

Treatment Outcomes of Systemic Therapies for Infiltrative Hepatocellular Carcinoma

Po-Yi Chen^{1,2}, Chih-Kai Chang³, Bang-Bin Chen³, Chih-Hung Hsu^{1,2,4}, Ann-Lii Cheng^{1,2,4}, Yu-Yun Shao^{1,2,4}

¹Department of Medical Oncology, National Taiwan University Cancer Center, Taipei, Taiwan; ²Department of Oncology, National Taiwan University Hospital, Taipei, Taiwan; ³Department of Medical Imaging, National Taiwan University Hospital, Taipei, Taiwan; ⁴Graduate Institute of Oncology, College of Medicine, National Taiwan University, Taipei, Taiwan

Correspondence: Yu-Yun Shao, Department of Oncology, National Taiwan University Hospital, 7 Chung-Shan South Road, Taipei, 10002, Taiwan, Tel +886 2 23123456 ext. 266008, Fax +886 2 23711174, Email yuyunshao@gmail.com

Purpose: Outcomes in the treatment of unresectable infiltrative hepatocellular carcinoma (HCC) are poorly understood, and infiltrative HCC is generally underrepresented in clinical trials. The present study explored outcomes associated with the treatment of infiltrative HCC with various systemic therapies.

Patients and Methods: We enrolled all patients with Barcelona Clinic Liver Cancer stage C infiltrative or multinodular HCC who received first-line systemic therapy between January 2015 and December 2021 at a single center. We compared baseline characteristics and treatment outcomes for the two HCC subtypes.

Results: In total, 260 patients were enrolled, 128 (49.2%) of whom had infiltrative HCC. Patients with infiltrative HCC were more likely to have macrovascular invasion (91.4% vs 68.2%, $p < 0.001$) but less likely to have extrahepatic spread (32.0% vs 54.5%, $p < 0.001$) than patients with multinodular HCC. In patients who received multikinase inhibitors alone, the time to treatment failure (TTF) and overall survival (OS) were similar for the 2 HCC subtypes. In patients who received immune checkpoint inhibitor (ICI)-based therapy, multivariate analyses revealed that infiltrative HCC was associated with shorter TTF (HR: 4.07, 95% CI: 2.13–7.79, $p < 0.001$) and poorer OS (HR: 3.27, 95% CI: 1.76–6.11, $p < 0.001$).

Conclusion: In patients receiving ICI-based therapy for HCC, infiltrative HCC was associated with poorer outcomes.

Keywords: hepatocellular carcinoma, HCC, infiltrative, systemic therapy, multikinase inhibitor, immune checkpoint-inhibitor

Introduction

Liver cancer is the sixth most common cancer and the third leading cause of cancer-related deaths worldwide. Hepatocellular carcinoma (HCC) accounts for 75% to 85% of liver cancer cases.¹ Patients with HCC present with single nodular, multinodular, or infiltrative patterns.² Infiltrative type of HCC, which accounts for 8% to 18% of HCC cases and is notable for its microscopic spread across the liver parenchyma and blood vessels, often presents in imaging with characteristics such as an incomplete or absent capsule and indistinct demarcation and is frequently associated with portal vein tumor thrombus.³ Few studies have compared the characteristics of infiltrative HCC with those of the more common nodular HCC.^{4,5}

Infiltrative HCC is difficult to detect from the background of cirrhosis using ultrasound because of its borderless and infiltrative appearance. Consequently, the diagnosis of infiltrative HCC tends to be delayed until the tumor has progressed to an advanced stage. Accordingly, compared with patients with nodular HCC, those with infiltrative HCC are less likely to receive curative treatment, which typically involves surgical resection, liver transplantation, or local ablation.^{6,7} The overall survival (OS) rate for infiltrative HCC is worse than that for other HCC subtypes; at advanced stages, OS without treatment is only 1.5 to 3 months.^{8,9}

The treatment options for advanced HCC include sorafenib, lenvatinib, and combination immunotherapies such as bevacizumab plus atezolizumab and durvalumab plus tremelimumab.^{10–15} Patients with infiltrative HCC are usually underrepresented in clinical trials because they do not have measurable lesions. Historically, the multikinase inhibitor (MKI) sorafenib had been the standard first-line therapy for advanced HCC.^{10,16–18} Unfortunately, MKIs have limited

efficacy against infiltrative HCC. A retrospective study ($n = 40$) reported a median OS of only 4 months among patients with infiltrative HCC receiving an MKI.¹⁹ Data regarding the effectiveness of combination immunotherapies for infiltrative HCC are lacking. This study examined the efficacy of systemic therapies for the treatment of infiltrative HCC. Patients with multinodular HCC were also included for comparison.

Methods and Patients

Patients

We enrolled all patients with Barcelona Center Liver Cancer (BCLC) stage C infiltrative or multinodular HCC who received first-line systemic therapies, between January 2015 and December 2021 at National Taiwan University Hospital (NTUH) in Taipei, Taiwan. HCC diagnoses were based on the American Association for the Study of Liver Disease criteria.²⁰ Infiltrative HCC was defined as HCC involving nonnodular and nonencapsulated lesions with a margin poorly demarcated on computed tomography or magnetic resonance imaging (Figure S1). One radiologist and one medical oncologist independently reviewed all imaging results to determine whether tumors were infiltrative. Disagreement was resolved through consultation with another radiologist not informed of the initial determinations. All investigators were blinded to clinical outcomes. Systemic therapies included MKIs (sorafenib or lenvatinib) alone, immune checkpoint inhibitor (ICI) monotherapy, and combination immunotherapies (atezolizumab plus bevacizumab, MKI plus ICI, or dual ICIs).

Patients who completed at least 3 clinical visits after the initiation of systemic treatment were included for analysis. Patients were excluded if they received simultaneous locoregional therapy or an early-phase investigational agent or if they had a diagnosis of HCC harboring sarcomatoid differentiation, combined cholangiocarcinoma, or double cancer.

Data Collection

We reviewed the medical records of the enrolled patients to obtain demographic information, clinical history, laboratory data, and imaging results. This study was approved by the Institutional Review Board of NTUH. The last follow-up date was December 31, 2022.

Statistical Analysis

Frequency tables were generated for categorical variables. Continuous variables are presented as means and standard deviations. The chi-square test or Fisher's exact test was used to analyze between-group differences in nominal variables, and the independent t test or Mann–Whitney U -test was used to analyze continuous variables. For univariate survival analysis, the Kaplan–Meier method with the Log rank test was employed. A Cox proportional hazards model was used for multivariate analysis. All statistical analyses were performed in SAS version 9.4 (SAS Institute, Cary, NC, USA). A two-sided p value of ≤ 0.05 was considered statistically significant.

Time to treatment failure (TTF) was defined as the interval between treatment initiation and discontinuation due to disease progression, an adverse event, or death. OS was defined as the interval between treatment initiation and the time of death.

Results

Patient Characteristics

A total of 899 patients who received first-line therapy for BCLC stage C HCC were initially identified. After screening, 260 patients were included in our analysis (Figure S2). Most of the patients had hepatitis B virus–induced HCC (65%), Child-Pugh class A (61.9%) liver reserve, tumor involvement of more than 50% of the liver parenchyma (62.7%), and a serum alpha-fetoprotein level of ≥ 400 ng/mL (60.0%; Table 1). These findings reflect the hepatitis B virus–predominant nature of HCC in Taiwan and the advanced tumor stage with impaired liver reserve of this patient cohort.

Interobserver disagreement regarding imaging interpretation was achieved for 39 (15%) patients. Regarding HCC morphology, HCC was infiltrative in 128 (49.2%) patients, and multinodular in 132 (50.8%) patients. Patients with infiltrative HCC, were more likely to be male (86.7% vs 74.2%, $p = 0.011$), and have macrovascular invasion (91.4% vs 68.2%, $p < 0.001$), main portal vein thrombosis (52.3% vs 22.0%, $p < 0.001$), and a shorter time from diagnosis to first systemic treatment (7.3 weeks vs 10.7 weeks, $p = 0.040$). Extrahepatic spread was less common in patients with

Table 1 Patient Characteristics

N (%)	All	Multinodular	Infiltrative	p
Total	260 (100)	132 (100)	128 (100)	
Age, mean± SD, years	60.6±11.4	61.2±12.3	59.9±10.4	0.288
Male gender	209 (80.4)	98 (74.2)	111 (86.7)	0.011
Time from diagnosis to first systemic treatment, mean± SD, weeks	9.0±15.5	10.7±18.2	7.3±11.9	0.040
Prior local treatment	70 (26.9)	41 (31.1)	29 (22.7)	0.127
HBsAg (+)	169 (65)	84 (63.6)	85 (66.4)	0.640
Anti-HCV (+)	38 (14.6)	18 (13.6)	20 (15.6)	0.650
Child-Pugh class				0.169
A	161 (61.9)	89 (67.4)	72 (56.3)	
B	93 (35.8)	40 (30.3)	53 (41.4)	
B7	47 (18.1)	20 (15.2)	27 (21.1)	
C	6 (2.3)	3 (2.3)	3 (2.3)	
Tumor involvement>50% of liver	163 (62.7)	88 (66.7)	75 (58.6)	0.178
Macrovascular invasion	207 (79.6)	90 (68.2)	117 (91.4)	<0.001
Main portal vein thrombosis	96 (36.9)	29 (22.0)	67 (52.3)	<0.001
Extrahepatic spread	113 (43.5)	72 (54.5)	41 (32.0)	<0.001
Platelet, mean±SD, K/μL	229.0± 119.4	253.6± 127.8	203.6± 104.7	0.001
Thrombocytopenia	76 (29.2)	28 (21.2)	48 (37.5)	0.004
Grade 1	62 (23.8)	22 (16.7)	40 (31.3)	
Grade 2	9 (3.5)	5 (3.8)	4 (3.1)	
Grade 3 and 4	5 (1.9)	1 (0.8)	4 (3.1)	
WBC, mean±SD, K/μL	7.3± 2.9	7.6± 3.1	7.0± 2.6	0.160
Leukocytosis	55 (21.2)	32 (24.2)	23 (18.0)	0.216
Leukopenia	13 (5.0)	6 (4.5)	7 (5.5)	0.733
Grade 1	7 (2.7)	2 (1.5)	5 (3.9)	
Grade 2	5 (8.3)	3 (2.3)	2 (1.6)	
Grade 3 and 4	1 (0.4%)	1 (0.8%)	0 (0)	
AFP≥ 400 ng/mL	156 (60)	76 (57.6)	80 (62.5)	0.418
ALBI grade				0.222
1	73 (28.1)	39 (29.5)	34 (26.6)	
2a	53 (20.4)	32 (24.2)	21 (16.4)	
2b	110 (42.3)	52 (39.4)	58 (45.3)	
3	24 (9.2)	9 (6.8)	15 (11.7)	
1st-line systemic treatments				
MKI alone	178 (68.5)	89 (67.4)	89 (69.5)	0.715
Sorafenib	151 (58.1)	73 (55.3)	78 (60.9)	
Lenvatinib	27 (10.4)	16 (18.0)	11 (8.6)	
ICI monotherapy	33 (12.7)	13 (9.8)	20 (15.6)	0.162
Atezolizumab+ Bevacizumab	25 (9.6)	15 (11.4)	10 (7.8)	0.332
MKI + ICI	14 (5.4)	8 (6.1)	6 (4.7)	0.624
Dual ICIs	9 (3.5)	6 (4.6)	3 (2.3)	0.501

Abbreviations: HBsAg, hepatitis B surface antigen; anti-HCV, antibody against hepatitis C virus; AFP, alpha-fetoprotein; ALBI, albumin-bilirubin; MKI, multikinase inhibitor; ICI, immune checkpoint inhibitor.

infiltrative HCC than in patients with multinodular HCC (32.0% vs 54.5%, $p < 0.001$). Patients with infiltrative HCC also had a lower mean platelet level than did patients with multinodular HCC (203.6 vs 253.6 K/μL, $p = 0.001$; Table 1).

Most patients in both the morphology subtype groups received a MKI alone as their first-line systemic treatment (68.5%). The type of systemic therapy used was similar between patients with multinodular versus infiltrative HCC (Table 1). Subsequent treatments were administered to 111 patients (42.7%).

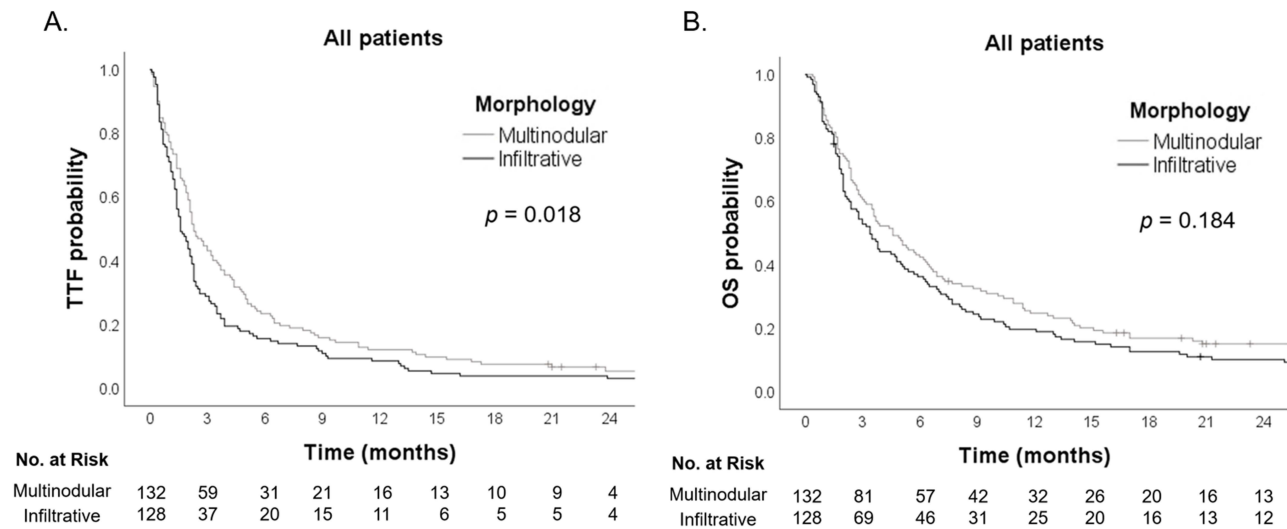


Figure 1 Kaplan-Meier curves of (A) time to treatment failure (TTF) and (B) overall survival (OS) for patients with infiltrative or multinodular hepatocellular carcinoma (HCC). p values were determined using the Log rank test.

Clinical Outcomes of Systemic Treatments

Patients with infiltrative HCC had significantly shorter TTF (median 1.6 vs 2.3 months, $p = 0.018$; Figure 1A) than did patients with multinodular HCC but had similar OS (median 3.4 vs 4.6 months, $p = 0.184$; Figure 1B). In multivariate analysis, infiltrative HCC was an independent predictor of shorter TTF (HR: 1.34; 95% CI: 1.00–1.78; $p = 0.049$; Table 2) and was borderline significant in predicting a shorter OS (HR: 1.30; 95% CI: 0.96–1.75; $p = 0.092$; Table 2). These results suggest that infiltrative HCC has poor response to treatment even after controlling other potential factors.

In patients receiving an MKI alone as a first-line therapy, median TTF (2.0 vs 2.2 months, $p = 0.895$) and OS (4.5 vs 3.8 months, $p = 0.326$) were similar in the infiltrative and multinodular HCC groups (Figure 2A and B). By contrast, in patients who received ICI-based treatment as first-line therapy, those with infiltrative HCC had a significantly shorter median TTF (1.3 vs 4.9 months, $p < 0.001$; Figure 2C) and OS (2.0 vs 10.9 months, $p < 0.001$; Figure 2D) than did those

Table 2 Multivariate Analysis for Predictors of Time to Treatment Failure and Overall Survival for All Patients

Variables	Time to Treatment Failure		Overall Survival	
	HR (95% CI)	p	HR (95% CI)	p
Infiltrative HCC (vs multinodular)	1.34 (1.00–1.78)	0.049	1.30 (0.96–1.75)	0.092
Age	0.99 (0.98–1.00)	0.088	1.00 (0.98–1.01)	0.621
Male gender	0.84 (0.60–1.18)	0.305	0.87 (0.61–1.24)	0.440
Prior local Treatment	1.03 (0.75–1.40)	0.868	0.93 (0.68–1.28)	0.675
HBsAg (+)	1.00 (0.71–1.41)	0.980	1.09 (0.77–1.54)	0.636
Anti-HCV (+)	0.90 (0.57–1.44)	0.670	1.04 (0.65–1.68)	0.862
Child-Pugh class B or C (vs A)	1.70 (1.28–2.24)	<0.001	2.18 (1.63–2.91)	<0.001
AFP ≥ 400 ng/mL	1.49 (1.13–1.97)	0.005	1.66 (1.24–2.22)	0.001
Liver involvement $>50\%$	1.35 (0.99–1.82)	0.057	1.65 (1.20–2.26)	0.002
Macrovascular invasion	0.94 (0.63–1.39)	0.742	1.05 (0.70–1.58)	0.810
Main portal vein thrombosis	1.17 (0.84–1.62)	0.356	1.06 (0.77–1.46)	0.742
Extrahepatic spread	1.15 (0.86–1.52)	0.346	1.47 (1.10–1.96)	0.010
Platelet (K/ μ L)	1.00 (0.99–1.01)	0.413	1.00 (1.00–1.01)	0.379
WBC (K/ μ L)	1.08 (1.02–1.13)	0.005	1.126 (1.07–1.19)	<0.001

Abbreviations: HBsAg, hepatitis B virus surface antigen; HCV, hepatitis C virus; AFP, alpha-fetoprotein; WBC, white blood cell count.

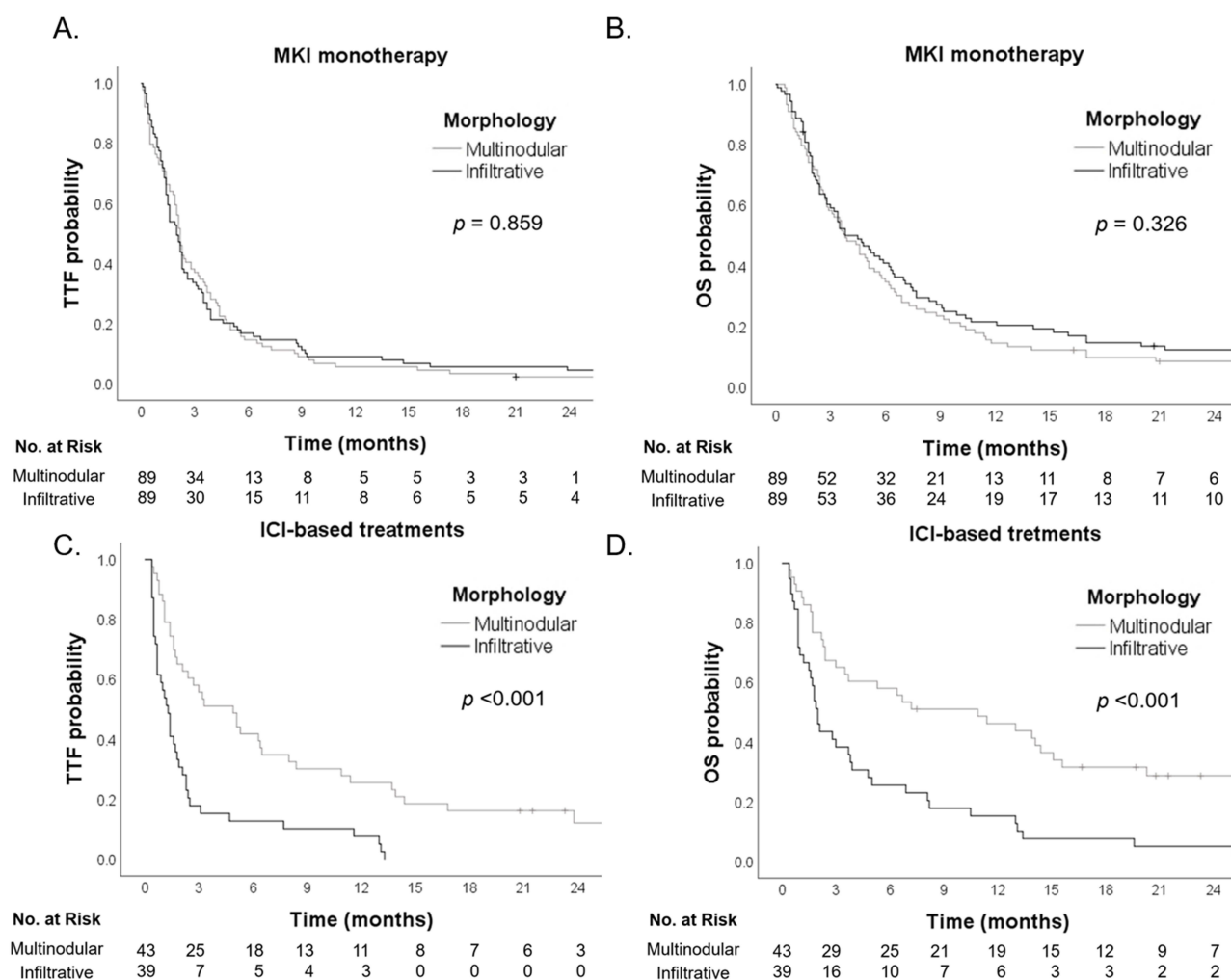


Figure 2 Kaplan-Meier curves of (A) time to treatment failure (TTF) and (B) overall survival (OS) of patients with infiltrative or multinodular hepatocellular carcinoma (HCC) receiving multikinase inhibitor (MKI) monotherapy; Kaplan-Meier curves of (C) TTF and (D) OS of patients with infiltrative or multinodular HCC receiving immune checkpoint inhibitor (ICI)-based treatments. p values were determined using the Log rank test.

with multinodular HCC. In multivariate analysis of the outcomes for these patients, infiltrative HCC remained an independent predictor of a shorter TTF (HR: 4.07; 95% CI: 2.13–7.79; $p < 0.001$) and OS (HR: 3.27; 95% CI: 1.76–6.11, $p < 0.001$; Table 3).

Table 3 Multivariate Analysis for Predictors of Time to Treatment Failure and Overall Survival for Patients Receiving Immune-Checkpoint-Inhibitor-Based Treatments

Variables	Time to Treatment Failure		Overall Survival	
	HR (95% CI)	p	HR (95% CI)	p
Morphology- infiltrative type	4.07 (2.13–7.79)	<0.001	3.27 (1.76–6.11)	<0.001
Age	0.98 (0.96–1.01)	0.159	0.99 (0.97–1.02)	0.461
Male gender	0.36 (0.16–0.79)	0.011	0.44 (0.19–0.99)	0.048
Prior local treatment	0.96 (0.47–1.95)	0.905	1.13 (0.52–2.48)	0.752
HBsAg (+)	4.47 (1.85–10.80)	0.001	3.76 (1.43–9.89)	0.007
Anti-HCV (+)	2.46 (0.95–6.40)	0.064	2.66 (0.93–7.63)	0.069

(Continued)

Table 3 (Continued).

Variables	Time to Treatment Failure		Overall Survival	
	HR (95% CI)	p	HR (95% CI)	p
Child-Pugh class B or C (vs A)	1.60 (0.93–2.77)	0.091	2.87 (1.64–5.04)	<0.001
AFP ≥ 400 ng/mL	1.18 (0.68–2.03)	0.559	1.33 (0.75–2.33)	0.327
Tumor > 50% of liver	1.97 (1.00–3.89)	0.051	4.54 (2.04–10.11)	<0.001
Macrovascular invasion	0.78 (0.36–1.71)	0.539	0.84 (0.35–2.00)	0.686
Main portal vein thrombosis	0.58 (0.28–1.17)	0.129	0.94 (0.49–1.79)	0.850
Extrahepatic spread	0.62 (0.37–1.06)	0.083	1.04 (0.61–1.77)	0.896
Platelet (K/μL)	1.00 (0.996–1.001)	0.129	1.00 (0.995–1.000)	0.097
WBC (K/μL)	1.12 (1.02–1.23)	0.014	1.13 (1.03–1.25)	0.010

Abbreviations: HBsAg, hepatitis B virus surface antigen; HCV, hepatitis C virus; AFP, alpha-fetoprotein; WBC, white blood cell count.

Clinical Outcomes of ICI Monotherapy versus Combination Immunotherapies

ICIs may be used alone or in combination with bevacizumab, an MKI, or another ICI. In the current study, when combination immunotherapies were used, the median TTF (1.6 vs 6.4 months, $p < 0.001$) and OS (4.8 vs 15.1 months, $p < 0.001$) were shorter for patients with infiltrative HCC than for patients with multinodular HCC. By contrast, when ICI monotherapy was used, the median TTF (0.5 vs 1.4 months, $p = 0.276$) and OS (1.0 vs 1.7 months, $p = 0.473$) were similar in the two groups. However, patients with infiltrative HCC who received combination immunotherapy still had a longer median TTF (1.6 vs 0.5 months, $p = 0.013$) and longer OS (4.8 vs 1.0 months, $p = 0.051$) than did patients who received ICI monotherapy (Figure 3A and B). In 46 patients with Child-Pugh class A liver function who received combination immunotherapy, the differences remained in median TTF (1.7 vs 8.0 months, $p < 0.001$) and OS (3.9 vs 15.6 months, $p < 0.001$) between the HCC subtype groups (Figure S3).

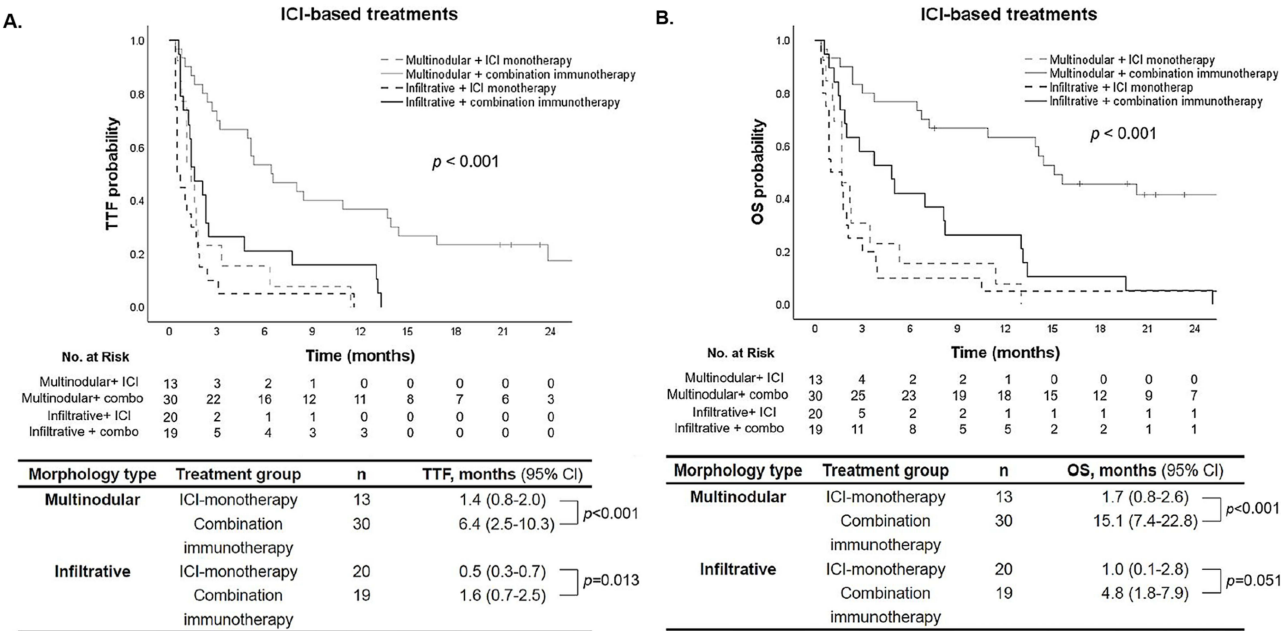


Figure 3 Kaplan-Meier curves of (A) time to treatment failure (TTF) and (B) overall survival (OS) of patients with different morphology subtypes receiving immune checkpoint inhibitor (ICI) monotherapy or combination immunotherapy. p values were determined using the Log rank test.

Discussion

This study discovered treatment outcomes differences based on HCC morphology subtype (infiltrative vs multinodular HCC). Patients who received ICI-based therapies had different TTF and OS, depending on their tumor's morphology, whereas patients who received a MKI did not. Moreover, this difference was more pronounced in patients who received combination immunotherapies. These findings indicate that the 2 morphology subtypes have distinct tumor biology and microenvironments that affect the efficacy of immunotherapies. To our knowledge, this is the first study to report such findings.

Other retrospective studies have indicated that infiltrative HCC accounts for only 8% to 18% of all HCC cases.^{4,5} In the present study, among advanced HCC cases in particular, the infiltrative and multinodular HCC subtypes were represented nearly equally (49.2% vs 50.8%). The higher prevalence of infiltrative HCC in patients with advanced HCC than in non-advanced HCC reflects the greater difficulty of obtaining an early diagnosis and the associated lower likelihood that curative therapy will be initiated in cases of infiltrative HCC than in cases of nodular HCC. Moreover, this disparity in patient composition also disclosed the difference between real-world practice and clinical trials.

Several mechanisms may account for the prognostic differences observed between infiltrative and multinodular HCC treated with ICIs. First, the immunosuppressive tumor microenvironment may hinder antitumor immunity through the accumulation of regulatory T cells, inhibitory B cells, myeloid-derived suppressor cells, and M2-polarized tumor-associated macrophages.²¹ Second, HCC cells harboring β -catenin mutations may exhibit reduced lymphocyte infiltration and resistance to PD-1 blockade.²² Other tumor cell-intrinsic mechanisms have also been implicated in ICI resistance, examples include insufficient expression of tumor-specific neoantigens²³ and compromised antigen processing and presentation due to loss of heterozygosity in human leukocyte antigen alleles.²⁴ These potential mechanisms have all been tested in patients with HCC. Nevertheless, studies focused specifically on infiltrative HCC are lacking.

In the current study, ICI monotherapy was not superior to MKIs in terms of improving OS. Adding bevacizumab or a MKI to a ICI or employing dual ICI therapy may counteract the immunosuppressive tumor microenvironment²⁵ and increase the likelihood of a tumor response, thereby improving survival.^{12,15,26} Our study revealed that although patients with infiltrative HCC and those with multinodular HCC both derived benefits from combination immunotherapy, patients with infiltrative HCC exhibited less improvement (in terms of both TTF and OS). This may be attributable to diminished T cell infiltration, T cell exhaustion, an increase in regulatory T cells, and downregulation of natural killer cell activators.²⁷ Further research is required to elucidate the distinct microenvironmental differences between these HCC subtypes to develop innovative combination therapies that enhance immune responsiveness.

Our study has several limitations. First, this was a retrospective study conducted at a single center without a validation cohort. Further validation through multicenter prospective studies is needed. Second, a substantial proportion of the included patients received MKI monotherapy, which is now considered merely an alternative first-line therapy. Third, multiple regimens of combination immunotherapy were used. Nevertheless, this study obtained an interesting finding that has not been reported in the literature on this often-ignored disease subtype.

Conclusion

Among patients receiving ICI-based therapy for HCC, those with infiltrative HCC have poorer treatment outcomes than those with multinodular HCC. This association may be limited to combination immunotherapy. The underlying mechanism warrants further exploration.

Data Sharing Statement

All data generated or analyzed during this study are included in this article and its online [supplementary material files](#). Further enquiries can be directed to the corresponding author.

Ethics Approval Statement

The study protocol conformed to the ethical guidelines of the 2013 Declaration of Helsinki and the 2018 edition of the Declaration of Istanbul; it was approved by the Institutional Review Board of National Taiwan University Hospital (202211099RINB). Formal consent by written signature was not required for this type of study due to the retrospective

nature of anonymous clinical data use, based on the Ethical Guidelines for Medical and Biological Research Involving Human Subjects in Taiwan. No transplant patients were included in this study.

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Disclosure

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