Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Impact of Initial Therapy and Treatment Interval on Survival in Hepatocellular Carcinoma by Tumor Stage and Child–Pugh Class: Korean Primary Liver Cancer Registry Analysis

Woo Sun Rou
Chungnam National University College of Medicine
Hyuk Soo Eun
hyuksoo@cnuh.co.kr

Chungnam National University College of Medicine
In Sun Kwon
DreamCIS incorporated
Hong Jae Jeon
Chungnam National University College of Medicine
Jong Seok Joo
Chungnam National University College of Medicine
Ju Seok Kim
Chungnam National University College of Medicine
Eaum Seok Lee
Chungnam National University College of Medicine
Seok Hyun Kim
Chungnam National University College of Medicine
Byung Seok Lee
Chungnam National University College of Medicine

Research Article

Keywords: Treatment Outcome, Carcinoma, Hepatocellular, Survival Analysis, Child–Pugh Classification

Posted Date: June 28th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-9806269/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Additional Declarations: No competing interests reported.

Abstract

Background

Curative treatment is the primary goal for hepatocellular carcinoma; however, recurrence or residual disease often necessitates subsequent therapy. A short interval between initial and subsequent treatments may reflect limited treatment durability, contribute to hepatic functional deterioration, and adversely affect prognosis. This study aimed to evaluate survival outcomes according to the initial treatment modality and investigate the association between the first-to-second treatment interval and overall survival (OS).

Methods

A total of 10,742 patients from the Korean Primary Liver Cancer Registry were analyzed. Survival outcomes according to initial treatment were assessed in 9,156 patients, and treatment interval analysis was performed in 3,874 patients, with patients stratified according to tumor stage and Child–Pugh class. OS was analyzed, and multivariate Cox regression was used to evaluate treatment interval as an independent prognostic factor.

Results

Across most Barcelona Clinic Liver Cancer stages and Child–Pugh class subgroups, surgical resection and local ablative therapies were associated with superior OS compared to locoregional and systemic therapies. Treatment intervals differed significantly according to initial treatment modality, with curative or near-curative treatments showing longer intervals than non-curative approaches, consistently observed across all tumor stages. A longer first-to-second treatment interval was independently associated with improved OS (hazard ratio, 0.981; $p < 0.001$).

Conclusions

First-to-second treatment interval was independently associated with survival in hepatocellular carcinoma patients and varied according to the initial treatment modality. These findings suggest that selecting curative-intent treatment as the initial strategy may prolong treatment intervals and may be associated with improved clinical outcomes.

Background

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related mortality worldwide, with an estimated 5-year overall survival (OS) of 18% [1, 2]. Curative treatments, including liver transplantation (LT), surgical resection, and radiofrequency ablation (RFA), are feasible in only approximately one-third of

patients with HCC. The remaining patients typically present with advanced disease, impaired hepatic function, or poor performance status [2, 3]. These patients are commonly treated with non-curative modalities, such as transarterial chemoembolization (TACE), radiotherapy, or systemic therapies, including molecular-targeted agents and immunotherapy [4].

Tumor stage is the primary determinant of initial treatment selection, with hepatic function serving as a critical additional factor. The Barcelona Clinic Liver Cancer (BCLC) staging system, the most widely used framework, incorporates both tumor burden and hepatic function. Within this system, patients with Child–Pugh class (CPC) C are classified as BCLC stage D regardless of tumor characteristics. BCLC stages A through C include patients with CPC–A and CPC–B, although recommended treatment strategies may differ between these groups [5]. In contrast, the modified Union for International Cancer Control (mUICC) staging system, commonly used in South Korea and Japan, is based solely on tumor characteristics and does not incorporate hepatic function. As a result, studies evaluating initial treatment selection and prognosis using both tumor stage and hepatic functional status remain limited [6].

The management of recurrent or residual disease is a distinct consideration beyond the initial treatment decision. Despite curative-intent therapy, approximately 70% of patients with HCC develop recurrence within 5 years [2, 4]. These recurrences frequently require additional interventions for residual or recurrent disease. Previous studies report a median of three treatment sessions, with approximately 27.3% of patients undergoing six or more sessions, underscoring the frequent need for repeated treatment [7].

Although repeated interventions may reduce tumor burden, they often contribute to progressive hepatic injury and functional decline [8–10]. Given that approximately 80% of patients with HCC have underlying cirrhosis [5], the liver's capacity for regeneration following treatment-related injury is limited [11, 12]. Consequently, cumulative hepatic dysfunction during treatment constrains therapeutic options and is associated with poorer prognosis.

Accordingly, this study aimed to evaluate patient outcomes according to initial treatment modality, stratified by tumor stage and hepatic functional status, using nationwide cohort data from the Korean Primary Liver Cancer Registry (KPLCR). We also examined the interval between the first and second treatments and assessed its independent association with patient survival.

Methods

Study population

We retrospectively analyzed data extracted from the KPLCR, a nationally representative database comprising approximately 15% of newly diagnosed primary liver cancer cases in South Korea, through stratified random sampling by geographic region and hospital type, selected from the Korea Central Cancer Registry. We included patients registered between 2008 and 2015, and the initial dataset included 10,742 patients with diagnoses of primary liver malignancy. HCC was diagnosed through

histology or based on characteristic imaging findings (arterial phase hyperenhancement with portal or delayed phase washout) using contrast-enhanced computed tomography or magnetic resonance imaging.

Of these, 9,156 patients were included in Analysis 1 (initial treatment comparison cohort) after excluding those with (1) combined HCC and cholangiocarcinoma, other hepatic malignancies, or uncertain pathological diagnosis; (2) insufficient information regarding the modality or date of the initial treatment; (3) missing or incomplete data regarding mUICC, BCLC stage, or CPC; and (4) insufficient survival data (Fig. 1). For Analysis 2 (treatment interval cohort), additional exclusions were applied to patients who (1) received supportive care as the initial treatment, (2) received supportive care as the second treatment or had insufficient data regarding the second treatment, or (3) had insufficient information on the treatment interval. Consequently, 3,874 patients were included in Analysis 2.

This study was reviewed and approved by the Institutional Review Board of Chungnam National University Hospital (CNUH IRB: 2020-04-028) and was conducted in accordance with the Declaration of Helsinki. Informed consent was waived by the ethics committee due to the retrospective nature of the study.

Data collection and definitions

Using the KPLCR dataset, data on age, sex, presence of diabetes mellitus and hypertension, body mass index, smoking status, alcohol intake, suspected etiology of HCC, performance status, Child–Pugh score, and model for end-stage liver disease score were collected. Laboratory data included platelet count, serum albumin, sodium, total bilirubin, creatinine, international normalized ratio, alpha-fetoprotein (AFP), and protein levels induced by vitamin K absence or antagonist-II (PIVKA-II). Tumor characteristics were assessed using dynamic computed tomography or magnetic resonance imaging, and both the mUICC and BCLC staging systems were used for tumor staging.

Treatment classification and interval definition

Treatments were categorized into five modalities: (1) Surgical therapy: surgical resection and LT; (2) Local ablative therapy: RFA, percutaneous ethanol injection, microwave ablation, and other focal ablative techniques; (3) Locoregional therapy: TACE, transarterial chemoinfusion, transarterial radioembolization, and external beam radiotherapy; (4) Systemic therapy: Tyrosine kinase inhibitors (sorafenib, lenvatinib), immunotherapy agents, and combination regimens; and (5) Supportive care.

Study design

Analysis 1 stratified patients with HCC by tumor stage, defined using the BCLC and mUICC staging systems, and further stratified by CPC. Patients were initially categorized into 12 groups based on the

combination of mUICC stage and CPC. The combined BCLC stage and CPC stratification yielded eight groups, as all CPC–C patients were classified as BCLC stage D. OS, defined as the interval from HCC diagnosis to death from any cause or the last follow-up (censored), was subsequently compared according to the initial treatment. Analysis 2 investigated the differences in treatment intervals according to the initial treatment modality and assessed their impact on OS.

Statistical analysis

Categorical variables are presented as frequencies and percentages, whereas continuous variables are summarized as means with standard deviations or medians with interquartile ranges. OS was estimated using the Kaplan–Meier method, and survival differences were compared using the log-rank test. Cox proportional hazards regression analysis was performed to evaluate the effect of the treatment interval between the first and second treatments on patient survival. Variables with a p-value < 0.1 in univariate analysis were subsequently entered into the multivariate analysis using the backward stepwise method, with $p < 0.05$ retained in the final models. Hazard ratios (HR) and 95% confidence intervals (CI) were determined. All statistical analyses were performed using IBM SPSS (version 29.0; IBM Corp., Armonk, NY).

Results

Baseline characteristics

A total of 9,156 patients were included in Analysis 1, and 3,874 patients were included in Analysis 2. Their baseline characteristics are summarized in Table 1. The mean age of the patients in Analysis 1 was 60 years, and 79.2% were male. The most common etiology of HCC was hepatitis B virus infection (63.4%), followed by alcohol consumption (32.7%) and hepatitis C virus infection (12.9%). CPC–A, CPC–B, and CPC–C were observed in 72.8%, 22.1%, and 5.1% of patients, respectively. BCLC stages 0, A, B, C, and D accounted for 6.9%, 39.6%, 11.4%, 35.6%, and 6.4% of patients, respectively, whereas those with mUICC stages I, II, III, IVA, and IVB accounted for 14.9%, 37.1%, 25.4%, 12.0%, and 10.6%, respectively.

Table 1
Baseline characteristics.

Characteristics	Analysis 1 (n = 9,156)	Analysis 2 (n = 3,874)
Age (year)	60.0 ± 11.4	59.4 ± 10.8
Mean ± SD	59.0 (52.0–68.0)	59.0 (52.0–68.0)
Median (IQR)		
Sex, male	7249 (79.2%)	3096 (79.9%)
DM	2223 (24.5%), missing 79	947 (24.5%), missing 11
HTN	2949 (32.5%), missing 86	1273 (33.0%), missing 15
BMI, median (IQR)	23.6 (21.6–25.8)	23.8 (21.8–25.9)
HBsAg positive	5648 (63.4%), missing 247	2504 (66.3%), missing 95
HCV Ab positive	1110 (12.9%), missing 538	503 (13.7%), missing 215
Alcohol intake	2944 (32.7%), missing 156	1259 (32.9%), missing 49
Smoking	4128 (45.5%), missing 80	1859 (48.1%), missing 8
Child–Pugh class, A/B/C	6666 (72.8%)/2024 (22.1%)/466 (5.1%)	3187 (82.3%)/627 (16.2%)/60 (1.5%)
MELD score, median (IQR)	8.0 (7.0–11.0), missing 362	8.0 (7.0–10.0), missing 130
Ascites, present	2201 (24.2%), missing 53	622 (16.1%), missing 22
Hepatic encephalopathy history, present	201 (2.2%), missing 30	50 (1.3%), missing 10
ECOG, 0/1/2/3/4	5242 (76.3%)/1189 (17.3%)/265 (3.9%)/106 (1.5%)/66 (1.0%), missing 2288	2528 (82.1%)/482 (15.7%)/60 (1.9%)/5 (0.2%)/4 (0.1%), missing 795
Tumor number, 1/2–3/4≤	5586 (61.0%)/1632 (17.8%)/1937 (21.2%), missing 1	2299 (59.3%)/901 (23.3%)/674 (17.4%)
Tumor maximum diameter, < 2 cm/2 cm to 5 cm/5 cm≤	2399 (26.2%)/3281 (35.9%)/3468 (37.9%), missing 8	1028 (26.5%)/1557 (40.2%)/1289 (33.3%)
Vessel invasion, present	2340 (25.6%)	802 (20.7%)

Abbreviations: AFP, alpha-fetoprotein; Ab, antibody; BCLC, Barcelona Clinic Liver Cancer; BD, bile duct; BMI, body mass index; DM, diabetes mellitus; ECOG, Eastern Cooperative Oncology Group performance status; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HTN, hypertension; INR, international normalized ratio; IQR, interquartile range; LN, lymph node; MELD, Model for End-stage Liver Disease; mUICC, modified Union for International Cancer Control; PIVKA-II, protein induced by vitamin K absence-II; PT, prothrombin time; SD, standard deviation.

Characteristics	Analysis 1 (n = 9,156)	Analysis 2 (n = 3,874)
BD invasion, present	225 (2.5%)	77 (2.0%)
LN metastasis, present	700 (7.6%)	200 (5.2%)
Distant metastasis, present	973 (10.6%)	262 (6.8%)
mUICC, stage I/II/III/IV–A/IV–B	1362 (14.9%)/3393 (37.1%)/2328 (25.4%)/1100 (12.0%)/973 (10.6%)	530 (13.7%)/1521 (39.3%)/1178 (30.4%)/383 (9.9%)/262 (6.8%)
BCLC stage 0/A/B/C/D	629 (6.9%)/3630 (39.6%)/1046 (11.4%)/3261 (35.6%)/590 (6.4%)	260 (6.7%)/1655 (42.7%)/583 (15.0%)/1308 (33.8%)/68 (1.8%)
AFP, ng/mL	13181.3 ± 103889.2	10614.1 ± 102954.1
Mean ± SD	28.2 (5.1–554.5)	26.5 (5.7–387.9)
Median (IQR)		
PIVKA-II, mAU/mL	4671.3 ± 18629.9	3839.5 ± 12323.6
Mean ± SD	129.0 (28.0–1757.0)	129.5 (29.0–1569.3)
Median (IQR)		
Albumin, mean ± SD, g/dL	3.7 ± 0.7	3.8 ± 0.6
Total bilirubin, mean ± SD, mg/dL	1.7 ± 3.0	1.2 ± 1.8
PT, INR, mean ± SD	1.2 ± 0.8	1.1 ± 0.2
Platelet count, mean ± SD, ×103/μL	156.6 ± 88.8	149.3 ± 80.8
First treatment, Surgical therapy/Local ablative therapy/Locoregional therapy/Systemic therapy/Supportive care	1817 (19.8%)/1038 (11.3%)/4167 (45.5%)/490 (5.4%)/1644 (18.0%)	614 (15.8%)/441 (11.4%)/2661 (68.7%)/158 (4.1%)
Second treatment, Surgical therapy/Local ablative therapy/Locoregional therapy/Systemic therapy	248 (2.7%)/665 (7.3%)/2688 (29.4%)/306 (3.3%)/432 (4.7%), missing 4817	246 (6.4%)/661 (17.1%)/2661 (68.7%)/306 (7.9%)

Abbreviations: AFP, alpha-fetoprotein; Ab, antibody; BCLC, Barcelona Clinic Liver Cancer; BD, bile duct; BMI, body mass index; DM, diabetes mellitus; ECOG, Eastern Cooperative Oncology Group performance status; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HTN, hypertension; INR, international normalized ratio; IQR, interquartile range; LN, lymph node; MELD, Model for End-stage Liver Disease; mUICC, modified Union for International Cancer Control; PIVKA-II, protein induced by vitamin K absence-II; PT, prothrombin time; SD, standard deviation.

Age and sex demographics of the patients in Analysis 2 were similar to those in Analysis 1. Analysis 2 included a higher proportion of patients with CPC–A and a lower proportion with CPC–C as well as

relatively more patients with BCLC stage B and mUICC stage III, reflecting the exclusion of supportive care patients.

Initial and second treatment patterns

Locoregional therapy (45.5%) was the most frequently administered initial treatment, followed by surgery (19.8%), local ablative therapy (11.3%), supportive care (18%), and systemic therapy (5.4%) (Table 1). The most common secondary treatments were locoregional therapy (62.4%, 51.0%, and 74.2%), local ablative therapy (21.2%, 42.6%, and 12.9%), and surgical treatment (5.9%, 5.4%, and 6.9%) in patients who initially received surgical, local ablative, and locoregional therapies, respectively (Supplementary Table 1).

Cumulative survival rates based on initial treatment in groups classified by BCLC stage and CPC

In CPC–A, surgical therapy was associated with the highest survival rates in BCLC stages 0 and A, followed by local ablative and locoregional therapies (Fig. 2a, 2b). However, in BCLC stages B and C, no significant survival differences were observed between surgical and local ablative therapies. Locoregional therapy showed lower survival rates than surgical therapy and local ablative therapy in BCLC stages B and C, but demonstrated better survival rates than supportive care or systemic therapy in CPC–A patients (Fig. 2d, 2f). In CPC–B, the survival patterns in BCLC stages A and C showed that surgical therapy yielded the most favorable outcomes, followed by local ablative and locoregional therapies. However, no significant differences were observed in BCLC stage B (Fig. 2c, 2e, 2g). Locoregional therapy was associated with better survival than systemic or supportive therapies in patients with BCLC stages B and C (Fig. 2e, g). For BCLC stage D, patients who underwent any treatment demonstrated improved survival compared with those who received supportive care alone (Fig. 2h).

Cumulative survival rates based on initial treatment in groups classified by mUICC stage and CPC

In CPC–A, surgical therapy was associated with better survival than local ablation therapy in patients with mUICC stages I and II. In stages III–IV, there was no significant difference in survival between the two treatments in CPC–A. Locoregional therapy was associated with worse survival than surgical or local ablative therapy, but better survival than supportive care or systemic therapy (Fig. 3a, 3d, 3g, 3j). For CPC–B, survival after surgical therapy was similar to that after local ablation or locoregional therapy in patients with mUICC stage I. In stages II and III, surgical therapy was associated with better survival than local ablation or locoregional therapy (Fig. 3b, 3e, 3h). In mUICC stage IV, surgical therapy was associated with better survival than locoregional therapy, whereas no difference was found when compared with local ablation therapy (Fig. 3k). In CPC–C, no significant differences in survival were observed between surgical therapy, local ablation therapy, and locoregional therapy, except for mUICC stage II (Fig. 3c, f, i, l).

Treatment interval

Across all BCLC stages and Child–Pugh classes, treatment intervals varied consistently according to the type of initial therapy (Table 2). Curative-intent treatments, including resection, LT, and local ablative therapy, are associated with substantially longer treatment intervals than non-curative approaches.

Table 2
Treatment Interval according to initial treatment in groups classified by BCLC stage and CPC.

Group (n, %)	First treatment (n, %)	Treatment interval, months, median (IQR)	Group (n, %)	First treatment (n, %)	Treatment interval, months, median (IQR)
BCLC 0 & CPC–A (260, 6.7%)	Resection, LT (27, 10.4%)	14.01 (4.96–22.00)	BCLC B & CPC CPC–B (73, 1.9%)	Resection, LT (3, 4.1%)	1.02 (NA)
	Local ablative therapy (94, 36.2%)	13.02 (4.04–23.01)		Local ablative therapy (1, 1.4%)	7.07 (NA)
	Locoregional therapy (n = 139, 53.5%)	3.03 (1.02–15.03)		Locoregional therapy (69, 94.5%)	2.01 (1.02–3.03)
	Systemic therapy (0, 0%)	NA		Systemic therapy (0, 0%)	NA
BCLC A & CPC–A (1,416, 36.6%)	Resection, LT (340, 24.0%)	10.52 (4.94–20.01)	BCLC C & CPC CPC–A (997, 25.7%)	Resection, LT (129, 12.9%)	4.04 (2.01–12.02)
	Local ablative therapy (235, 16.6%)	10.98 (4.01–21.01)		Local ablative therapy (37, 3.7%)	5.98 (1.02–17.54)
	Locoregional therapy (833, 58.8%)	2.93 (1.02–7.99)		Locoregional therapy (725, 72.7%)	1.02 (0.99–2.04)
	Systemic therapy (8, 0.6%)	0 (0–0.74)		Systemic therapy (106, 10.6%)	0.99 (0–1.96)
BCLC A & CPC–B (239, 6.2%)	Resection, LT (16, 6.7%)	6.51 (3.00–13.50)	BCLC C & CPC–B (311, 8.0%)	Resection, LT (20, 6.4%)	5.03 (1.00–15.77)
	Local ablative therapy (45, 18.8%)	6.05 (1.48–15.01)		Local ablative therapy (8, 2.6%)	18.54 (4.98–22.50)
	Locoregional therapy (176, 73.6%)	3.03 (1.02–8.06)		Locoregional therapy (246, 79.1%)	1.02 (0.98–2.04)
	Systemic therapy (2,	0 (0–2.39)		Systemic therapy (37,	0 (0–1.02)

Abbreviations: BCLC, Barcelona Clinic Liver Cancer; CPC, Child–Pugh class; LT, liver transplantation; IQR, interquartile range; SD, standard deviation.

Group (n, %)	First treatment (n, %)	Treatment interval, months, median (IQR)	Group (n, %)	First treatment (n, %)	Treatment interval, months, median (IQR)
	0.8%)			11.9%)	
BCLC B & CPC–A (n = 510, 13.2%)	Resection, LT (76, 14.9%)	7.02 (2.01–16.01)	BCLC D & CPC–A–C (68, 1.8%)	Resection, LT (3, 4.4%)	1.02 (NA)
	Local ablative therapy (11, 2.2%)	6.05 (1.02–18.02)		Local ablative therapy (10, 14.7%)	3.95 (0–16.00)
	Locoregional therapy (420, 82.4%)	2.01 (1.02–4.01)		Locoregional therapy (53, 77.9%)	2.01 (1.02–3.52)
	Systemic therapy (3, 0.6%)	1.02 (NA)		Systemic therapy (2, 2.9%)	1.51 (NA)
Overall (n = 3,874)	Resection, LT (614, 15.8%)	8.98 (3.03–17.04)			
	Local ablative therapy (441, 11.4%)	10.98 (3.03–20.98)			
	Locoregional therapy (2,661, 68.7%)	2.01 (1.02–4.04)			
	Systemic therapy (158, 4.1%)	0.99 (0–1.02)			

Abbreviations: BCLC, Barcelona Clinic Liver Cancer; CPC, Child–Pugh class; LT, liver transplantation; IQR, interquartile range; SD, standard deviation.

In early stage disease (BCLC 0–A with CPC–A), patients who underwent resection or local ablation demonstrated the longest intervals to subsequent treatment (median, approximately 10–14 months), whereas those who received locoregional therapy showed markedly shorter intervals (median, approximately 3 months). This pattern persisted in intermediate-stage disease (BCLC B with CPC–A), with curative treatments maintaining longer intervals than locoregional therapies. In advanced-stage disease (BCLC stage C with CPC–A), the overall treatment intervals were shorter across all modalities; however, the relative differences remained consistent. Patients treated with resection or ablation had longer intervals (median, approximately 4–6 months) than those who received locoregional (approximately 1–2 months) or systemic therapy (approximately 0–2 months). A similar trend was observed in the patients with impaired liver function (CPC–B), although the absolute intervals were generally shorter. In the overall cohort, median treatment intervals were longest for local ablative therapy

(10.98 months) and resection/LT (8.98 months), followed by locoregional therapy (2.01 months) and systemic therapy (0.99 months). Collectively, these findings demonstrate that initial curative or near-curative treatments are associated with prolonged treatment intervals across disease stages, whereas non-curative approaches are linked to a rapid need for subsequent therapy.

Factors associated with patient survival

In the univariate analysis, multiple clinical, tumor-related, and treatment variables were significantly associated with OS, including demographic factors, liver function, tumor burden, and treatment-related variables (Table 3). In multivariate analysis, the treatment interval emerged as an independent predictor of OS (HR 0.981, 95% CI 0.975–0.986; $p < 0.001$), demonstrating that a longer first-to-second treatment interval was significantly associated with better survival (Table 3). Several well-established prognostic factors reflecting tumor burden and disease extent—such as larger tumor size, a greater number of tumors, vascular invasion, lymph node involvement, distant metastasis, and an AFP level ≥ 200 ng/mL—were independently associated with worse OS. Indicators of impaired liver function, including ascites and lower serum albumin levels, were also significant predictors of poor OS. Treatment modality remained an independent determinant of survival. Compared to surgical therapy, locoregional therapy was associated with inferior outcomes in both initial- and second-line settings, whereas systemic therapy showed the highest risk of mortality in second-line treatment.

Table 3
Treatment interval as independent factors of overall survival.

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	*p*-value	HR	95% CI	p-value
Age (years)	1.004	1.001–1.008	0.017	1.010	1.006–1.014	< 0.001
Sex, male	1.160	1.055–1.275	0.002			
DM	0.970	0.890–1.058	0.497			
HTN	1.044	0.965–1.130	0.285			
BMI, vs. Normal (18.5 ≤ < 23)	Ref	–	< 0.001	Ref	–	0.013
Underweight (< 18.5)	1.292	1.045–1.598	0.018	1.327	1.061–1.659	0.013
Obesity (23≤)	0.831	0.768–0.900	< 0.001	0.957	0.880–1.041	0.309
Smoking	1.185	1.100–1.277	< 0.001			
HBV infection	0.870	0.804–0.941	< 0.001			
HCV infection	1.108	0.995–1.234	0.060			
Alcohol	1.232	1.138–1.333	< 0.001			
Hepatic encephalopathy history, present	1.409	1.031–1.925	0.031			
Ascites, present	2.104	1.914–2.314	< 0.001	1.466	1.310–1.641	< 0.001
Tumor maximum size, < 2 cm vs.	Ref	–	< 0.001	Ref	–	< 0.001
2 cm to 5 cm	1.313	1.188–1.452	< 0.001	1.145	1.021–1.284	0.020
5 cm≤	3.034	2.746–3.353	< 0.001	1.701	1.493–1.938	< 0.001

Abbreviations: AFP, alpha-fetoprotein; BMI, body mass index; CI, confidence interval; DM, diabetes mellitus; HBV, hepatitis B virus; HCV, hepatitis C virus; HR, hazard ratio; HTN, hypertension; INR, international normalized ratio; PT, prothrombin time.

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	*p*-value	HR	95% CI	p-value
Tumor number, single vs.	Ref	–	< 0.001	Ref	–	< 0.001
2–3	1.241	1.132–1.360	< 0.001	1.143	1.032–1.265	0.010
3<	2.644	2.402–2.910	< 0.001	1.449	1.295–1.620	< 0.001
Vascular invasion, present	3.087	2.831–3.367	< 0.001	1.544	1.388–1.719	< 0.001
Bile duct invasion, present	1.493	1.158–1.925	0.002			
Lymph node metastasis, present	3.427	2.947–3.984	< 0.001	1.364	1.132–1.645	0.001
Distant metastasis, present	5.380	4.712–6.142	< 0.001	2.391	2.027–2.820	< 0.001
AFP, 200 ng/mL≤	1.784	1.648–1.930	< 0.001	1.175	1.072–1.289	< 0.001
Albumin	0.634	0.598–0.672	< 0.001	0.744	0.692–0.799	< 0.001
Total bilirubin	1.044	1.027–1.062	< 0.001	1.018	0.999–1.037	0.058
PT, INR	1.164	1.052–1.289	0.003			
Creatinine	1.021	0.971–1.073	0.412			
Platelet	1.002	1.001–1.002	< 0.001			
Initial treatment, Surgical therapy vs.	Ref	–	< 0.001	Ref	–	0.002
Local ablative therapy	0.858	0.728–1.012	0.068	1.154	0.955–1.394	0.137
Locoregional therapy	1.769	1.579–1.982	< 0.001	1.269	1.112–1.447	< 0.001
Systemic therapy	4.892	4.017–5.957	< 0.001	1.068	0.844–1.353	0.583

Abbreviations: AFP, alpha-fetoprotein; BMI, body mass index; CI, confidence interval; DM, diabetes mellitus; HBV, hepatitis B virus; HCV, hepatitis C virus; HR, hazard ratio; HTN, hypertension; INR, international normalized ratio; PT, prothrombin time.

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	*p*-value	HR	95% CI	p-value
Second treatment, Surgical therapy vs.	Ref	–	< 0.001	Ref	–	< 0.001
Local ablative therapy	1.269	1.015–1.585	0.036	1.455	1.143–1.852	0.002
Locoregional therapy	2.817	2.303–3.444	< 0.001	2.273	1.828–2.827	< 0.001
Systemic therapy	6.238	4.956–7.852	< 0.001	3.398	2.623–4.402	< 0.001
Interval between first and second treatment, months	0.963	0.958–0.968	< 0.001	0.981	0.975–0.986	< 0.001

Abbreviations: AFP, alpha-fetoprotein; BMI, body mass index; CI, confidence interval; DM, diabetes mellitus; HBV, hepatitis B virus; HCV, hepatitis C virus; HR, hazard ratio; HTN, hypertension; INR, international normalized ratio; PT, prothrombin time.

Discussion

HCC frequently recurs even after curative treatment and often requires multiple subsequent treatments [7, 13]. These repeated treatments may adversely affect the non-tumorous liver parenchyma, leading to deterioration of hepatic function, limiting subsequent treatment options, and ultimately affecting OS. Here, a longer interval between the first and second treatments was independently associated with improved OS, irrespective of the tumor stage, baseline liver function, and treatment modality. Furthermore, this interval varied according to the initial treatment approach, with curative modalities such as surgical resection and local ablative therapy demonstrating longer intervals than locoregional or systemic therapies. Taken together, these findings suggest that the first-to-second treatment interval may reflect the early treatment course after initial therapy and provide clinically meaningful prognostic information in patients with HCC.

Several mechanisms may explain the association between the shorter interval from the first to the second treatment and poorer survival. A second treatment is usually required when the initial treatment fails to achieve durable tumor control or when recurrent or progressive disease becomes clinically evident. Incomplete response and early recurrence after curative treatment are associated with worse survival, likely reflecting more aggressive tumor biology [13–17]. Similarly, in advanced HCC, a shorter time-to-progression or progression-free survival is closely associated with worse OS [18]. Another possible explanation is that repeated treatment may contribute to the deterioration of hepatic function [9]. Unlike many other solid tumors, the prognosis of HCC is determined by tumor progression and the preservation of hepatic function, particularly because most patients have underlying chronic liver disease or cirrhosis. Consistent with this finding, TACE-based studies have shown that shorter retreatment intervals are associated with poor survival outcomes [19]. This consideration may be even

more relevant in the current systemic treatment era, in which immunotherapy-based regimens can achieve durable responses and prolonged survival in a subset of patients with unresectable HCC [8, 20–22]. In this context, a shorter interval between the first and second treatments may reflect several overlapping aspects of the clinical course, including limited durability of the initial treatment, more aggressive tumor biology, and impaired hepatic functional reserve. These considerations may collectively explain the independent association between the treatment interval and OS.

The first-to-second treatment interval patterns according to treatment modality in our study are also noteworthy. Local ablative therapy had the longest overall median interval, followed by surgical treatment, whereas locoregional and systemic therapies were associated with substantially shorter treatment intervals. This pattern was consistently observed across BCLC stage and CPC subgroups, with treatment intervals progressively shortening as the disease stage advanced. These findings are consistent with prior longitudinal studies demonstrating that curative treatments such as resection and RFA are associated with longer treatment intervals than TACE and that treatment intervals decrease with increasing tumor stage [7]. This pattern suggests that treatment modalities that achieve a more durable initial disease control are associated with longer intervals before retreatment. This aligns with the superior local tumor control achieved with surgical resection and ablative therapies in patients with localized HCC [23, 24]. Simultaneously, these interval differences should not be overinterpreted as direct treatment effects because treatment allocation in this registry was inherently influenced by baseline tumor stage, hepatic function, and other clinical factors.

Stratified survival analyses yielded several clinically relevant results. Within the same BCLC or mUICC stage, patients with CPC–B were more likely to receive non-curative treatment, and local ablative therapy was more commonly used than resection, likely reflecting concerns regarding limited hepatic reserve. Nevertheless, in some strata, particularly BCLC stage A with CPC–B, surgical resection was associated with better survival than other modalities. This observation is consistent with accumulating evidence that carefully selected patients with impaired but still acceptable liver function may derive benefit from resection [25, 26]. Conversely, the favorable outcomes of surgery or local ablation in some advanced-stage strata should be interpreted with caution. In these subgroups, the observed differences likely reflected the selection of biologically favorable or technically amenable patients.

Our study had some limitations. First, the KPLCR registry does not provide information on indications for second-line treatment. This limits causal interpretation because a shorter treatment interval may reflect heterogeneous clinical scenarios, including incomplete initial response, local recurrence, or intrahepatic metastasis. Accordingly, the treatment interval should be interpreted as a composite clinical marker rather than as a direct surrogate for tumor recurrence. Second, the dynamic changes in hepatic function during the treatment interval were not captured. Therefore, the impact of interval duration and treatment modality on longitudinal hepatic function deterioration could not be directly assessed. Third, because this was a retrospective observational study, the possibility of residual confounding and selection biases cannot be excluded, particularly in subgroup analyses with relatively small sample sizes. Finally, the cohort was derived from registry data collected between 2008 and 2015, which may limit the

generalizability of our findings to current clinical practice. Contemporary systemic therapies, including atezolizumab plus bevacizumab and other immunotherapy-based regimens, were not included in this dataset.

Despite these limitations, our findings are clinically meaningful. While this study did not establish a causal relationship between a prolonged first-to-second treatment interval and improved survival, it highlights that this interval reflects an important integrative aspect of HCC management that is not fully captured by conventional prognostic factors such as tumor stage or baseline liver function. In particular, the treatment interval appears to encompass both tumor biology and the effectiveness of the initial therapeutic strategy, thereby providing additional prognostic insights beyond established clinical parameters. From a clinical perspective, these findings support the importance of selecting initial treatment modalities that achieve durable disease control, as this may translate into longer treatment intervals and, ultimately, more favorable outcomes. Further large-scale prospective studies are warranted to validate these observations, clarify the causal relationship between treatment interval and survival, and determine how this parameter can be incorporated into clinical decision-making in the era of evolving therapeutic options.

Conclusion

In this nationwide cohort study of patients with hepatocellular carcinoma, a longer interval between the first and second treatments was independently associated with better overall survival after adjustment for tumor burden, hepatic function, and treatment-related factors. The treatment interval varied according to the initial treatment modality, with surgical resection and local ablative therapy generally associated with longer intervals than locoregional or systemic therapies. These findings suggest that the first-to-second treatment interval may serve as a clinically meaningful marker of the treatment course in patients with hepatocellular carcinoma.

Abbreviations

AFP, Alpha-fetoprotein

BCLC, Barcelona Clinic Liver Cancer

CI, Confidence interval

CNUH, Chungnam National University Hospital

CPC, Child–Pugh class

HCC, Hepatocellular carcinoma

HR, Hazard ratio

IRB, Institutional Review Board

KPLCR, Korean Primary Liver Cancer Registry

LT, Liver transplantation

mUICC, Modified Union for International Cancer Control

OS, Overall survival

PIVKA-II, Protein induced by vitamin K absence or antagonist-II

RFA, Radiofrequency ablation

TACE, Transarterial chemoembolization.

Declarations

Ethics approval and consent to participate

Ethical approval was obtained from the Institutional Review Board of Chungnam National University Hospital (CNUH IRB: 2020-04-028).

Consent for publication

The requirement for informed consent was waived by the ethics committee because of the retrospective nature of the study.

Conflict of Interest

The authors declare no conflicts of interest.

Funding

The authors received no specific funding for this work.

Author Contribution

Study concept and design: H.S.E. and W.S.R. Data acquisition, analysis, and interpretation: H.S.E., W.S.R., and H.J.J. Drafting of the manuscript: W.S.R. and H.S.E. Critical revision of the manuscript for important intellectual content: H.S.E. and B.S.L. Statistical analysis: W.S.R., H.S.E., and I.S.K. Administrative, technical, or material support: J.S.J., J.S.K., E.S.L., and S.H.K. Approval of the final manuscript: All authors.

Acknowledgments

This research was supported by a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (grant number: RS-2025-25460125, RS-2020-KH088690).

The database used in this study was provided by the Korean Central Cancer Registry, the Ministry of Health and Welfare, South Korea, and the Korean Liver Cancer Association; we would like to thank the Korean Liver Cancer Association.

Availability of data and materials

The data were provided by the Korean Liver Cancer Association and the Ministry of Health & Welfare, Korea Central Cancer Registry. The datasets generated and analyzed during this study are not publicly available owing to the authority of these data belonging to the Korean Liver Cancer Study Group and the Ministry of Health & Welfare's Korea Central Cancer Registry; data access was granted by these authorities to the first author, and upon reasonable request. The data can only be assessed with approval from the Korean Liver Cancer Association, the Ministry of Health & Welfare, and the Korea Central Cancer Registry.

References

1. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2024;74(3):229–63.
2. Vogel A, Meyer T, Sapisochin G, Salem R, Saborowski A. Hepatocellular carcinoma. Lancet. 2022;400(10360):1345–62.
3. Cucchetti A, Elshaarawy O, Han G, Chong CCN, Serra C, O'Rourke JM, et al. Potentially curative therapies' for hepatocellular carcinoma: how many patients can actually be cured? Br J Cancer. 2023;128(9):1665–71.
4. Torimura T, Iwamoto H. Treatment and the prognosis of hepatocellular carcinoma in Asia. Liver Int. 2022;42(9):2042–54.
5. Singal AG, Llovet JM, Yarchoan M, Mehta N, Heimbach JK, Dawson LA, et al. AASLD Practice Guidance on prevention, diagnosis, and treatment of hepatocellular carcinoma. Hepatology. 2023;78(6):1922–65.
6. Cho Y, Kim BH, Park JW. Overview of Asian clinical practice guidelines for the management of hepatocellular carcinoma: An Asian perspective comparison. Clin Mol Hepatol. 2023;29(2):252–62.
7. Moon H, Choi JE, Lee IJ, Kim TH, Kim SH, Ko YH, et al. All-treatment array of hepatocellular carcinoma from initial diagnosis to death: observation of cumulative treatments. J Cancer Res Clin

Oncol. 2017;143(11):2327–39.
8. Ogasawara S, Ooka Y, Koroki K, Maruta S, Kanzaki H, Kanayama K, et al. Switching to systemic therapy after locoregional treatment failure: Definition and best timing. Clin Mol Hepatol. 2020;26(2):155–62.
9. Miksad RA, Ogasawara S, Xia F, Fellous M, Piscaglia F. Liver function changes after transarterial chemoembolization in US hepatocellular carcinoma patients: the LiverT study. BMC Cancer. 2019;19(1):795.
10. Yoshitomi K, Hayashi T, Oe S, Shibata M, Honma Y, Harada M, et al. Child-Pugh grade deterioration stratified by the etiology after transcatheter arterial chemoembolization as initial treatment for hepatocellular carcinoma. Sci Rep. 2024;14(1):3707.
11. Aierken Y, Kong LX, Li B, Liu XJ, Lu S, Yang JY. Liver fibrosis is a major risk factor for liver regeneration: A comparison between healthy and fibrotic liver. Med (Baltim). 2020;99(22):e20003.
12. Liu H, Gai X, Wang X, Liu L, Tian L, Zhou B. Analysis of the factors influencing liver regeneration after hepatectomy in hepatocellular carcinoma patients and the relationship between liver regeneration and prognosis. Sci Rep. 2025;15(1):26874.
13. Herrero A, Toubert C, Bedoya JU, Assenat E, Guiu B, Panaro F, et al. Management of hepatocellular carcinoma recurrence after liver surgery and thermal ablations: state of the art and future perspectives. Hepatobiliary Surg Nutr. 2024;13(1):71–88.
14. Memon K, Kulik L, Lewandowski RJ, Wang E, Riaz A, Ryu RK, et al. Radiographic response to locoregional therapy in hepatocellular carcinoma predicts patient survival times. Gastroenterology. 2011;141(2):526–35.
15. Park C, Chu HH, Kim JH, Kim SY, Alrashidi I, Gwon DI, et al. Clinical Significance of the Initial and Best Responses after Chemoembolization in the Treatment of Intermediate-Stage Hepatocellular Carcinoma with Preserved Liver Function. J Vasc Interv Radiol. 2020;31(12):1998–2006. e1.
16. Portolani N, Coniglio A, Ghidoni S, Giovanelli M, Benetti A, Tiberio GA, et al. Early and late recurrence after liver resection for hepatocellular carcinoma: prognostic and therapeutic implications. Ann Surg. 2006;243(2):229–35.
17. Yang C, Luo YG, Yang HC, Yao ZH, Li X. Effects of Early TACE Refractoriness on Survival in Patients with Hepatocellular Carcinoma: A Real-World Study. J Hepatocell Carcinoma. 2022;9:621–31.
18. Terashima T, Yamashita T, Toyama T, Arai K, Kawaguchi K, Kitamura K, et al. Surrogacy of Time to Progression for Overall Survival in Advanced Hepatocellular Carcinoma Treated with Systemic Therapy: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Liver Cancer. 2019;8(2):130–9.
19. Yang ZW, He W, Zheng Y, Zou RH, Liu WW, Zhang YP, et al. The efficacy and safety of long- versus short-interval transarterial chemoembolization in unresectable hepatocellular carcinoma. J Cancer. 2018;9(21):4000–8.
20. Kudo M, Han KH, Ye SL, Zhou J, Huang YH, Lin SM, et al. A Changing Paradigm for the Treatment of Intermediate-Stage Hepatocellular Carcinoma: Asia-Pacific Primary Liver Cancer Expert Consensus

Statements. Liver Cancer. 2020;9(3):245–60.
21. Cheng AL, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, et al. Updated efficacy and safety data from IMbrave150: Atezolizumab plus bevacizumab vs. sorafenib for unresectable hepatocellular carcinoma. J Hepatol. 2022;76(4):862–73.
22. El-Khoueiry AB, Trojan J, Meyer T, Yau T, Melero I, Kudo M, et al. Nivolumab in sorafenib-naive and sorafenib-experienced patients with advanced hepatocellular carcinoma: 5-year follow-up from CheckMate 040. Ann Oncol. 2024;35(4):381–91.
23. Patel KR, Menon H, Patel RR, Huang EP, Verma V, Escorcia FE. Locoregional Therapies for Hepatocellular Carcinoma: A Systematic Review and Meta-Analysis. JAMA Netw Open. 2024;7(11):e2447995.
24. Park MS, Cho JY, Kim E, Na HY, Choi Y, Kim NR, et al. Surgical treatment of hepatocellular carcinoma: an expert consensus-based practical recommendation from the Korean Liver Cancer Association. J Liver Cancer. 2025;25(2):140–59.
25. Zhao S, Zhu Y, Zhu J, Wang B, Wang E, Zhu J, et al. Liver resection versus interventional treatments for hepatocellular carcinoma patients with hypohepatia: a multicenter study. Surg Endosc. 2025;39(7):4205–16.
26. Romano F, Chiarelli M, Garancini M, Scotti M, Zago M, Cioffi G et al. Rethinking the Barcelona clinic liver cancer guidelines: Intermediate stage and Child-Pugh B patients are suitable for surgery? World J Gastroenterol. 2021;27(21):2784-94. Tables.

Figures

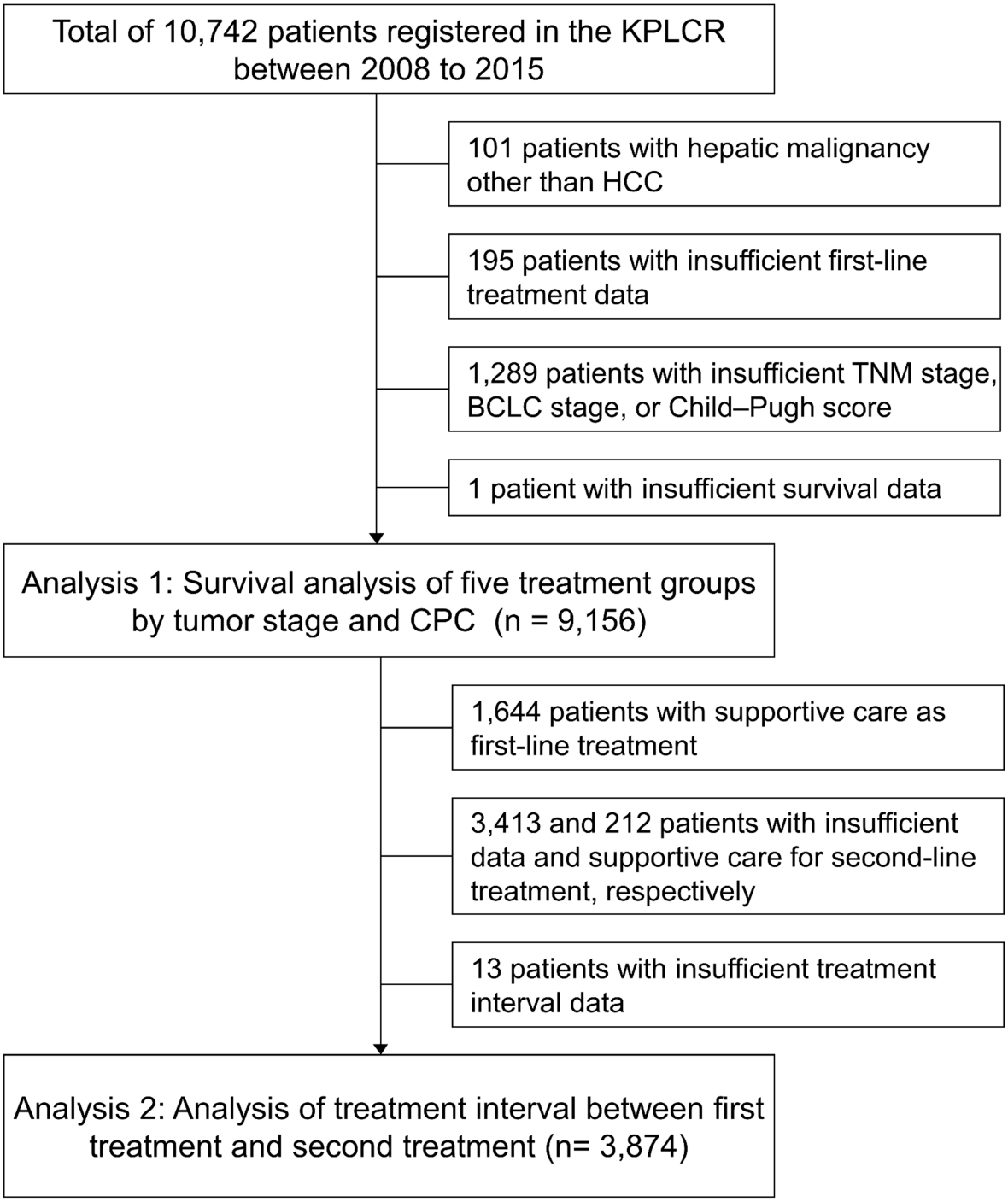


Figure 1

Flow Diagram of the Study Population.

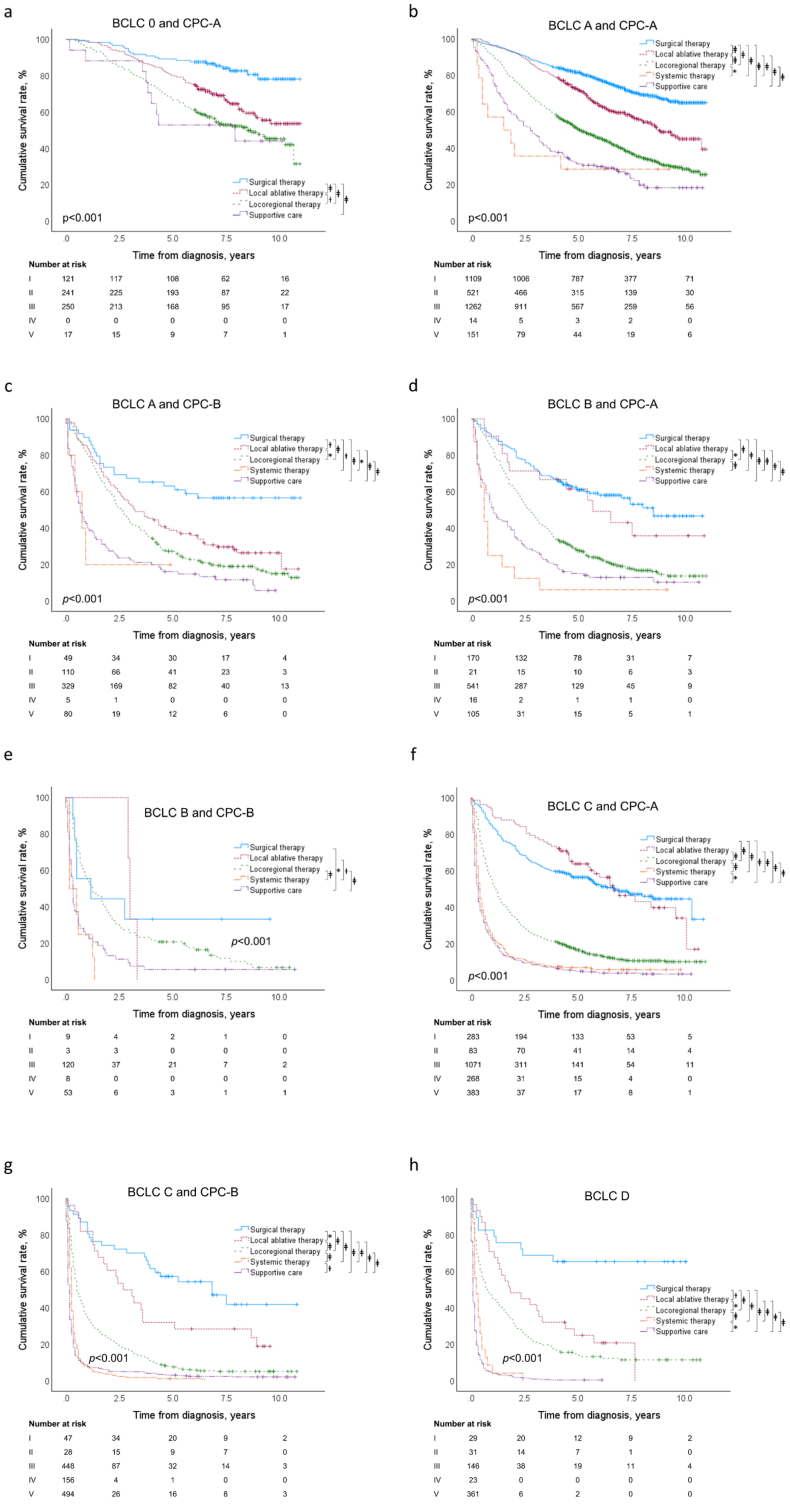


Figure 2

Kaplan–Meier overall survival curves by initial treatment modality, stratified by BCLC stage and CPC. Panels are arranged by BCLC stage and CPC as follows: stage 0 (a), stage A (b, c), stage B (d, e), stage C (f, g), and stage D (h), with CPC subgroups shown where applicable. In CPC–A, surgical treatment showed the most favorable survival in BCLC stages 0 and A (a, b). In BCLC stages B and C (d, f), survival differences between surgical and local ablative therapy were not observed, although both were

associated with better survival than locoregional or systemic therapy. In CPC–B, a similar pattern was observed in BCLC stages A and C (c, g), whereas no significant difference was observed in stage B (e). In BCLC stage D (h), curative treatment was associated with better survival than supportive care alone. Overall survival was estimated using the Kaplan–Meier method and compared using the log-rank test. BCLC, Barcelona Clinic Liver Cancer; CPC, Child–Pugh class. *p < 0.05, †p < 0.01, ‡p < 0.001).

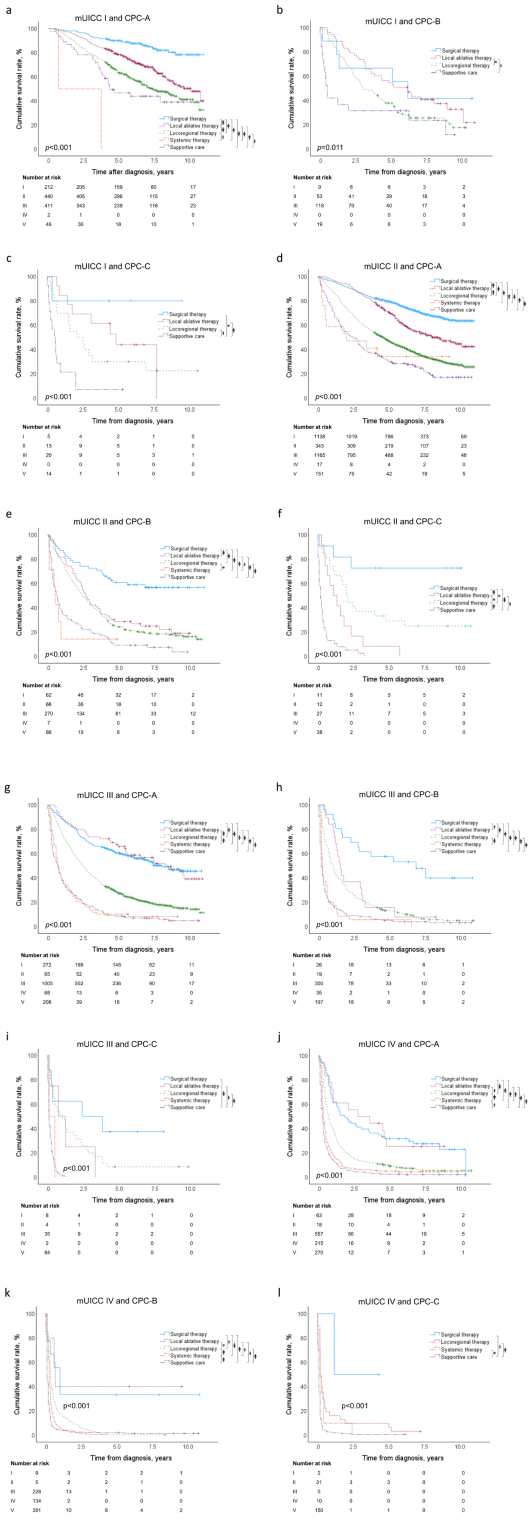


Figure 3

Kaplan–Meier overall survival curves by initial treatment modality, stratified by mUICC stage and CPC. Panels are arranged by mUICC stage and CPC as follows: stage I (a–c), stage II (d–f), stage III (g–i), and stage IV (j–l), with CPC–A, CPC–B, and CPC–C shown in each stage, respectively. In CPC–A, surgical treatment was associated with better survival than local ablative therapy in mUICC stages I and II (a, d), but not in stages III and IV (g, j). In CPC–B, surgical treatment was associated with better survival than local ablative or locoregional therapy in stages II and III (e, h), but not in stage I (b); in stage IV (k), it was associated with better survival than locoregional therapy only. In CPC–C (c, f, i, l), survival differences among active treatment modalities were not consistent across stages, except for stage II (f). Overall survival was estimated using the Kaplan–Meier method and compared using the log-rank test. mUICC, modified Union for International Cancer Control; CPC, Child–Pugh class. *$p < 0.05$, †$p < 0.01$, ‡$p < 0.001$).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementalMaterials.docx