with resectable HCC within Milan criteria (MC) via nationwide data.
Methods: Patients with resectable HCC (Child-Pugh class A; platelet count, ≥100,000/μL) within MC from the Korean Liver Cancer Association databank were analyzed, retrospectively. Outcomes according to initial treatment and subgroups according to tumor size and number were analyzed. Overall survival (OS) rates after initial treatment were compared.
Results: A total of 3,241 patients who underwent LR (n = 1,371), LT (n = 12), RFA (n = 679), or TACE (n = 1,179) were included. The 5-year OS rates differed significantly between the groups ($P < 0.05$), except for LT (LR, 84.9%; LT, 82.5%; RFA, 76.2%; and TACE, 59.9%). For patients with a single tumor of any size, the 5-year OS rates of the LR group were significantly higher than RFA and TACE groups. For patients with multiple tumors, the 5-year OS rates were 78.2%, 100%, 74.3%, and 53.0% for the LR, LT, RFA, and TACE groups, respectively, but without significant difference between LR and RFA ($P = 0.86$).
Conclusion: For resectable HCC within MC, the LR had the highest OS rate for a single tumor of any size. LR and RFA showed no significant differences in OS rate for multiple tumors. LR has a much more optimistic outlook for HCC within MC.
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Key Words: Hepatectomy, Hepatocellular carcinoma, Radiofrequency ablation, Survival

INTRODUCTION

Hepatocellular carcinoma (HCC), accounting for 75%–85% of all primary malignant liver neoplasm, ranks as the third-highest leading cause of cancer-related death worldwide [1]. Liver resection (LR) is usually performed as the primary treatment for HCC. However, for unresectable cases of HCC, methods such as radiofrequency ablation (RFA) or transarterial

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chemoembolization (TACE) are often attempted. Also, liver transplantation (LT) has shown promising results as a therapeutic option for treating HCC [2].

The Milan criteria (MC) suggested by Mazzaferro et al. [3] have shown excellent outcomes in patients with HCC receiving LT within specific criteria. The MC has been widely adopted as the main indication for LT in patients with HCC. It also serves as a reference point for the general plan for HCC [4].

The 2022 revised Barcelona Clinic Liver Cancer (BCLC) guidelines for staging and managing HCC prioritize RFA or LT for multiple tumors within MC, which can be categorized as very early stage (0) and early stage (A) [5]. The BCLC recommends TACE as an alternative to LR in cases where RFA or LT cannot be performed. The Korean guidelines revised by the Korean Liver Cancer Association (KLCA)-National Cancer Center (NCC) in 2022 also recommend LT, RFA, and TACE as primary treatment options for multiple HCC tumors smaller than 2 cm, while LR is considered an alternative [6].

However, numerous studies have suggested that LR has outcomes comparable to or better than those of RFA and TACE for multiple HCCs. Zhang et al. [7] analyzed 976 patients with Child-Pugh (CP) class A or B and HCC within MC and reported that LR results in better outcomes than RFA in single tumor and comparable outcomes in multiple tumors. Another study analyzed 276 patients with CP class A and multiple HCCs within MC and reported that, compared with RFA and TACE, LR has better recurrence-free survival (RFS) and overall survival (OS) rates [8]. To further build on these findings, this study aimed to compare the outcomes of patients with resectable HCC within MC following various initial treatments via Korean nationwide data.

METHODS

Ethics statement

This study protocol was reviewed and approved by the Institutional Review Board of Samsung Medical Center (No. 2024-05-060). Owing to the retrospective study design and the very low possibility of adding risk to patients, this study was granted a waiver of written informed consent.

Patient selection

This study retrospectively enrolled adult patients diagnosed with HCC between 2008 and 2016, using data obtained from the KLCA database. The main indication criteria were MC and HCC resectability. The MC includes a single tumor ≤5 cm in size or up to 3 tumors with each tumor ≤3 cm in size without vascular invasion or extrahepatic metastasis. CP class A and no sign of portal hypertension (platelet count ≥100,000/μL) were selected as indicators for "resectability." The data for these patients are updated annually in January.

Only patients who underwent LR, LT, RFA, or TACE as initial treatment were included. Patients who received other treatments, such as radiotherapy or systemic chemotherapy, were excluded. Pediatric and adolescent patients (aged <18 years) were also excluded. Data lacking key indicators, such as albumin, bilirubin, tumor size, and number, were excluded.

Additionally, patients were further stratified according to tumor size and number. Subgroup 1 (SubG-1) included single HCC patients whose tumor size was ≤3 cm. Subgroup 2 (SubG-2) included single HCC patients whose tumor size ranged from 3 to 5 cm. Subgroup 3 (SubG-3) included multiple HCC patients.

Baseline characteristics

Patient data, including age, sex, body mass index, history of hypertension, diabetes mellitus (DM), hepatitis B, hepatitis C, and alcoholic liver disease (ALD), were collected. Performance status based on the Eastern Cooperative Oncology Group was collected. Laboratory parameters such as the albumin level, bilirubin level, PT, international normalized ratio (INR), creatinine level, platelet count, and indocyanine green (ICG) retention rate at 15 minutes (ICG R15) were also analyzed. The CP score, albumin-bilirubin (ALBI) score with grade, and Model for End-stage Liver Disease (MELD) score were calculated. The ALBI score was calculated with the following formula: ALBI score = $-0.085 \times$ (albumin [g/L]) $+ 0.66 \times \log_{10}$ (total bilirubin [μmol/L]) [9]. The ALBI grade categories included grade 1 (ALBI score, ≤−2.60), grade 2 (ALBI score, >−2.60 to ≤−1.39), and grade 3 (ALBI score, >−1.39). The MELD score was calculated as $9.57 \times \log_e$ (creatinine [mg/dL]) $+ 11.2 \times \log_e$ (INR) $+ 3.78 \times \log_e$ (bilirubin [mg/dL]) + 6.43 [10].

Radiological tumor size and number and the levels of α-FP and protein induced by vitamin K antagonist-II (PIVKA-II) were assessed. These baseline parameters were compared via Pearson chi-square test and analysis of variance.

Outcomes and risk factors

The OS rate and survival curve after initial treatment according to treatment modality were analyzed via Kaplan-Meier analysis. Risk factors affecting OS rate were analyzed via the Cox regression model. Statistical significance was set at $P < 0.05$. Since the KLCA database does not contain information on HCC recurrence, the recurrence state and RFS were not analyzed. All the statistical analyses were performed via IBM SPSS Statistics ver. 20 (IBM Corp.). No artificial intelligence tool was used in the writing of this article.

RESULTS

Eligible patients and baseline characteristics

Among a total of 13,838 HCC patients registered in the KLCA database, 3,635 patients were eligible for resectable

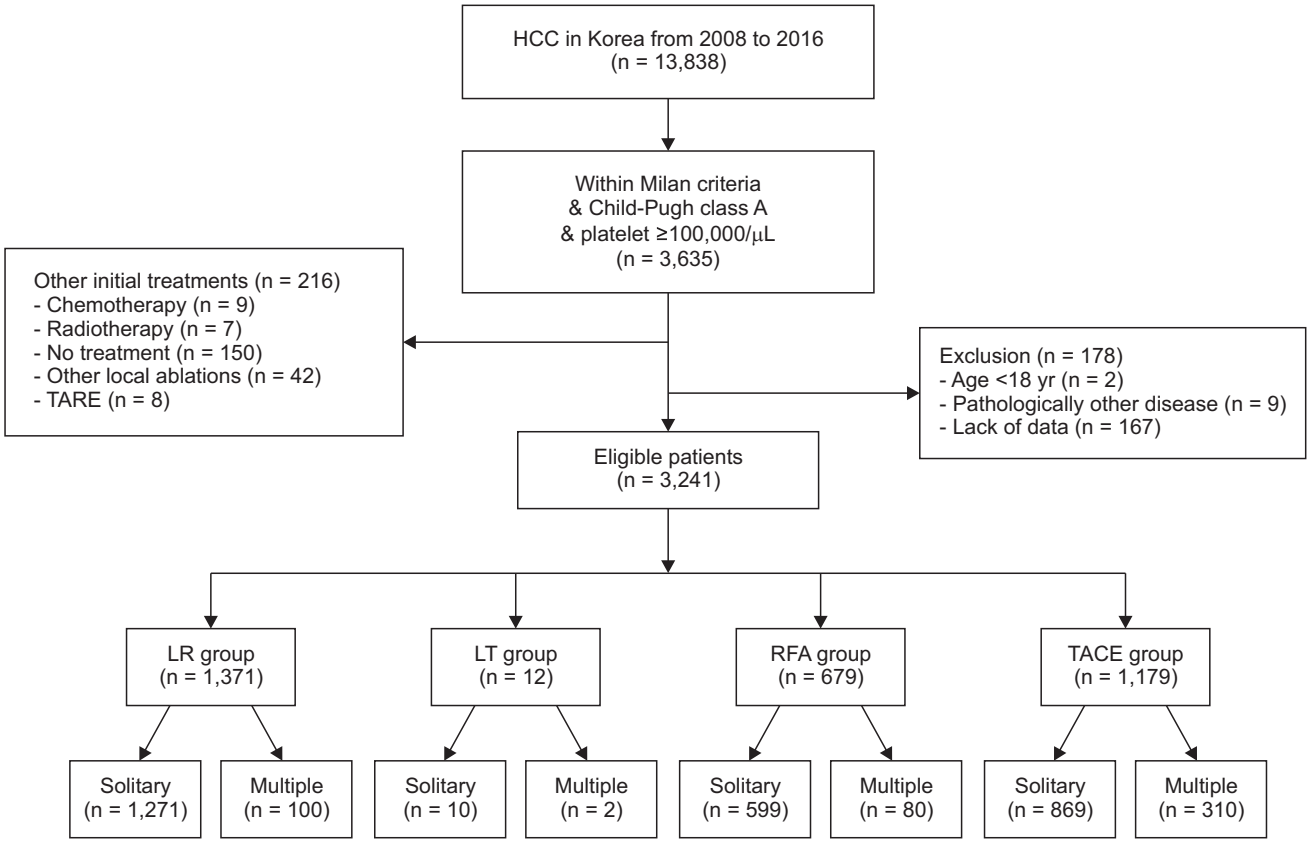

Fig. 1. Flowsheet of patient enrollment. HCC, hepatocellular carcinoma; TARE, transarterial radioembolization ; LR, liver resection; LT, liver transplantation; RFA, radiofrequency ablation; TACE, transarterial chemoembolization.

HCC within MC (Fig. 1). After excluding patients who received other treatments and pediatric patients, 3,241 patients were ultimately analyzed, including 1,371 patients (42.3%) who underwent LR, 12 (0.4%) who underwent LT, 679 (21.0%) who underwent RFA, and 1,179 (36.4%) who underwent TACE.

Some baseline characteristics of patients were significantly different between the treatment groups (Table 1). The LT group had the youngest average age (51.7 years), followed by the LR (57.5 years), RFA (61.7 years), and TACE (62.9 years) groups ($P < 0.001$). The TACE group had the highest prevalence of hypertension (43.7%, $P = 0.007$) and DM (30.9%, $P < 0.001$). The proportion of patients in a well-performing state (grade 0) was the lowest in the TACE group (86.9%, $P = 0.015$). The TACE group had the highest proportion of ALBI grade II patients (35.2%, $P < 0.001$). The average AFP and PIVKA-II levels were the lowest in the RFA group (113 ng/mL and 84.5 mAU/mL, $P = 0.006$ and $P = 0.004$, respectively). The TACE group had the highest proportion of patients with multiple tumors (26.3%, $P < 0.001$), whereas the RFA group had the smallest average tumor size (1.85 cm, $P < 0.001$).

Survival outcomes and risk factors

The median follow-up period after the initial treatment was 62.9 months. The 5-year OS rates in the LR, LT, RFA, and TACE groups were 84.9%, 82.5%, 76.2%, and 59.9%, respectively (Fig. 2). The 5-year OS rate was not significantly different between the LT group and the other groups. However, the OS rates of the LR, RFA, and TACE groups were significantly different ($P < 0.05$).

Risk factors affecting patient survival were analyzed (Table 2). According to the multivariate analysis, the RFA (hazard ratio [HR], 1.64; 95% confidence interval [CI], 1.29–2.08; $P < 0.001$) and TACE groups (HR, 2.50; 95% CI, 2.07–3.03; $P < 0.001$) induced poorer OS rates than did the LR group. Old age (10-unit increase: HR, 1.30; 95% CI, 1.19–1.43; $P < 0.001$) and ALD (HR, 1.29; 95% CI, 1.09–1.53; $P = 0.003$) negatively affected survival. Poor performance status, including grade 3 (HR, 3.49; 95% CI, 1.08–11.29; $P = 0.037$) and grade 4 (HR, 3.48; 95% CI, 1.09–11.12; $P = 0.035$), was associated with poor survival. A high albumin level had a positive impact on OS rate (HR, 0.63; 95% CI, 0.48–0.84; $P < 0.001$), whereas ALBI grade II had a negative impact on OS rate (HR, 1.32; 95% CI, 1.04–1.67; $P = 0.022$). The largest maximum tumor size negatively affected the OS rate (HR, 1.24; 95% CI, 1.15–1.34; $P < 0.001$). A high MELD score also negatively affected the OS rate (HR, 10.8; 95% CI, 1.02–1.14; $P = 0.013$).

Table 1. Baseline characteristics of each treatment group

Characteristic	LR group	LT group	RFA group	TACE group	P-value
No. of patients	1,371	12	679	1,179	
Age (yr)	57.5 ± 10.2	51.7 ± 6.5	61.7 ± 10.1	62.9 ± 10.4	<0.001
Male sex	1,093 (79.7)	9 (75.0)	520 (76.6)	903 (76.6)	0.207
BMI (kg/m^2)	24.3 ± 3.0	23.6 ± 3.3	24.4 ± 3.3	24.4 ± 3.2	0.764
Smoking	610 (44.6)	6 (50.0)	271 (40.0)	496 (42.2)	0.232
DM	303 (22.2)	2 (16.7)	183 (27.0)	363 (30.9)	<0.001
Hypertension	504 (36.9)	4 (33.3)	272 (40.2)	513 (43.7)	0.007
HBV	997 (73.7)	11 (91.7)	390 (60.7)	712 (63.2)	<0.001
HCV	76 (6.0)	1 (8.3)	98 (16.4)	149 (14.2)	<0.001
ALD	361 (26.7)	2 (16.7)	179 (26.9)	358 (30.7)	0.090
Performance					
0	1,006 (91.1)	9 (90.0)	457 (90.3)	797 (86.9)	0.015
1	92 (8.3)	1 (10.0)	47 (9.3)	98 (10.7)	
2	6 (0.5)	0 (0)	1 (0.2)	16 (1.7)	
3	0 (0)	0 (0)	1 (0.2)	2 (0.2)	
4	0 (0)	0 (0)	0 (0)	4 (0.4)	
Albumin (mg/dL)	4.25 ± 0.12	4.23 ± 0.32	4.15 ± 0.42	4.04 ± 0.45	<0.001
Bilirubin (mg/dL)	0.80 ± 0.37	0.86 ± 0.36	0.81 ± 0.38	0.83 ± 0.39	0.152
ALBI score	2.89 ± 0.36	–2.85 ± 0.31	–2.81 ± 0.38	–2.71 ± 0.40	<0.001
ALBI grade					
1	1,102 (80.4)	10 (83.3)	506 (74.5)	764 (64.8)	<0.001
2	269 (19.6)	2 (16.7)	173 (25.5)	415 (35.2)	
PT (sec)	12.4 ± 1.34	12.9 ± 1.07	12.6 ± 1.34	12.6 ± 1.43	<0.001
INR	1.05 ± 0.09	1.07 ± 0.07	1.07 ± 0.09	1.08 ± 0.10	<0.001
Creatinine (mg/dL)	0.93 ± 0.56	0.83 ± 0.16	0.96 ± 0.66	0.98 ± 0.80	0.233
Platelet (×10^3/μL)	175 ± 53.1	154.8 ± 35.4	160.4 ± 52.3	159.4 ± 55.5	<0.001
α-FP (ng/mL)	434.1 ± 2,549	340.6 ± 635.9	113 ± 563.9	419.3 ± 2,507	0.006
PIVKA-II (mAU/mL)	331.7 ± 1,381.8	138.8 ± 294.3	84.5 ± 344.3	325.4 ± 1,413.2	0.004
No. of tumors					
1	1,271 (92.7)	10 (83.3)	599 (88.2)	869 (73.7)	<0.001
2	90 (6.6)	1 (8.3)	75 (11.0)	227 (19.3)	
3	10 (0.7)	1 (8.3)	5 (0.7)	83 (7.0)	
Max tumor size (cm)	2.80 ± 1.03	2.59 ± 1.13	1.85 ± 0.72	2.42 ± 1.07	<0.001
Child-Pugh score	5.09 ± 0.29	5.08 ± 0.29	5.13 ± 0.34	5.19 ± 0.39	<0.001
MELD score	7.67 ± 1.73	7.50 ± 0.80	8.03 ± 1.99	8.18 ± 2.13	<0.001

Values are presented as number only, mean ± standard deviation, or number (%).
Some variables had missing data: Smoking,7; DM,10; Hypertension,12; HBV,107; HCV,307; ALD,42; Performance,704; PT,43; INR,5; creatinine, 7; α-FP,168; PIVKA-II,948; MELD,79.
LR, liver resection; LT, liver transplantation; RFA, radiofrequency ablation; TACE, transarterial chemoembolization; BMI, body mass index; DM, diabetes mellitus; ALD, alcoholic liver disease; ALBI, albumin-bilirubin; INR, international normalized ratio; PIVKA-II, protein induced by Vitamin K absence or antagonist-II; ICG R15, indocyanine green retention rate at 15 minutes; MELD, Model for End-stage Liver Disease.

Subgroup analysis: tumor size and numbers

Three subgroups were established according to tumor characteristics (Table 3). SubG-1 consisted of 1,796 patients (55.4%) with a single HCC ≤3 cm in size, including 695 (38.7%) who underwent LR, 5 (0.3%) who received LT, 543 (30.2%) who underwent RFA, and 553 (30.8%) who underwent TACE. The 5-year OS rates for SubG-1 patients treated with LR, LT, RFA, and TACE were 90.4%, 80.0%, 76.4%, and 52.1%, respectively (Fig. 3A). Although the LT group exhibited no statistically significant difference in survival, significant differences in survival were observed among the LR, RFA, and TACE groups (P < 0.001).

SubG-2 comprised 953 patients (29.4%) with a single HCC 3–5 cm in size, 576 (60.4%) who underwent LR, 5 (0.5%) who received LT, 56 (5.9%) who underwent RFA, and 316 (33.2%) who underwent TACE. The 5-year OS rates for SubG-2 patients treated with LR, LT, RFA, and TACE were 79.7%, 80.0%, 78.1%, and 47.3%, respectively (Fig. 3B). Compared with the other groups, the LT group showed no statistically significant difference in the OS rate. However, the LR group presented a significantly higher OS rate than did the RFA group (P = 0.01)

Table 2. Risk factors affecting patient death

Risk factor	Patient death (n = 3,241, events = 1,089)			
	Univariate		Multivariate	
	HR (95% CI)	P-value	HR (95% CI)	P-value
1st treatment (reference, LR)		<0.001		<0.001
LT	1.17 (0.37–3.64)	0.789	1.83 (0.58–5.74)	0.302
RFA	1.67 (1.40–1.99)	<0.001	1.64 (1.29–2.08)	<0.001
TACE	3.03 (2.63–3.50)	<0.001	2.50 (2.07–3.03)	<0.001
Age (yr)/10	1.62 (1.53–1.72)	<0.001	1.30 (1.19–1.43)	<0.001
Female sex	0.91 (0.79–1.05)	0.207		
BMI (kg/m^2)	0.97 (0.95–0.99)	0.007		
Smoking	1.01 (0.89–1.14)	0.896		
DM	1.51 (1.32–1.71)	<0.001	1.14 (0.96–1.35)	0.135
Hypertension	1.43 (1.27–1.62)	<0.001	0.96 (0.82–1.14)	0.660
HBV	0.56 (0.50–0.64)	<0.001	0.90 (0.74–1.09)	0.264
HCV	1.81 (1.53–2.14)	<0.001	1.16 (0.92–1.46)	0.215
ALD	1.28 (1.12–1.45)	<0.001	1.29 (1.09–1.53)	0.003
Performance (reference, 0)		<0.001		0.019
1	1.09 (0.86–1.38)	0.466	0.93 (0.72–1.19)	0.564
2	3.38 (2.02–5.64)	<0.001	1.57 (0.91–2.69)	0.104
3	12.92 (4.15–40.2)	<0.001	3.49 (1.08–11.29)	0.037
4	11.94 (3.83–37.2)	<0.001	3.48 (1.09–11.12)	0.035
Albumin (g/dL)	0.35 (0.30–0.39)	<0.001	0.63 (0.48–0.84)	<0.001
Bilirubin (mg/dL)	1.17 (1.00–1.36)	0.053		
ALBI score	3.17 (2.74–3.66)	<0.001		
ALBI grade 2 (reference, 1)	2.38 (2.11–2.68)	<0.001	1.32 (1.04–1.67)	0.022
PT (sec)	1.07 (1.03–1.11)	0.002		
INR	5.75 (3.58–9.24)	<0.001	1.19 (0.46–3.14)	0.718
Creatinine (mg/dL)	1.14 (1.09–1.20)	<0.001	1.05 (0.92–1.20)	0.501
Platelet (×10^3/μL)[a]	0.79 (0.69–0.89)	<0.001	0.88 (0.76–1.01)	0.066
α-FP (ng/mL)[a]	1.00 (1.00–1.00)	0.479		
PIVKA-II (mAU/mL)[a]	1.01 (1.01–1.02)	<0.001		
No. of tumors (reference, 1)		<0.001		0.152
2	1.33 (1.13–1.58)	0.001	1.10 (0.88–1.36)	0.399
3	2.24 (1.70–2.94)	<0.001	1.38 (0.98–1.95)	0.064
Max tumor size (cm)	1.13 (1.07–1.20)	<0.001	1.24 (1.15–1.34)	<0.001
Child-Pugh score	2.39 (2.08–2.76)	<0.001	1.14 (0.90–1.44)	0.285
MELD score	1.14 (1.11–1.16)	<0.001	1.08 (1.02–1.14)	0.013

HR, hazard ratio; CI, confidence interval; LT, liver transplantation; RFA, radiofrequency ablation; TACE, transarterial chemoembolization; BMI, body mass index; DM, diabetes mellitus; ALD, alcoholic liver disease; ALBI, albumin-bilirubin; INR, international normalized ratio; PIVKA-II, protein induced by Vitamin K absence or antagonist-II; MELD, Model for End-stage Liver Disease

[a]Platelet count, α-FP, and PIVKA-II levels were scaled by dividing their numerical values by 100 before conducting Cox regression analysis, due to the magnitude of original numerical values.

and the TACE group ($P < 0.001$). The RFA group also had a significantly higher OS rate than the TACE group ($P = 0.02$).

SubG-3 comprised 492 patients (15.2%) with multiple HCCs, including 100 (20.3%) who underwent LR, 2 (0.4%) who received LT, 80 (16.3%) who underwent RFA, and 310 (62.5%) who underwent TACE. The 5-year OS rates for SubG-3 patients treated with LR, LT, RFA, and TACE were 78.2%, 100.0%, 74.3%, and 53.0%, respectively (Fig. 3C). While the LR and RFA groups had significantly higher OS rates than did the TACE group ($P < 0.05$), there was no significant difference in the OS rate between the LR and RFA groups ($P = 0.86$).

On the basis of certain guidelines for single or multiple HCCs with a tumor size ≤2 cm [6,11], additional analysis was performed. For patients with a single HCC ≤2 cm treated with LR, LT, RFA, or TACE, the 5-year OS rates were 90.6%, 75.0%, 78.4%, and 68.5%, respectively (Fig. 4A). All groups except for the LT group showed significant differences ($P < 0.001$) in the OS rate. For patients with multiple HCCs ≤2 cm treated with

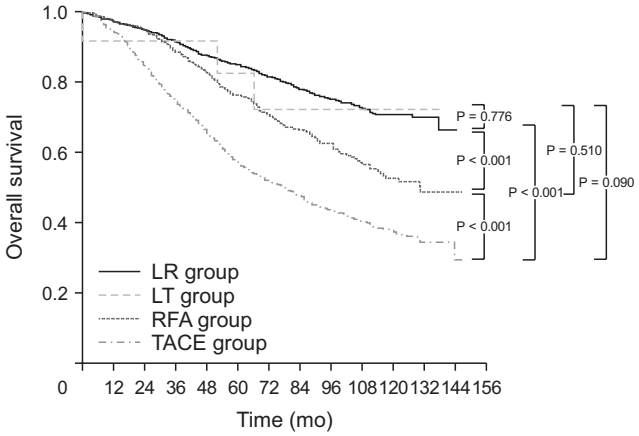

Fig. 2. Overall survivals according to initial treatment. LR, liver resection; LT, liver transplantation; RFA, radiofrequency ablation; TACE, transarterial chemoembolization.

LR, LT, RFA, and TACE, the 5-year OS rates were 72.4%, 100%, 77.2%, and 58.7%, respectively (Fig. 4B). Only the RFA group had a significantly higher OS rate than did the TACE group (P = 0.01).

Additional analyses: patient age, treatment period, and albumin-bilirubin grade

Separate analyses for older (≥65 years, n = 1,130) and younger (<65 years, n = 2,111) patients were carried out (Table 4 and Fig. 5A, B). Significant differences in the 5-year OS rate were observed among older patients who underwent LR (76.1%), RFA (67.1%), and TACE (46.8%). Separate analyses of patients who received initial treatment in the early period (2008–2012, n = 1,621) and late period (2013–2016, n = 1,620) were performed (Table 5 and Fig. 5C, D). The proportion of patients who underwent LR was higher in the late period (39.0% to 45.6%), whereas the proportion of patients who underwent TACE was lower in the late period (39.4% to 33.4%). The 5-year OS rates were similar among the different treatment groups (LR > RFA > TACE) during the early period (86.1%, 77.5%, and 56.7%, respectively) and the late period (83.4%, 73.3%, and 55.0%, respectively). Additionally, we analyzed patients with ALBI grades I (n = 2,382) and II (n = 859). The results are shown in Table 6 and Fig. 5E, F. Patients with ALBI grade II had a lower OS rate than those with ALBI grade I. However, for patients with ALBI grade II, significant (P < 0.05) differences were observed in the 5-year OS rate between the treatment groups: LR (74.0%) > RFA (60.4%) > TACE (42.5%).

DISCUSSION

Among a total of 13,838 patients with HCC, only 3,635 patients (26.3%) satisfied the MC. The HCC was considered resectable when it met the traditional criteria: CP class A and a platelet count ≥100,000/μL. The percentage of patients who underwent LR was the highest (n = 1,371, 42.3%), followed by those who underwent TACE (n = 1,179, 36.4%), RFA (n = 679, 21.0%), and LT (n = 12, 0.4%) as the initial treatment. Typically, older patients with poor performance status and multiple tumors tend to undergo TACE.

Among all enrolled patients, the LR group had the highest 5-year OS rate (84.9%), followed by the LT (82.5%), RFA (76.2%), and TACE (59.9%) groups. Although the OS rate of the LT group did not significantly differ, the other groups presented significant differences (P < 0.001) in terms of the 5-year OS rate.

Cox regression analysis revealed that, unlike the LR group, the RFA and TACE groups showed factors such as a history of ALD, poor performance status (grades 3 and 4), ALBI grade 2, larger maximum tumor size, and higher MELD scores, all of which negatively impacted patient survival in the multivariate analysis.

Tumor size and number are the main factors that can influence the prognosis of patients with HCC [6]. Owing to the known effectiveness of RFA for HCCs <3 cm in size, we subdivided patients into 3 subgroups: single HCC within 3 cm (SubG-1), single HCC between 3 and 5 cm (SubG-2), and multiple HCC (SubG-3) [7,12].

In SubG-1 (n = 1,796), the proportion of patients in the RFA-treated group (30.2%) was relatively greater than that in the other subgroups, which was expected based on the guidelines. However, the survival rate was the highest in the LR group (5-year OS rate, 90.5%) (Fig. 3A). In SubG-2 (n = 953), which included large HCC, the LT group had the highest 5-year OS rate (80.0%), followed by LR (79.7%), RFA (78.1%), and TACE (47.3%, P < 0.001) groups. The 5-year OS rates were similar between the LR and RFA groups. However, at the 10-year mark, the difference widened significantly (LR, 66.7% *vs.* RFA, 41.4%). Considering that this result reflects the OS rate but not the RFS rate of patients, RFA-treated patients might benefit from additional locoregional treatment despite HCC recurrence. In addition, the higher average age of the RFA group (66.0 years) than of the LR group (58.4 years) might have contributed to poorer patient survival beyond 5 years after treatment. In SubG-3 (n = 492), which included patients with multiple HCCs, the TACE group had the highest proportion of patients (63.0%), followed by the LR (20.3%), RFA (16.3%), and LT (0.4%) groups (Fig. 3C). However, the 5-year OS rate was lower in the TACE group (53.0%) than in the LR group (78.2%) and the RFA group (74.3%) (P < 0.05). The survival rates of patients with multiple tumors were not significantly different between the LR and RFA groups (P = 0.86).

In summary, for patients with resectable HCC within MC, the OS rate of patients with a single tumor was the best when they received LR, followed by those who received RFA and TACE. This result was consistent with several guidelines and previous

Table 3. Baseline characteristics according to subgroups

Characteristic	LR group	LT group	RFA group	TACE group	P-value
Subgroup 1 (single <3 cm)					
No. of patients	695	5	543	553	
Age (yr)	56.7 ± 10.2	52.6 ± 7.4	61.4 ± 10.2	61.8 ± 10.3	<0.001
DM	160 (23.1)	1 (20.0)	145 (26.8)	166 (30.1)	0.048
HBV	519 (75.4)	5 (100)	311 (60.5)	344 (65.2)	<0.001
HCV	36 (5.6)	0 (0)	78 (16.5)	67 (13.8)	<0.001
Performance					
0	522 (92.7)	3 (75.0)	360 (90.2)	393 (89.5)	0.398
4	0 (0)	0 (0)	0 (0)	1 (0.1)	
Albumin (g/dL)	4.26 ± 0.42	4.24 ± 0.43	4.17 ± 0.42	4.08 ± 0.43	<0.001
ALBI grade 2	128 (18.4)	1 (20.0)	132 (24.3)	181 (32.7)	<0.001
INR	1.05 ± 0.85	1.07 ± 0.11	1.07 ± 0.09	1.08 ± 0.11	<0.001
Platelet ($\times 10^3/\mu L$)	169.8 ± 48.4	151.8 ± 30.3	158.7 ± 49.7	154.7 ± 49.0	<0.001
α-FP (ng/mL)	284.0 ± 995.2	504.2 ± 833.9	110.1 ± 571.6	193.6 ± 700.3	0.002
Max tumor size (cm)	2.05 ± 0.51	1.96 ± 0.43	1.69 ± 0.51	1.80 ± 0.60	<0.001
Child-Pugh score	5.07 ± 0.26	5.20 ± 0.45	5.12 ± 0.32	5.16 ± 0.37	<0.001
MELD score	7.61 ± 1.66	7.60 ± 1.14	8.05 ± 2.07	8.19 ± 2.09	<0.001
Subgroup 2 (single ≥3 cm)					
No. of patients	576	5	56	316	
Age (yr)	58.4 ± 10.2	51.6 ± 7.5	66.0 ± 10.2	64.6 ± 11.1	<0.001
DM	123 (21.4)	0 (0)	15 (26.8)	107 (34.0)	<0.001
HBV	398 (70.2)	5 (100)	27 (50.0)	174 (57.6)	<0.001
HCV	33 (6.1)	0 (0)	11 (22.0)	38 (13.0)	<0.001
Performance					
0	412 (89.6)	4 (100)	35 (85.4)	193 (82.8)	0.010
4	0 (0)	0 (0)	0 (0)	2 (0.9)	
Albumin (g/dL)	4.24 ± 0.41	4.32 ± 0.19	4.10 ± 0.41	4.01 ± 0.47	<0.001
ALBI grade 2	117 (20.3)	0	14 (25.0)	120 (38.0)	<0.001
INR	1.05 ± 0.09	1.08 ± 0.04	1.06 ± 0.09	1.07 ± 0.09	0.185
Platelet ($\times 10^3/\mu L$)	181.4 ± 58.2	170.8 ± 40.9	167.4 ± 42.9	174.5 ± 72.7	0.231
α-FP (ng/mL)	774.2 ± 3,710.7	309.8 ± 571.5	127.1 ± 326.6	980.5 ± 4,605.6	0.508
Max tumor size (cm)	3.80 ± 0.63	3.74 ± 0.48	3.52 ± 0.50	3.83 ± 0.70	0.012
Child-Pugh score	5.11 ± 0.31	5.00 ± 0.00	5.13 ± 0.33	5.21 ± 0.41	<0.001
MELD score	7.75 ± 1.81	7.40 ± 0.55	7.85 ± 1.88	8.20 ± 2.12	0.010
Subgroup 3 (multiple)					
No. of patients	100	2	80	310	
Age (yr)	57.2 ± 9.1	49.5 ± 0.7	60.2 ± 9.0	62.9 ± 9.7	<0.001
DM	32 (32.0)	0 (0)	30 (37.5)	146 (47.4)	0.020
HBV	80 (81.6)	1 (50.0)	52 (70.3)	194 (65.3)	0.022
Performance					0.976
0	72 (88.9)	2 (100)	62 (93.9)	211 (86.1)	
4	0 (0)	0 (0)	0 (0)	1 (0.4)	
Albumin (g/dL)	4.18 ± 0.45	3.95 ± 0.07	4.08 ± 0.44	4.02 ± 0.44	0.023
ALBI grade 2	24 (24.0)	1 (50.0)	27 (33.8)	114 (36.8)	0.124
INR	1.05 ± 0.07	1.06 ± 0.0	1.09 ± 0.08	1.09 ± 0.10	0.007
Platelet ($\times 10^3/\mu L$)	175.0 ± 50.0	122.5 ± 6.4	167.0 ± 71.3	152.4 ± 41.9	<0.001
α-FP (ng/mL)	347.2 ± 1,542.2	8.4 ± 1.0	122.6 ± 644.2	248.0 ± 1,006.9	0.592
No. of tumors					
2	90 (90.0)	1 (50.0)	75 (93.8)	227 (73.2)	<0.001
3	10 (10.0)	1 (50.0)	5 (6.2)	83 (26.8)	
Max tumor size (cm)	2.26 ± 0.60	1.30 ± 0.71	1.72 ± 0.54	2.07 ± 0.63	<0.001
Child-Pugh score	5.14 ± 0.35	5.00 ± 0.00	5.23 ± 0.42	5.21 ± 0.41	0.374
MELD score	7.67 ± 1.79	7.50 ± 0.71	8.03 ± 1.47	8.14 ± 2.22	0.254

Values are presented as number only, mean ± standard deviation, or number (%).
Some variables had missing data as follows. Subgroup 1: DM, 6; HBV, 61; HCV, 191; performance, 391; INR, 3; α-FP, 105; MELD, 49. Subgroup 2: DM, 2; HBV, 25; HCV, 66; performance, 215; INR, 2; α-FP, 47; MELD, 18. Subgroup 3: DM, 2; HBV, 21; performance, 98; α-FP, 16; MELD, 12.
LR, liver resection; LT, liver transplantation; RFA, radiofrequency ablation; TACE, transarterial chemoembolization; DM, diabetes mellitus; ALBI, albumin-bilirubin; INR, international normalized ratio; MELD, Model for End-stage Liver Disease.

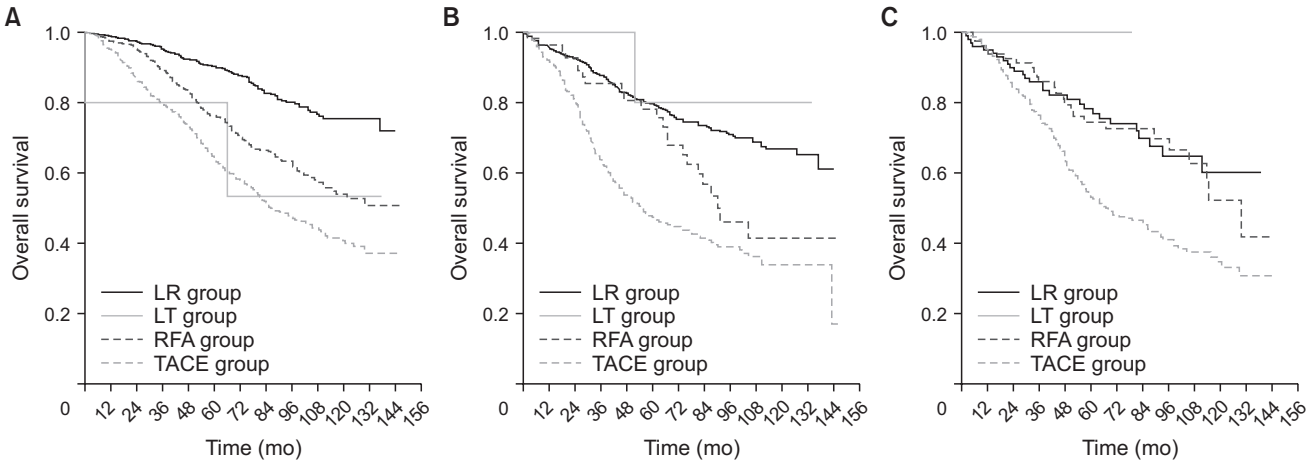

Fig. 3. Overall survivals of subgroups according to tumor size and numbers. (A) Subgroup 1, a single hepatocellular carcinoma (HCC) case with a size equal to or smaller than 3 cm. (B) Subgroup 2, a single HCC case with a size ranging from 3 to 5 cm. (C) Subgroup 3, multiple HCC cases. LR, liver resection; LT, liver transplantation; RFA, radiofrequency ablation; TACE, transarterial chemoembolization.

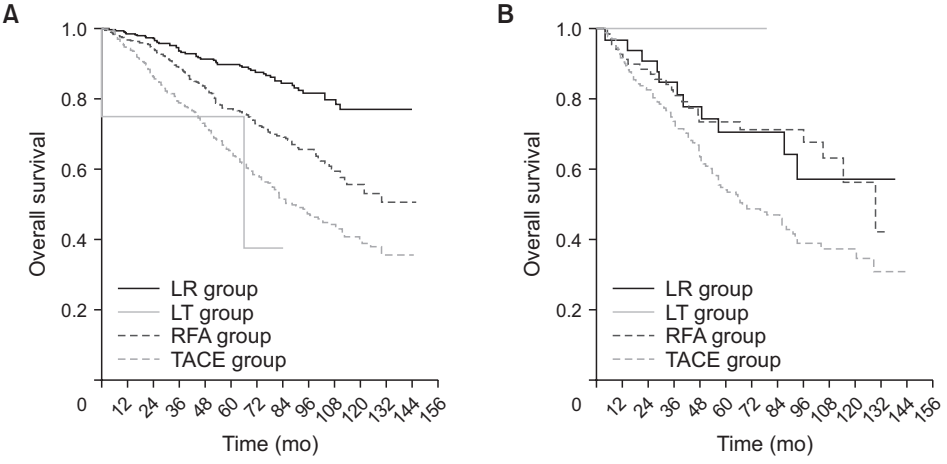

Fig. 4. Overall survivals according to some additional tumor types. (A) A single hepatocellular carcinoma (HCC) case with a size equal to or smaller than 2 cm. (B) Multiple HCC cases with a size equal to or smaller than 2 cm. LR, liver resection; LT, liver transplantation; RFA, radiofrequency ablation; TACE, transarterial chemoembolization.

studies. The BCLC group recommends LR for single lesions at an early stage with stable portal pressure and bilirubin [5]. When portal pressure or bilirubin levels are elevated, the BCLC group recommends LT whenever possible. However, for very early-stage patients with a single HCC lesion within 2 cm, the BCLC group opted for RFA over LR. Moreover, the KLCA-NCC practice guidelines recommend LR and RFA equally for single HCCs within 2 cm [6]. The Asian Pacific Association for the Study of the Liver (APASL) guidelines recommend LR for CP class A patients only for resectable HCC cases. However, for HCCs ≤2 cm, RFA is recommended as a first-line treatment according to this guideline. In contrast, our additional analysis of a single HCC <2 cm (n = 1,152) revealed that, compared with RFA, LR resulted in a significantly higher 5-year OS rate (90.6% *vs.* 78.4%, P < 0.001) (Fig. 4A). The survival rate gap between LR and RFA widened over time, reaching 77.4% and 59.0%, respectively, at the 10-year mark. This result emphasizes the preference for LR over RFA, even in cases with very small single HCC. A previous study with 976 HCC patients within MC also emphasized that LR is superior to RFA for single HCCs of any size [7].

In the case of multiple HCCs, our results revealed that survival rates were similar between the LR and RFA groups, with the TACE group having the lowest survival rate. However, the BCLC group forgoes the option of LR. Instead, LT or RFA is recommended as the first-line treatment for multiple HCCs within MC, with TACE as an alternative. The KLCA-NCC group also recommended LT, RFA, and TACE as primary options, with LR as an alternative. In contrast, the APASL guidelines recommend LR for resectable cases, including those with multiple HCCs, with RFA as an acceptable alternative. Our results emphasize the role of LR in multiple HCCs, similar to the APASL guidelines. One recent study of 276 patients with multiple HCCs within MC reported better outcomes with LR than with RFA and TACE [8]. One recent study comparing

Table 4. Baseline characteristics according to patient's age

Characteristic	LR group	LT group	RFA group	TACE group	P-value
Age <65 yr					
No. of patients	1,025	12	407	667	
Age (yr)	53.1 ± 7.6	51.7 ± 6.5	54.9 ± 6.3	55.4 ± 6.5	<0.001
DM	197 (19.3)	2 (16.7)	84 (20.7)	173 (26.1)	0.010
HBV	851 (83.9)	11 (91.7)	302 (78.4)	512 (79.3)	0.025
HCV	36 (3.8)	1 (8.3)	36 (10.3)	51 (8.7)	<0.001
ALD	257 (25.4)	2 (16.7)	116 (29.1)	223 (33.7)	0.003
Performance					
0	764 (92.5)	9 (90.0)	285 (92.8)	477 (89.7)	0.334
4	0 (0)	0 (0)	0 (0)	1 (0.2)	
Albumin (mg/dL)	4.28 ± 0.42	4.23 ± 0.32	4.19 ± 0.41	4.12 ± 0.43	<0.001
ALBI grade 2	177 (17.3)	2 (16.7)	94 (23.1)	188 (28.2)	<0.001
INR	1.05 ± 0.08	1.07 ± 0.07	1.07 ± 0.10	1.08 ± 0.10	<0.001
Platelet ($\times 10^3/\mu L$)	173.9 ± 52.1	154.8 ± 35.4	160.0 ± 52.6	155.1 ± 45.8	<0.001
α-FP (ng/mL)	567.1 ± 2,830.6	340.6 ± 635.9	134.5 ± 691.1	468.9 ± 3,038.4	0.053
PIVKA-II (mAU/mL)	272.4 ± 908.9	138.8 ± 294.3	51.5 ± 91.7	271.5 ± 1,157.0	0.005
No. of tumors					
1	947 (92.4)	10 (83.3)	355 (87.2)	486 (72.9)	<0.001
2	74 (7.2)	1 (8.3)	49 (12.0)	129 (19.3)	
3	4 (0.4)	1 (8.3)	3 (0.7)	52 (7.8)	
Max tumor size (cm)	2.75 ± 1.01	2.59 ± 1.13	1.78 ± 0.69	2.31 ± 1.05	<0.001
Child-Pugh score	5.09 ± 0.28	5.08 ± 0.29	5.11 ± 0.32	5.14 ± 0.35	0.005
MELD score	7.60 ± 1.72	7.50 ± 0.80	8.02 ± 2.12	8.01 ± 1.92	<0.001
Age ≥65 yr					
No. of patients	346		272	512	
Age (yr)	70.3 ± 4.2		71.8 ± 5.1	72.6 ± 5.2	<0.001
Male sex	267 (77.2)		192 (70.6)	352 (68.8)	0.024
HCV	40 (12.4)		62 (25.3)	98 (20.9)	<0.001
Performance					
0	242 (87.1)		172 (86.4)	320 (83.1)	0.298
4	0 (0)		0 (0)	3 (0.8)	
Albumin (mg/dL)	4.14 ± 0.39		4.10 ± 0.42	3.95 ± 0.45	<0.001
ALBI grade 2	92 (26.6)		79 (29.0)	227 (44.3)	<0.001
INR	1.06 ± 0.10		1.07 ± 0.08	1.08 ± 0.10	0.014
Platelet ($\times 10^3/\mu L$)	178.6 ± 55.8		161.0 ± 51.8	165.0 ± 65.6	<0.001
α-FP (ng/mL)	376.0 ± 1,385.3		79.2 ± 256.6	355.1 ± 1,575.6	0.027
PIVKA-II (mAU/mL)	512.2 ± 2,275.7		134.5 ± 531.5	393.7 ± 1,682.3	0.084
No. of tumors					
1	324 (93.6)		244 (89.7)	383 (74.8)	<0.001
2	16 (4.6)		26 (9.6)	98 (19.1)	
3	6 (1.7)		2 (0.7)	31 (6.1)	
Max tumor size (cm)	2.93 ± 1.06		1.95 ± 0.76	2.55 ± 1.09	<0.001
Child-Pugh score	5.11 ± 0.32		5.16 ± 0.37	5.24 ± 0.43	<0.001
MELD score	7.88 ± 1.75		8.04 ± 1.79	8.41 ± 2.36	<0.001

Values are presented as number only, mean ± standard deviation, or number (%).
Some variables had missing data as follows. Age <65 years: DM, 7; HBV, 54; HCV, 213; ALD, 28; performance, 436; INR, 4; α-FP, 99; PIVKAII, 594; MELD, 53. Age ≥65 years: HCV, 94; performance, 268; INR, 1; α-FP, 69; PIVKA-II, 354; MELD, 26.
LR, liver resection; LT, liver transplantation; RFA, radiofrequency ablation; TACE, transarterial chemoembolization; DM, diabetes mellitus; ALD, alcoholic liver disease; ALBI, albumin-bilirubin; INR, international normalized ratio; PIVKA-II, protein induced by Vitamin K absence or antagonist-II; MELD, Model for End-stage Liver Disease.

107 cases of LR and 376 cases of TACE with propensity score matching reported much higher OS and RFS rates in the LR group than in the TACE group (5-year OS rate: 89.7% *vs.* 74.1%, P = 0.008; 5-year RFS: 35.9% *vs.* 8.8%, P < 0.001) [13]. Additionally, our analysis of patients with multiple HCCs within 2 cm revealed a greater 5-year OS rate in the LR group (72.4%) than

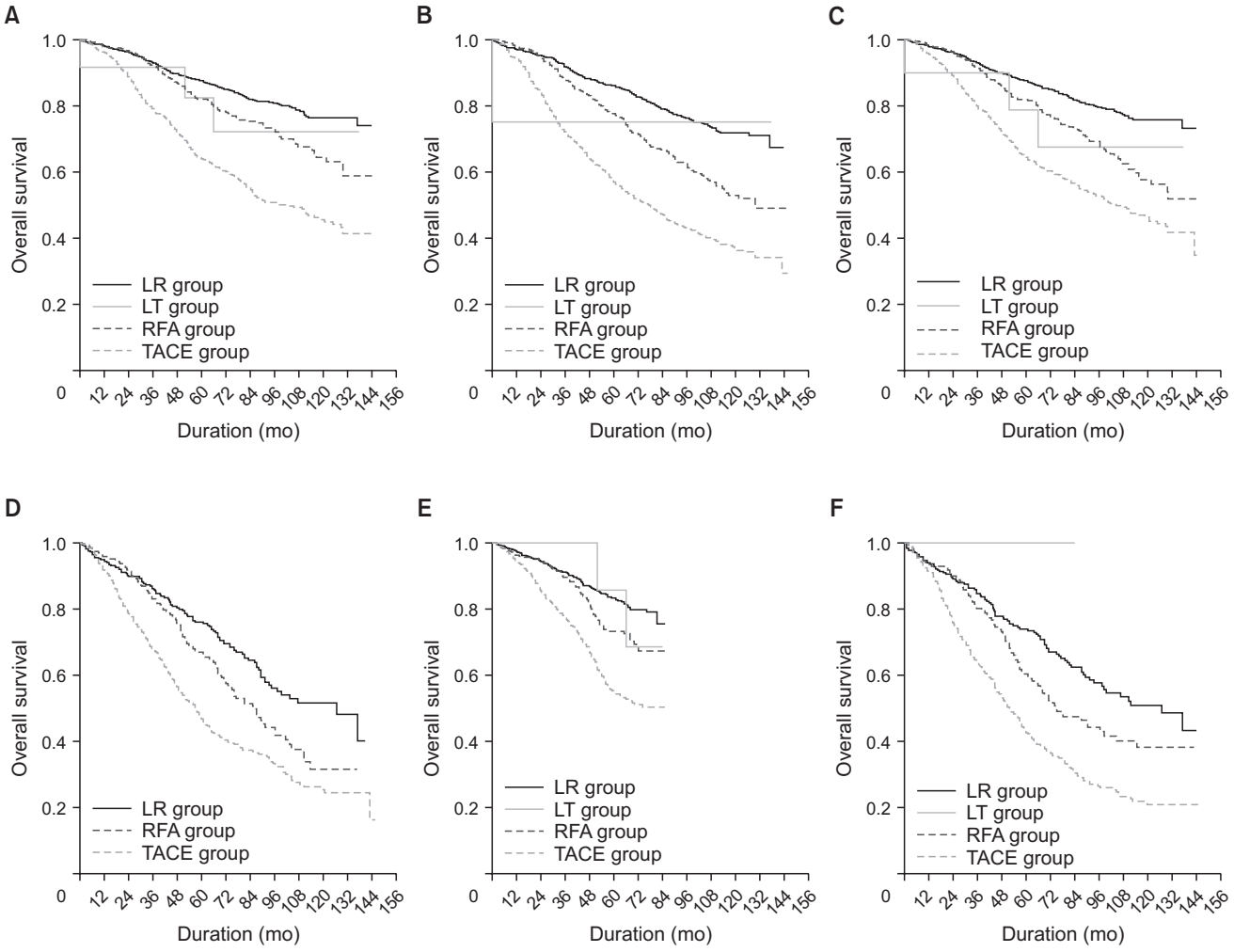

Fig. 5. Overall survivals of additional subgroups. (A) Patients with age equal or older than 65 years. (B) Patients with ages younger than 65 years. (C) Patients who received initial treatment in the early period (2008–2012). (D) Patients who received initial treatment in the late period (2013–2016). (E) Patients with ALBI grade I. (F) Patients with ALBI grade II. LR, liver resection; LT, liver transplantation; RFA, radiofrequency ablation; TACE, transarterial chemoembolization.

in the TACE group (58.7%). However, this difference was not statistically significant (P = 0.12), probably because of the small number of LR cases (n = 31). One meta-analysis review article summarized 7 randomized control trial (RCT) studies and 18 non-RCT studies, with 2,865 cases of LR and 2,764 cases of ablation, including RFA, microwave ablation, and RFA plus TACE [14]. Although there was no significant difference in OS rate in this study, LR was associated with significantly better RFS than RFA in both the RCT and non-RCT studies (HR, 0.57; 95% CI, 0.62–0.92, P = 0.006 in the RCTs), which emphasizes the role of LR even in multiple HCCs within MC.

Multiple official guidelines refraining from recommending LR might be due to past reports of perioperative morbidities [15]. Currently, with the development of perioperative skills, medical support, and minimally invasive surgery, recoveries after LR are more stable [16]. With advances in surgical management and positive findings from multiple studies, prioritizing LR for HCC patients seems reasonable and reliable.

In clinical settings, treatment decisions are significantly influenced by patient age. In our study, a lower proportion of older patients (aged >65 years) underwent LR, whereas a greater proportion of them underwent RFA and TACE (Table 4). However, the survival rate of the LR group (5-year, 76.1%) was also higher than that of the RFA group (67.1%, P = 0.004) and the TACE group even for older patients (46.8%, P < 0.001) (Fig. 5B).

RFA and TACE, which are highly performed for older patients, could be linked to practical issues such as the presence of comorbidities and poor performance. However, considering the better outcomes of LR, it is advisable to assess the risks carefully and consider LR rather than opting for RFA or TACE on the basis solely of age. Our study revealed that older patients who underwent LR had an acceptable 5-year OS rate of 76.1%. Recent advances in minimally invasive LR have benefited older patients.

Table 5. Baseline characteristics according to treatment period

Characteristic	LR group	LT group	RFA group	TACE group	P-value
Between 2008 and 2012					
No. of patients	632	4	347	638	
Age (yr)	56.2 ± 10.3	55.0 ± 9.6	60.4 ± 10.4	62.4 ± 10.4	<0.001
DM	122 (19.4)	1 (25.0)	93 (26.9)	161 (25.4)	0.023
Hypertension	199 (31.6)	3 (75.0)	126 (36.4)	266 (42.0)	0.001
HBV	474 (75.4)	4 (100)	205 (60.7)	401 (64.6)	<0.001
HCV	38 (6.3)	0 (0)	57 (17.2)	80 (13.4)	<0.001
Performance					
0	475 (92.4)	4 (100)	243 (95.7)	455 (90.5)	0.132
4	0 (0)	0 (0)	0 (0)	1 (0.2)	
Albumin (mg/dL)	4.23 ± 0.42	4.25 ± 0.17	4.15 ± 0.41	4.03 ± 0.45	<0.001
ALBI grade 2	142 (22.5)	0	94 (27.1)	227 (35.6)	<0.001
INR	1.05 ± 0.09	1.07 ± 0.07	1.07 ± 0.09	1.07 ± 0.10	<0.001
Platelet ($\times 10^3/\mu L$)	172.6 ± 51.9	156.8 ± 22.4	157.5 ± 49.1	160.3 ± 52.9	<0.001
α-FP (ng/mL)	592.5 ± 3,342.6	819.2 ± 975.5	145.3 ± 746.7	469.2 ± 2,370.7	0.093
PIVKA-II (mAU/mL)	327.1 ± 1,318.5	76.8 ± 51.6	76.9 ± 126.6	350.5 ± 1,528.5	0.089
No. of tumors					
1	582 (92.1)	4 (100)	311 (89.6)	477 (74.8)	<0.001
2	43 (6.8)	0 (0)	33 (9.5)	119 (18.7)	
3	7 (1.1)	0 (0)	3 (0.9)	42 (6.6)	
Max tumor size (cm)	2.87 ± 1.03	2.90 ± 0.90	1.75 ± 0.69	2.39 ± 1.08	<0.001
Child-Pugh score	5.09 ± 0.29	5.00 ± 0.00	5.11 ± 0.32	5.19 ± 0.39	<0.001
MELD score	7.64 ± 1.62	7.00 ± 0.82	8.05 ± 2.17	8.03 ± 1.92	0.001
Between 2013 and 2016					
No. of patients	739	8	332	541	
Age (yr)	58.5 ± 9.9	50.0 ± 4.1	62.9 ± 9.7	63.4 ± 10.5	<0.001
DM	181 (24.6)	1 (12.5)	90 (27.1)	202 (37.3)	<0.001
HBV	523 (72.2)	7 (87.5)	185 (60.9)	311 (61.5)	<0.001
HCV	38 (5.7)	1 (12.5)	41 (15.5)	69 (15.2)	<0.001
Performance					
0	531 (90.0)	5 (83.3)	214 (84.9)	342 (82.6)	0.009
4	0 (0)	0 (0)	0 (0)	3 (0.7)	
Albumin (mg/dL)	4.27 ± 0.41	4.21 ± 0.38	4.15 ± 0.43	4.05 ± 0.44	<0.001
ALBI grade 2	127 (17.2)	2 (25.0)	79 (23.8)	188 (34.8)	<0.001
Platelet ($\times 10^3/\mu L$)	177.1 ± 54.0	153.9 ± 41.9	163.5 ± 55.2	158.3 ± 58.4	<0.001
α-FP (ng/mL)	410.2 ± 1,582.5	101.3 ± 176.7	79.6 ± 262.5	361.6 ± 2,658.1	0.067
PIVKA-II (mAU/mL)	335.0 ± 1,427.2	169.9 ± 362.8	90.1 ± 441.9	306.4 ± 1,320.9	0.067
No. of tumors					
1	689 (93.2)	6 (75.2)	288 (86.7)	392 (72.5)	<0.001
2	47 (6.4)	1 (12.5)	42 (12.7)	108 (20.0)	
3	3 (0.4)	1 (12.5)	2 (0.6)	41 (7.6)	
Max tumor size (cm)	2.74 ± 1.02	2.44 ± 1.26	1.85 ± 0.76	2.45 ± 1.06	<0.001
Child-Pugh score	5.09 ± 0.29	5.13 ± 0.35	5.15 ± 0.36	5.18 ± 0.39	<0.001
MELD score	7.70 ± 1.83	7.75 ± 0.71	8.00 ± 1.80	8.35 ± 2.35	0.001

Values are presented as number only, mean ± standard deviation, or number (%).
Some variables had missing data as follows. Between 2008 and 2012: DM, 8; hypertension, 8; HBV, 29; HCV, 80; performance, 346; INR, 5; α-FP, 93; PIVKA-II, 646; MELD, 63. Between 2013 and 2016: DM, 2; hypertension, 4; HBV, 78; HCV, 227; performance, 358; α-FP, 75; PIVKA-II, 302; MELD, 16.
LR, liver resection; LT, liver transplantation; RFA, radiofrequency ablation; TACE, transarterial chemoembolization; DM, diabetes mellitus; ALBI, albumin-bilirubin; INR, international normalized ratio; PIVKA-II, protein induced by Vitamin K absence or antagonist-II; MELD, Model for End-stage Liver Disease.

One recent study analyzing 367 older patients (aged ≥70 years) suggested that even elderly patients (aged ≥85 years) may have acceptable outcomes after LR when selected carefully [17].

Additional analysis based on the treatment period also revealed that the LR group had the highest OS rate, followed by the RFA and TACE groups, irrespective of the treatment

Table 6. Baseline characteristics according to ALBI grade

Characteristic	LR group	LT group	RFA group	TACE group	P-value
ALBI grade I					
No. of patients	1,102	10	506	764	
Age (yr)	57.1 ± 9.9	52.0 ± 7.1	61.1 ± 9.9	61.4 ± 10.3	<0.001
Male sex	886 (80.4)	8 (80.0)	392 (77.5)	606 (79.3)	0.608
DM	233 (21.2)	2 (20.0)	131 (25.9)	230 (30.3)	<0.001
Hypertension	408 (37.2)	4 (40.0)	203 (40.3)	336 (44.2)	0.025
HBV	829 (76.1)	10 (100)	309 (64.5)	491 (67.7)	<0.001
HCV	48 (4.7)	0 (0)	63 (14.4)	81 (12.0)	<0.001
Performance					
0	817 (91.5)	7 (87.5)	342 (91.7)	529 (88.0)	0.231
4	0 (0)	0 (0)	0 (0)	0 (0)	
Albumin (g/dL)	4.39 ± 0.31	4.33 ± 0.20	4.33 ± 0.28	4.29 ± 0.28	<0.001
ALBI score	–3.02 ± 0.25	–2.96 ± 0.19	–2.98 ± 0.24	–2.94 ± 0.22	<0.001
INR	1.04 ± 0.08	1.07 ± 0.08	1.05 ± 0.08	1.06 ± 0.09	0.002
Platelet (×10^3/μL)	176.1 ± 51.7	161.0 ± 35.7	162.2 ± 49.0	163.9 ± 56.0	<0.001
α-FP (ng/mL)	515.3 ± 2713.4	407.4 ± 681.5	111.6 ± 585.5	502.9 ± 3016.6	0.026
PIVKA-II (mAU/mL)	285.3 ± 962.0	162.8 ± 319.4	67.7 ± 141.8	338.7 ± 1427.7	0.002
No. of tumors					
1	1,026 (93.1)	9 (90.0)	453 (89.5)	588 (74.3)	<0.001
2	71 (6.4)	0 (0)	50 (9.9)	147 (19.2)	
3	5 (0.5)	1 (10.0)	3 (0.6)	49 (6.4)	
Max tumor size (cm)	2.80 ± 1.03	2.83 ± 1.05	1.83 ± 0.72	2.38 ± 1.05	<0.001
Child-Pugh score	5.04 ± 0.19	5.00 ± 0.00	5.03 ± 0.18	5.03 ± 0.17	0.807
MELD score	7.56 ± 1.73	7.50 ± 0.85	7.73 ± 1.91	7.87 ± 2.08	0.007
ALBI grade II					
No. of patients	739	8	332	541	
Age (yr)	59.1 ± 11.0	50.0 ± 1.4	63.1 ± 10.7	65.5 ± 10.2	<0.001
Male sex	207 (77.0)	1 (50.0)	128 (74.0)	297 (71.6)	0.387
DM	70 (26.2)	0 (0)	52 (30.1)	133 (32.0)	0.321
Hypertension	96 (36.0)	0 (0)	69 (39.9)	177 (42.7)	0.224
HBV	168 (63.9)	1 (50.0)	81 (49.7)	221 (55.0)	0.026
HCV	28 (11.3)	1 (50.0)	35 (21.9)	68 (18.1)	0.016
Performance					
0	189 (89.6)	2 (100)	115 (86.5)	268 (84.8)	0.381
4	0 (0)	0 (0)	0 (0)	4 (1.3)	
Albumin (g/dL)	3.66 ± 0.28	3.70 ± 0.28	3.63 ± 0.29	3.58 ± 0.31	0.009
ALBI score	–2.35 ± 0.22	–2.30 ± 0.15	–2.30 ± 0.24	–2.27 ± 0.26	0.001
INR	1.10 ± 0.11	1.05 ± 0.01	1.13 ± 0.11	1.12 ± 0.11	0.007
Platelet (×10^3/μL)	170.6 ± 58.5	124.0 ± 8.5	155.3 ± 60.6	151.0 ± 53.6	<0.001
α-FP (ng/mL)	40.9 ± 1,703.3	6.7 ± 3.4	117.1 ± 498.0	262.8 ± 1,000.3	0.113
PIVKA-II (mAU/mL)	550.9 ± 2,555.5	19.0 ± 8.5	131.7 ± 628.2	301.6 ± 1,389.4	0.217
No. of tumors					
1	245 (91.1)	1 (50.0)	146 (84.4)	301 (72.5)	<0.001
2	19 (7.1)	1 (50.0)	25 (14.5)	80 (19.3)	
3	5 (1.9)	0 (0)	2 (1.2)	34 (8.2)	
Max tumor size (cm)	2.81 ± 1.02	1.40 ± 0.85	1.90 ± 0.74	2.48 ± 1.10	<0.001
Child-Pugh score	5.33 ± 0.47	5.50 ± 0.71	5.42 ± 0.50	5.47 ± 0.50	0.002
MELD score	8.12 ± 1.68	7.50 ± 0.71	8.88 ± 1.97	8.75 ± 2.11	<0.001

Values are presented as number only, mean ± standard deviation, or number (%).
Some variables had missing data as follows. ALBI grade1: DM, 8; hypertension, 10; HBV, 78; HCV, 233; performance, 507; NR, 3; α-FP, 116; PIVKAII, 667; MELD, 54. ALBI grade II: DM, 2; hypertension, 2; HBV, 29; HCV, 74; performance, 197; INR, 2; α-FP, 52; PIVKA-II, 281; MELD, 25.
LR, liver resection; LT, liver transplantation; RFA, radiofrequency ablation; TACE, transarterial chemoembolization; DM, diabetes mellitus; ALBI, albumin-bilirubin; INR, international normalized ratio; PIVKA-II, protein induced by Vitamin K absence or antagonist-II; MELD, Model for End-stage Liver Disease.

period. However, the proportion of patients in the late period was greater in the LR group than in the early period (45.6% *vs.* 39.0%), and *vice versa* for the TACE group (33.4% *vs.* 39.0%) (Table 5). These trends might be attributed to clinicians' preference for LR over TACE over the expectation of better outcomes.

A unique factor that influences treatment decisions for HCC is 'reserved hepatic function.' Traditionally, the CP class has been most adapted for evaluating hepatic function. The BCLC group recommends LR only when patients have preserved liver function (compensated for CP class A) [18]. However, subjective parameters such as ascites and encephalopathy and the same weight of all 5 parameters are often regarded as limitations of the CP class. The recently introduced ALBI score and grade are considered good options for evaluating hepatic function [9]. The importance of the ALBI score has increased. It is now included as a decision factor for HCC treatment in the BCLC guidelines [5,19]. Some studies have shown an acceptable range of post-hepatectomy liver failure (PHLF) rates for ALBI grades I and II [20]. Therefore, in our study, we further subdivided patients into those with ALBI grades I and II.

There were 859 patients with ALBI grade II, accounting for 26.5% of all patients. Patients with ALBI grade II had a shorter OS rate than those with ALBI grade I (Fig. 5E, F). However, the 5-year OS rate following each treatment significantly differed in the following order: LR > RFA > TACE (74.0%, 60.4%, and 42.5%, respectively; $P < 0.05$) even in patients with ALBI grade II. TACE-treated patients accounted for the largest proportion of patients (n = 415, 48.3%). These patients had the lowest survival rate.

The postoperative 1-year OS rate of patients with ALBI grade II was 93.3%, which was acceptable. These findings suggest that HCC in patients with ALBI grade II may be resectable, although our study's ALBI grade II patients were limited by already meeting the CP class A criteria, potentially contributing to favorable outcomes. Zhang et al. analyzed 198 patients with ALBI grade II and reported that only 9.6% of patients experienced PHLF, whereas 66.7% of those with ALBI grade III experienced PHLF [20]. However, compared with patients with ALBI grade I, patients with ALBI grade II in this study did not gain a survival benefit from curative LR over RFA, thereby differing from our study's results.

There is no definite consensus on the cutoff value of platelets reflecting portal hypertension. In 2012, the European Association for the Study of the Liver (EASL) guidelines regarded a platelet count ≥100,000/μL as ideal for LR [21]. However, the EASL 2018 guidelines do not mention a specific "100,000/μL" value, with only the general concept of 'portal hypertension' remaining [6]. While definite portal hypertension, referred to as a hepatovenous pressure gradient ≥10 mmHg, can be measured only by invasive maneuvers, numerous noninvasive methods have been developed. The platelet count and presence of collateral vessels are still among the simplest and most prevalently used criteria [22]. Along with PHLF, thrombocytopenia complicates LR due to the risk of bleeding. However, minimally invasive surgery can reduce bleeding by creating a pneumoperitoneum to support minor hepatectomy in eligible patients with platelets between 50,000 and 100,000/μL.

Nevertheless, defining resectability is highly complicated and cannot be judged solely by CP class or portal hypertension. Numerous methods were used to evaluate reserved hepatic function. ICG R15 is one of the most prevalent methods for assessing PHLF. Usually, more than 15% of the ICG R15 is considered a contraindication for major hepatectomy in liver cirrhosis patients [23]. Future liver remnant (FLR) is also an important factor that affects postoperative outcomes [24]. Even if the tumor size and number are small, it is difficult to retain sufficient liver volume if the tumor is situated deep inside the liver. Some studies have shown a relationship between the ICG retention rate and FLR, thus affecting postoperative outcomes [25].

While indications for surgery are controversial, the overall proportion of patients who undergo RFA or TACE is relatively high (20.9% and 36.4%, respectively). The APASL group also noted that RFA for patients with resectable HCC (≤3 cm in size, ≤3 in number) is recommended as only an alternative treatment, although it is widely used in Asia-Pacific regions. One recent study including 2,533 patients with HCC from 8 Asia-Pacific countries showed approximately 20.8% of HCC patients with BCLC stage 0 and A received RFA as the initial treatment [26].

As shown in Table 2, various factors besides the first treatment type, patient age, and ALBI grade appear to affect patient OS rate. Conditions such as DM, hypertension, and HCV showed significant differences only in the univariate analysis, but not in the multivariate analysis. This is likely due to the higher proportion of these conditions in the RFA or TACE groups, which demonstrate relatively lower treatment efficacy. In the case of ALD, despite its high prevalence among RFA and TACE patients, it was associated with poor prognosis even in the multivariate analysis (HR, 1.29; $P = 0.003$). This may be due not only to the detrimental effects of alcohol on liver function but also to the fact that alcoholic patients may already have various undiagnosed underlying diseases as a result of alcohol abuse and poor self-management, as well as potentially lower post-treatment adherence [27,28].

Platelet count showed positive results for OS rate in the univariate analysis, but it did not reach statistical significance in the multivariate analysis ($P = 0.066$). This is likely because we set the resectability criterion for our patients at 100,000/μL, thereby excluding those with severe thrombocytopenia that would have significantly impacted patient prognosis. Regarding

tumor markers, AFP did not show a statistically significant difference, and although PIVKA-II was significant ($P < 0.001$), its HR did not indicate a substantial difference. It is well established in the literature that elevated tumor marker levels are associated with poor prognosis in HCC [29,30]. However, our study's focus on patients with early-stage HCC within MC, likely resulted in a cohort with lower overall tumor marker levels, which may have attenuated the prognostic effect. The CP score did not show statistical significance in the multivariate analysis, which can be attributed to our study population being limited to CP class A patients. However, it is noteworthy that even within this restricted patient cohort, the ALBI grade demonstrated statistical significance in the multivariate analysis (HR, 1.32; $P = 0.022$). This finding holds particular significance, as it suggests that the ALBI grade may offer more nuanced prognostic information even among patients with relatively well-preserved liver function Additionally, microscopic vascular invasion, which is not detectable on imaging, can lead to poor OS [31]. However, in our study, we did not conduct an analysis of this factor because pathological confirmation was not feasible for patients other than those who underwent LT or LT.

The main limitation of this study was the inability to analyze the RFS rate. The KLCA database does not retain data on HCC recurrence. RFS is known to contribute to a more refined understanding of treatment efficacy. However, despite numerous studies investigating its utility as a surrogate endpoint for OS rate in malignant tumors, controversies persist depending on tumor type. For instance, a meta-analysis examining the treatment response to immune checkpoint inhibitors in 5,144 patients with advanced HCC reported a moderate correlation between RFS and OS rate (correlation coefficient, 0.63) [32]. In the context of hepatobiliary and pancreatic cancers, a recent study revealed contrasting findings across different malignancies [33]. The study demonstrated strong correlations between RFS and OS rate in pancreatic ductal adenocarcinoma (correlation coefficient, 0.80) and biliary tract cancer (correlation coefficient, 0.75), whereas HCC (correlation coefficient, 0.67) and colorectal cancer liver metastases (correlation coefficient, 0.53) exhibited weaker correlations. Peng et al. [34] addressed this discrepancy, suggesting that the relatively longer survival periods of HCC and colorectal cancer liver metastases may contribute to the weak correlation between RFS and OS rate in these cancers. They also noted that the availability of multiple curative options even after recurrence can lead to favorable OS outcomes despite poor RFS. Aside from RFS, other surrogate endpoints have been widely discussed in the context of palliative therapy for unresectable HCC, including complete or partial remission as defined by the modified Response Evaluation Criteria in Solid Tumors (mRECIST) [35,36].

The outcomes of LT for patients with resectable HCC within MC were not compared because of the small cohort size ($n = 12$). It is noteworthy that the number of LT cases is so low, given that the superior outcomes of LT for patients within MC have been well established. Although there is a lack of studies clearly elucidating this trend in Korea, several factors may be considered. (1) Due to the low rate of brain-dead donors in Korea, most HCC patients with preserved liver function should undergo living donor liver transplantation (LDLT) [28]. However, since LDLT requires the sacrifice of a living donor, patients and their families may prefer other treatments if available before considering LT. Patients in our study had Child-Pugh class A and platelet counts above 100,000, making them resectable. Therefore, many patients may opt for other treatments first and consider LT only if the disease recurs. (2) Few hospitals can perform LDLT quickly, except for some large centers, due to constraints in LT donor and recipient evaluation and operating room availability. Consequently, RFA or TACE might be performed while waiting for LDLT. In such cases, our data would exclude these patients as LT was not regarded as their first treatment. (3) Various criteria for LT have been published, and studies have shown favorable outcomes for LT even when exceeding the MC. As a result, there may be less urgency to perform LT immediately when patients are within the MC [29]. (4) Furthermore, owing to the shortage of liver donors in the Asia-Pacific region, the APASL guidelines recommend LT as the first-line treatment for HCC patients with CP class B or C.

However, some recent studies continue to emphasize the role of LT for HCC within MC. One study included multiple HCCs within MC, but the AFP level was lower than 1,000 ng/mL, with 1,211 cases of LT compared with 335 cases of LR, and the survival of LT patients was much greater (HR, 0.34; 95% CI, 0.28–0.64; $P < 0.001$) [37]. Another study compared the outcomes of 117 LT cases and 905 LR cases within MC via a nomogram for predicting microvascular invasion (MVI) [38]. In both the high- and low-risk groups for MVI, the LT group had superior OS and RFS rates than the LR group did. One recent meta-analysis compared LR *vs.* LT for HCC within the MC, including 18,421 patients from 35 studies across 13 countries [39]. In this study, LR ($n = 8,204$) was associated with a poorer OS rate (HR, 1.44; $P < 0.01$) and RFS (HR, 2.71; $P < 0.01$) compared to LT ($n = 9,891$). However, no significant differences in OS rate were observed in studies conducted after 2010 ($P = 0.12$), studies on uninodular HCC ($P = 0.13$), and studies conducted in Asia ($P = 0.25$). Additionally, LDLT-only studies (936 patients) showed no significant difference in OS rate ($P = 0.30$). DFS in these 4 sub-analyses was improved in LT patients. Although this study differs from ours in that it did not specifically focus on resectable HCC, it is noteworthy that the overall trend remains similar—when considering sub-analyses of studies conducted after 2010, LDLT-only studies, and studies from Asia, LR and LT show no significant differences in

outcomes.

This study included patients with resectable HCC and revealed that the OS rate following initial treatment for HCC within MC was generally higher in the LR group than in the RFA and TACE groups. The LR group presented the highest OS rate for patients with single tumors of any size. However, in the case of multiple tumors, the LR and RFA groups showed no significant difference in OS rate. Although the treatment plan for HCC should be individualized, in cases of resectable HCC within MC, LR should be emphasized owing to its proven beneficial outcomes.

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Conflicts of Interest

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