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ORIGINAL RESEARCH

Efficacy and Safety of Radiotherapy Combined with PD-1 Inhibitors and Targeted Therapy for Unresectable Hepatocellular Carcinoma: A Retrospective, Real-World Multicenter Study

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Purpose: Real-world evidence concerning the triple-combination regimens of radiotherapy (RT), PD-1 inhibitors, and targeted therapy for unresectable hepatocellular carcinoma (uHCC) is limited. This study evaluated the efficacy and safety of this combination and identified predictors of survival.

Patients and Methods: In this multicenter retrospective study, 122 consecutive patients with uHCC received RT combined with PD-1 inhibitors and targeted therapy were analyzed. Objective response rate (ORR), disease control rate (DCR), overall survival (OS), progression-free survival (PFS) and treatment-related adverse events (TRAEs) were calculated. Cox regression was used to identify independent prognostic factors. Subgroup analysis explored the association between immunotherapy cycles and overall survival across tumor response stratification.

Results: The cohort included 53 patients with extrahepatic metastases and 48 with macrovascular invasion. Patients received RT with a median dose of 45 Gy (range: 32.3–58.5 Gy). Median follow-up was 14.2 months. According to the modified response evaluation criteria in solid tumor (mRECIST), the ORR and DCR were 18.85% and 73.78%, respectively. The median OS was 19.0 months (95% CI: 17.8–23.4 months), and the median PFS was 7.2 months (95% CI: 5.5–10.9 months). TRAEs of any grade occurred in 93 patients (76.23%), with grade 3–4 TRAEs observed in 40 patients (32.79%). No treatment-related death was observed. Multivariate analysis identified elevated AFP and higher mALBI grade as independent risk factors for OS. Higher mALBI grade and neutrophil-to-lymphocyte ratio (NLR) predicted worse PFS. Exploratory analysis suggested extending immunotherapy duration may improve OS in patients with stable disease.

Conclusion: The triple-combination of RT, PD-1 inhibitors, and targeted therapy demonstrates promising survival benefits and a manageable toxicity profile for uHCC. Baseline AFP, liver function, NLR level are key determinants of survival, supporting the individualized application of this multimodal approach.

Keywords: unresectable hepatocellular carcinoma, radiotherapy, PD-1 inhibitors, targeted therapy, multicenter study

Introduction

Representing the sixth most common cancer and the third leading cause of cancer-related death, hepatocellular carcinoma (HCC) remains a significant global health burden.[1,2] For most HCC diagnosis at advance stage, losing the opportunity for radical surgery, as well as the limited efficacy of conventional therapies, the overall survival was still dismal.[3,4] Even through revolutionary advances in the combination of immune checkpoint inhibitors (ICIs) and targeted drugs, such as the atezolizumab plus bevacizumab, have greatly improved both the overall survival (OS) and

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progression-free survival (PFS) endpoints, and established a new first-line standard.[5–8] The clinical outcomes remain suboptimal for a significant subset of patients. The objective response rate (ORR) is still limited. Also, for patients with high tumor burden or those progressing on standard therapy, therapeutic options remain scarce. How to optimize treatment regimens for unresectable HCC (uHCC) to overcome resistance and improve clinical outcomes yet impose a substantial challenge.

Currently, with advancements in dose optimization and precision irradiation, radiotherapy (RT) has been established as a safe and effective treatment for local control of advanced HCC.[9,10] Mechanistically, RT not only induces immunogenic cell death and antigen release but also modulates the tumor immune microenvironment, potentially sensitizing "cold" tumors to immunotherapy.[11,12] Furthermore, anti-angiogenic targeted therapy can improve tumor vascular normalization, which may also enhance radiation sensitivity.[13–15] The combination of locoregional RT treatment with ICIs-based therapy and targeted therapy tends to have synergistic effects for management of uHCC. Previous evidence indicated this triple therapy yield improved response rates and survival outcomes compared to dual systemic therapy alone.[16,17] However, the sample sizes in these studies were relatively small. Robust real-world data regarding the efficacy and safety of this triple-modality regimen remain scarce. And prognostic factors for worse outcomes have not been evaluated.

In this study, enrolling uHCC patients who received radiotherapy plus PD-1 inhibitors and anti-angiogenic therapy from three tertiary centers, we assessed the safety and efficacy of RT plus PD-1 inhibitors and targeted therapy. Furthermore, we identified potential risk factors for shorter survival and optimize therapeutic strategies for uHCC in real-world practice.

Materials and Methods

Patients

From September 2018 to November 2022, a total of 150 patients with uHCC who received RT in combination with PD-1 inhibitors and targeted therapy were identified from Mengchao Hepatobiliary Hospital of Fujian Medical University, the 900th Hospital of Joint Logistic Support Force and Fujian Provincial Cancer Hospital. After excluding 15 lost follow-up cases and 12 cases with incomplete data, 122 patients were ultimately recruited in the final analysis (Figure 1). The diagnosis of HCC was based on the American Association for Study of Liver Disease and Chinese Guidelines for Diagnosis and Treatment of Primary Liver Cancer.[18,19] The determination of unresectability was confirmed through a multidisciplinary team (MDT) consensus, involving senior hepatobiliary surgeons (>20 years of experience). The uHCC was defined as meeting one or more the following pathological or radiological evidences:[20,21] 1) post-operation residual liver volume ≤30% (for normal liver) or ≤40% (for cirrhotic liver) or inadequate safety margins, or complex involvement of critical vasculature; 2) Multifocal intrahepatic lesions; 3) invasion of major vessels, including the main trunk of the portal vein (Vp4) and the inferior vena cava (Vv3); 4) extrahepatic metastasis; 5) poor liver function (Child-Pugh grade C or higher) rendering the patients ineligible for surgery.

The inclusion criteria were: 1) diagnosis of uHCC; 2) age between 18 and 80 years; 3) receipt of targeted therapy and immunotherapy concurrently with or within 3 months of radiotherapy. The exclusion criteria were as follows: 1) presence of other concurrent malignancies; 2) severe comorbidities resulting in intolerance to the treatment (defined as Grade 3 or higher treatment-related adverse events unresponsive to supportive care or dose adjustments); 3) receipt of concurrent locoregional therapies (eg, TACE, HAIC) during the combination treatment period; or 4) unavailability of complete clinical or follow-up data.

The study was conducted in accordance with the Declaration of Helsinki, and the study protocol was approved by the Institutional Review Board of the Mengchao Hepatobiliary Hospital of Fujian Medical University on November 3, 2023 (ID: 2023_143_03). Written informed consent was obtained from all patients before they received radiotherapy combined with PD-1 inhibitors and targeted therapy. The Hospital Ethics Committee at the three medical centers granted approval for this study and exempted the requirement of written informed consent for accessing medical records due to its retrospective nature.

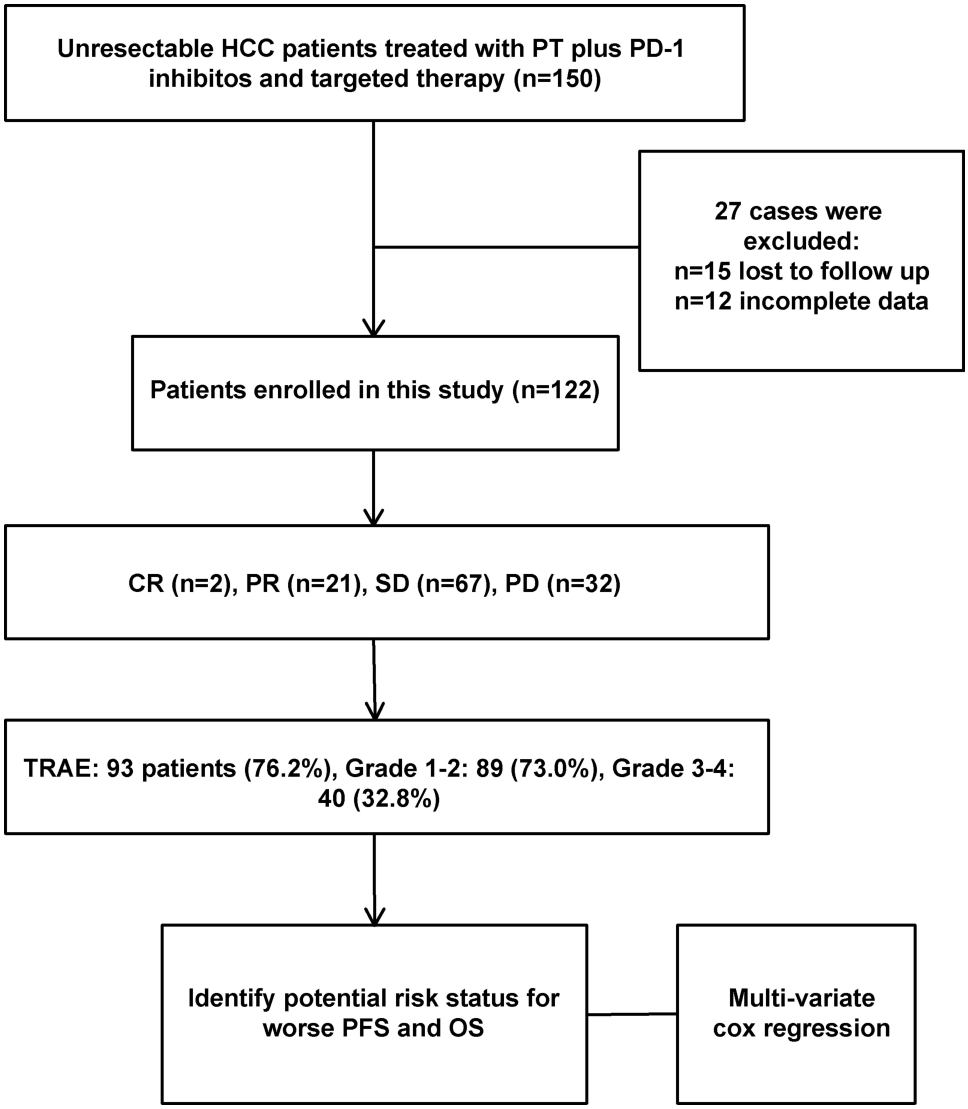

Figure 1 Workflow of this study.
Abbreviations: HCC, hepatocellular carcinoma; RT, radiotherapy; PD-1, programmed death-1; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; TRAE, treatment related adverse event; PFS, progression-free survival; OS, overall survival.

Treatment Protocol

The triple combination therapy consisted of radiotherapy, PD-1 inhibitors and targeted therapy. All patients received individual radiotherapy planning. The indications for treatment encompassed: 1) small hepatocellular carcinoma in a challenging location (eg, adjacent to major vessels or bile ducts) or intolerance to surgery; 2) macrovascular tumor thrombus or adjacent lesions; 3) residual disease after transarterial chemoembolization (TACE); 4) distant metastases requiring symptom control and tumor burden reduction. Intensity-modulated radiotherapy (IMRT) or stereotactic body radiotherapy (SBRT) was administrated based on tumor characteristics and hepatic function. Target delineation and margins varied by treatment modality. For patients receiving SBRT, the clinical target volume (CTV) was defined as the gross tumor volume (GTV) with a 0–2 mm margin. For patients receiving IMRT, the CTV comprised the GTV plus a 5–10 mm margin to cover potential microscopic spread, adjusted for anatomical barriers. The planning target volume (PTV) was created by expanding the CTV by 3–5 mm for SBRT and 5–10 mm for IMRT to account for setup uncertainties and respiratory motion. The irradiation sites included intrahepatic lesions, portal/venous tumor thrombi, and extrahepatic metastases. Strict radiation dose-volume constraints for organs at risk (OARs) were applied to ensure safety. For liver, total spared volume (Vtotal-V15 Gy) should be >700 mL and/or V15 Gy should be <1/3 Vtotal; for

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spinal cord, maximum dose (D_{max}) to 0.35 cc should be <18–22 Gy (depending on fractionation); for stomach, duodenum, and small bowel, the maximum dose (D_{max}) was strictly constrained (typically <30–35 Gy for 5-fraction SBRT schemes, or equivalent biological doses); for kidneys, mean dose should be <15–18 Gy. Radiation dose and fractionation were individualized; however, common regimens included 30–50 Gy in 3–5 fractions for SBRT and 45–60 Gy in 15–25 fractions for IMRT.

Immunotherapy and targeted therapy were initiated sequentially (concurrently with or within 3 months post-radiation). The median interval between radiotherapy and systemic therapy was 4 weeks to maximize synergistic effects. The PD-1 inhibitors used included camrelizumab, tislelizumab, sintilimab, toripalimab and nivolumab. Targeted agents consisted of vascular endothelial growth factor (VEGF) blockade (apatinib and bevacizumab) and multi-tyrosine kinase inhibitors (lenvatinib, sorafenib, anlotinib and donafenib). Drug selection was based on the latest efficacy and safety evidence, patient financial status and drug availability at each center. Dosing was calculated according to patients' height and weight. Treatment was interrupted or terminated in cases of patient intolerance, severe treatment-related adverse events (TRAEs), or disease progression.

Data Collection

Baseline demographics consisted of gender, age, HBV infection, Eastern Cooperative Oncology Group (ECOG) score, BCLC grade and treatment history. Data related to tumor features and treatment details were also extracted, including tumor number, maximum tumor size, presence of portal vein tumor thrombosis (PVTT), extrahepatic metastasis, types of PD-1 inhibitors and targeted agents, and radiotherapy parameters. Biochemical parameters, such as alpha-fetoprotein (AFP) level, albumin, neutrophil percentage, lymphocyte concentration, total bilirubin (TB) and platelet prothrombin time (PT), were collected before treatment initiation. Composite parameters, such as neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR) and prognostic nutritional index (PNI), were calculated and recorded accordingly. Particularly, PNI was calculated as Serum Albumin (g/L) + 5 × Total Lymphocyte Count ($\times 10^9$/L). It exhibited discriminatory performance in assessing the prognosis of HCC patients undergoing immunotherapy and other systemic treatments.[22,23] Liver function was also assessed by Child-Pugh scores and modified albumin-bilirubin (mALBI) grades.[24]

According to mRECIST criteria,[25] treatment response was evaluated by contrast-enhanced CT or magnetic resonance imaging every six to eight weeks after the first cycle of immunotherapy cycle. Progression-free survival (PFS) was defined as the time from treatment initiation to disease progression, while overall survival (OS) was referred to the interval from the initiation of treatment to the dearth or last follow-up. Throughout the treatment period, TRAEs were assessed and documented according to the US National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE v5.0). For each toxicity category, the highest grade observed per patient was recorded.

Statistical Analysis

Categorical variables were summarized by frequencies and percentages. Continuous variables were assessed for normality using the Shapiro–Wilk test. Data conforming to a normal distribution were presented as mean ± standard deviation (SD), while skewed data were presented as median with interquartile ranges (IQR). Survival outcomes, including OS and PFS were analyzed using the Kaplan–Meier method. The median OS (mOS) and median PFS (mPFS) were calculated accordingly. The association of baseline status with worse prognosis was evaluated by using univariate Cox regression and summarized with a hazard ratio (HR) and 95% confidence interval (CI). After setting the variables with a significance level of $P < 0.05$ and variance inflation factors < 5, a subsequent multivariate Cox regression was performed. Variables that remained statistically significant were determined as independent risk factors for uHCC treated with triple combination therapy of radiotherapy, PD-1 inhibitors and targeted therapy.

Results

Patient Characteristics

Overall, a total of 122 patients with unresectable HCC who received RT in combination with PD-1 inhibitors and targeted therapy were enrolled in this study. Baseline characteristics and treatment details were summarized in Table 1 and Table

Table 1 Baseline Characteristics of Patients with Unresectable Hepatocellular Carcinoma

Characteristic	Total (n=122)	Characteristic	Total (n=122)
Baseline data		PLR	113.73 (88.07, 161.67)
Gender, n(%)		TB (μmol/L)	23.48 (12.22, 28.80)
Male	111 (91.0%)	PLT (×109/L)	148.5 (103.25, 194.5)
Female	11 (9.0%)	PT (s)	13.23 ± 1.45
Age (yr)	53.3 ± 11.9	Child Pugh, n(%)	
HBV infection, n(%)		A	89 (72.95%)
No	12 (9.8%)	B	32 (26.23%)
Yes	110 (90.2%)	C	1 (0.82%)
ECOG PS, n(%)		mALBI grade, n(%)	
0	15 (12.30%)	1	30 (24.59%)
1	91 (74.59%)	2a	28 (22.95%)
2	16 (13.11%)	2b	60 (49.18%)
		3	4 (3.28%)
Tumor number, n(%)		BCLC, n(%)	
Solitary	44 (36.07%)	A	8 (6.56%)
Multiple	78 (69.93%)	B	7 (5.74%)
Maximum tumor size (cm)	6.50 (4.00, 10.28)	C	107 (87.7%)
PVTT, n(%)			
No	48 (39.34%)		
Yes	74 (60.66%)		
Extrahepatic metastasis, n(%)			
No	53 (43.44%)		
Yes	69 (56.56%)		
Baseline AFP, n(%)			
<100 ng/mL	48 (39.34%)		
≥100 ng/mL	74 (60.66%)		
Albumin (g/L)	36 (33.08, 39.52)		
NLR	3.04 (2.18, 4.53)		
PNI	43.03 (38.76, 47.35)		

Abbreviations: PVTT, portal vein tumor thrombosis; AFP, alpha-fetoprotein; HBV, hepatitis B virus; AFP, alpha-fetoprotein; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; PNI, prognostic nutritional index; TB, total bilirubin; ALB, albumin; PLT, platelet; PT, prothrombin time; mALBI grade, modified albumin-bilirubin grade; BCLC, Barcelona clinic liver cancer.

Table 2 Summary of Treatment Regimens

Regimens	Total (n=122)
Treatment history, n(%)	
No	70 (57.38%)
Yes	52 (42.62%)
Number of radiotherapy site	
Solitary	102 (83.61%)
Multiple	20 (16.39%)
Radiotherapy site (total, n=159)	
Liver	64 (52.0%)
Portal vein / venous tumor thrombus	49 (39.8%)
Metastasis lesion	37 (30.1%)
Lymph node	9 (7.3%)
Radiotherapy technique	
IMRT	99 (81.15%)
SBRT	23 (18.85%)

(*Continued*)

Table 2 (Continued).

Regimens	Total (n=122)
Radiotherapy dose (Gy)	45 (32.25, 58.50)
PD-1 class, n(%)	
Camrelizumab	71 (58.20%)
Tislelizumab	25 (20.49%)
Sintilimab	17 (13.93%)
Toripalimab	8 (6.56%)
Nivolumab	1 (0.82%)
Cycle of PD-1	4 (2, 6)
Type of targeted drug	
Lenvatinib	51 (41.80%)
Sorafenib	37 (30.33%)
Apatinib	21 (17.21%)
Anlotinib	6 (4.91%)
Bevacizumab	5 (4.10%)
Donafenib	2 (1.64%)

Abbreviations: IMRT, Intensity-modulated radiation therapy; SBRT, Stereotactic Body radiation therapy; PD-1, programmed death-1.

2. Among the 122 patients, 111 (91.0%) were male, and the mean age was 53.3 years (± 11.9 years). A history of HBV infection was present in 110 patients (90.2%). At baseline, the Eastern cooperation oncology group (ECOG) performance status scores were 0 in 15 patients (12.30%), 1 in 91 patients (74.59%) and 2 in 16 patients (13.11%). Solitary tumors were observed in 44 patients (36.07%). The median maximum tumor diameter was 6.50 cm (IQR, 4.00–10.28 cm). Portal vein invasion and extrahepatic metastasis were presented in 60.66% and 56.56% of patients. Regarding baseline laboratory data, alpha fetoprotein (AFP) levels ≥100 ng/mL were observed in 74 patients (60.66%). The median albumin level was 36 g/L (IQR, 33.08–39.52 g/L). For composite parameters, the median neutrophil to lymphocyte ratio (NLR) was 3.04 (IQR, 2.18–4.53), and the median prognostic nutritional index (PNI) was 43.03 (IQR, 38.76–47.35). Liver function assessment revealed a median total bilirubin (TB) of 23.48 μmol/L (IQR, 12.22–28.80 μmol/L), a median PLT of 148.5 $\times 10^9$/L (IQR, 103.25–194.5$\times 10^9$/L), and average PT of 13.23 seconds (± 1.45s). According to the Child-Pugh classification, 89 patients (72.95%) were class A, 32 (26.23%) class B and 1 (0.82%) class C. Based on the modified ALBI (mALBI) grading system, patients were categorized as grade 1 (n=30, 24.59%), grade 2a (n=28, 22.95%), grade 2b (n=60, 49.18%) or grade 3 (n=4, 3.28%). The majority of patients were classified as Barcelona Clinic Liver Cancer (BCLC) stage C (n=107, 87.7%), while 8 (6.56%) and 7 (5.74%) were stages A and B, respectively.

Patients Treatments

Most patients were treatment-naive (n=70, 57.38%). Intensity-modulated radiation therapy (IMRT) was administered to 99 patients (81.15%), while stereotactic body radiation therapy (SBRT) was used in 23 patients (18.85%). The majority of patients (n=102, 83.61%) received radiotherapy to a single site, whereas 20 patients (16.39%) had multiple sites irradiated. The most common radiotherapy site was the liver (n=64, 52.0%), followed by portal vein or venous tumor thrombus (n=49, 39.8%), metastasis lesions (n=37, 30.1%) and lymph nodes (n=9, 7.3%). The median radiotherapy dose was 45 Gy (IQR, 32.25–58.50 Gy). The most frequently used PD-1 inhibitors was camrelizumab (n=71, 58.20%), followed by tislelizumab (n=25, 20.49%), sintilimab (n=17, 13.93%), toripalimab (n=8, 6.56%) and nivolumab (n=1, 0.82%). The median number of immunotherapy cycles was 4 (IQR, 2–6). All patients received a concomitant combination of targeted therapy, including lenvatinib (n=51, 41.80%), sorafenib (n=37, 30.33%), apatinib (n=21, 17.21%), anlotinib (n=6, 4.91%), bevacizumab (n=5, 4.10%) and donafenib (n=2, 1.64%).

Table 3 Best Tumor Response According to mRECIST Criteria

Best Response, n(%)	Total (n=122)
CR	2 (1.64%)
PR	21 (17.21%)
SD	67 (54.92%)
PD	32 (26.23%)
ORR (95% CI)	18.85% (95% CI: 12.34%-26.93%)
DCR (95% CI)	73.78% (95% CI: 65.04%-81.32%)

Abbreviations: mRECIST, modified response evaluation criteria in solid tumors; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate.

Efficacy and Safety of Treatment

The median follow-up time was 14.2 months (IQR, 6.9–19.2 months). The best responses are shown in Table 2. Per mRECIST, the response distribution in the 122 patients were as follows: CR 1.64% (n=2), PR 17.21% (n=21), SD 54.92% (n=67) and PD 26.23% (n=32). This yields an ORR of 18.85% (95% CI: 12.34%–26.93%) and a DCR of 73.78% (95% CI: 65.04%-81.32%) (Table 3). By the data cutoff, progression and death were recorded in 90 (73.77%) and 60 patients (49.18%), respectively. The median OS was 19.0 months (95% CI: 17.8–23.4 months), and the median PFS was 7.2 months (95% CI: 5.5–10.9 months). The 1-year OS and PFS rates were 71.6% and 36.1%, declining to 35.8% and 19.1% at 2 years, respectively (Figure 2).

Treatment-related adverse events (TRAEs) were summarized in Table 4. Among the 122 patients, 93 patients (76.23%) experienced at least 1 TRAE. The most common TRAEs of any grade were leukopenia (n=50, 40.98%), thrombocytopenia (n=48, 39.34%), anaemia (n=40, 32.79%), hyperbilirubinemia (n=25, 20.49%), rash (n=19, 15.57%), and elevated ALT (n=16, 13.11%) and AST (n=15, 12.30%). Grade 3 or 4 TRAEs occurred in 40 patients (32.79%), primarily consisting of thrombocytopenia (n=17, 13.93%), leukopenia (n=12, 9.84%), hyperbilirubinemia (n=7, 5.74%) and anaemia (n=4, 3.28%). No treatment-related death was observed. Regarding the radiotherapy-related toxicities, 10 patients (8.19%) experienced acute radiation reactions, including radiation dermatitis (5.74%), radiation-induced oral mucositis (0.82%) and pyrexia (2.46%), all were alleviated with glucocorticoids and supportive care. Immune-related

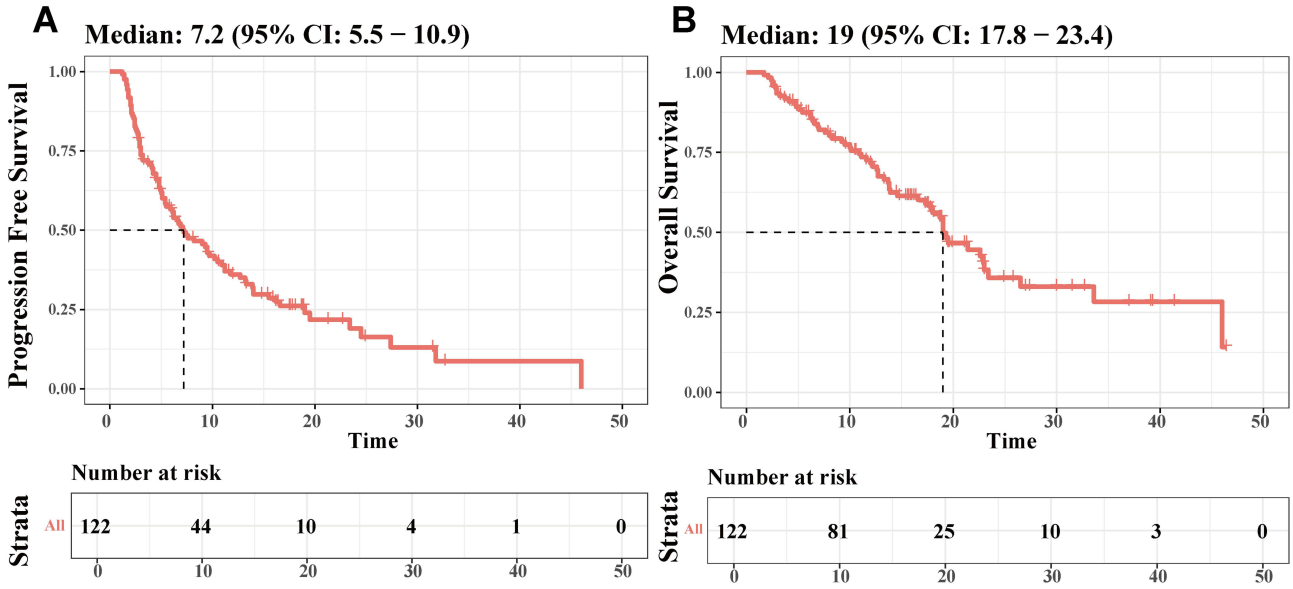

Figure 2 Kaplan–Meier curves of progression-free survival (**A**) and overall survival (**B**).

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Table 4 Treatment-Related Adverse Events

Adverse Events	All Patients (n=122)		
	Any Grade, n (%)	Grade 1–2, n (%)	Grade 3–4, n (%)
Anaemia	40 (32.79%)	36 (29.51%)	4 (3.28%)
Leukopenia	50 (40.98%)	38 (31.15%)	12 (9.84%)
Thrombocytopenia	48 (39.34%)	31 (25.41%)	17 (13.93%)
Elevated ALT	16 (13.11%)	14 (11.48%)	2 (1.64%)
Elevated AST	15 (12.30%)	12 (9.84%)	3 (2.46%)
Hyperbilirubinemia	25 (20.49%)	18 (14.75%)	7 (5.74%)
Rash	19 (15.57%)	19 (15.57%)	0
Pyrexia	3 (2.46%)	3 (2.46%)	0
Diarrhea	9 (7.38%)	9 (7.38%)	0
Gastrointestinal bleeding	7 (5.74%)	6 (4.92%)	1 (0.82%)
Hand-foot syndrome	8 (6.56%)	8 (6.56%)	0
Hypothyroidism	6 (4.92%)	4 (3.28%)	2 (1.64%)
Proteinuria	3 (2.46%)	2 (1.64%)	1 (0.82%)
Gum bleeding	3 (2.46%)	3 (2.46%)	0
Epistaxis	2 (1.64%)	2 (1.64%)	0
Immune-related pneumonia	6 (4.92%)	2 (1.64%)	4 (3.28%)
Immune-related myocarditis	5 (4.10%)	4 (3.28%)	1 (0.82%)
Radiation dermatitis	7 (5.74%)	7 (5.74%)	0
Radiation-induced oral mucositis	1 (0.82%)	1 (0.82%)	0

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

adverse events (irAEs) occurred in 15 patients (12.30%), manifesting as hypothyroidism (4.92%), immune-related myocarditis (4.10%) and immune-related pneumonia (4.92%). They were all managed via dose interruptions or corticosteroids. None led to treatment discontinuation. During targeted therapy, treatment was temporarily interrupted in 12 patients (9.8%) due to adverse events, including elevated transaminases (2.46%), rash (2.46%), epistaxis (1.64%), gum bleeding (1.64%), diarrhea (0.8%), and proteinuria (0.8%). All patients successfully resumed treatment after dose adjustment.

Risk Factors for OS and PFS

Via the univariate cox analysis of the baseline clinical-laboratory features, we determined potential risk status, including higher level of AFP ($p<0.001$), elevated NLR ($p=0.003$), longer PT ($p=0.025$), larger maximum tumor size ($p=0.009$), higher Child-Pugh grade ($p=0.013$) and higher mALBI ($p=0.003$) for shorter overall survival. On multivariate analysis, elevated AFP (HR= 2.683, 95% CI: 1.520–4.736) and higher mALBI grade (HR= 2.057, 95% CI: 1.166–3.484) remained independent risk factors for shorter OS (Table 5). To further explore the impact of treatment duration, patients were stratified by tumor response (objective response/PR+CR, SD, and PD groups). In an exploratory analysis specifically within the SD group, longer immunotherapy duration was associated with improved survival (p=0.003) (Table 6 and

Table 5 Univariate and Multivariate Analysis for Overall Survival

Characteristics	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Gender (male vs female)	1.878 (0.678, 5.203)	0.225		
Age	1.018 (0.995, 1.043)	0.131		
HBV (no vs yes)	0.773 (0.332, 1.802)	0.552		

(*Continued*)

Table 5 (Continued).

Characteristics	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Baseline laboratory data				
AFP (>100 ng/mL vs <=100 ng/mL)	2.955 (1.673, 5.218)	<0.001	2.683 (1.520, 4.736)	<0.001
NLR	1.122 (1.041, 1.209)	0.003		
PLR	1.001 (0.999, 1.003)	0.148		
PNI	0.970 (0.933, 1.009)	0.128		
TB	1.009 (0.999, 1.02)	0.084		
ALB	0.947 (0.931, 1.018)	0.244		
PLT	1.000 (0.997, 1.003)	0.987		
PT	1.18 (1.021, 1.363)	0.025		
Maximum tumor size	1.077 (1.019, 1.14)	0.009		
Tumor number (solitary vs multiple)	0.838 (0.497, 1.412)	0.507		
Child-Pugh (A vs B/C)	1.954 (1.153, 3.311)	0.013		
mALBI (1/2a vs 2b/3)	2.266 (1.318, 3.898)	0.003	2.057 (1.166, 3.484)	0.012
BCLC (A vs B/C)	1.99 (0.803, 4.404)	0.146		
Radiotherapy dose (Gy)	0.999 (0.989, 1.009)	0.804		

Abbreviations: HBV, hepatitis B virus; AFP, alpha-fetoprotein; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; PNI, prognostic nutritional index; TB, total bilirubin; ALB, albumin; PLT, platelet; PT, prothrombin time; mALBI grade, modified albumin-bilirubin grade; BCLC, Barcelona clinic liver cancer; mRECIST, modified response evaluation criteria in solid tumors; HR, hazard ratio; 95% CI, 95% confidence interval.

Table 6 Cox Regression Analysis Between Long Immunotherapy Cycle and Overall Survival

	Subgroup	Events (Number of Patients)	HR (95% CI)	p-value
Long cycle	Response			
	PR+CR	6 (23)	0.952 (0.849, 1.067)	0.918
	Non-response			
	SD	34 (67)	0.857 (0.774, 0.948)	0.003
	PD	20 (32)	0.952 (0.849, 1.067)	0.400

Abbreviations: HR, hazard ratio; 95% CI, 95% confidence interval; PR, partial response; CR, complete response; SD, stable disease; PD, progressive disease.

Figure 3). For PFS, older age (p=0.033), absence of HBV infection (p=0.028), elevated NLR (p=0.003), elevated PNI (p=0.025) and higher mALBI grade (p=0.001) were associated with early progression. Multivariate analysis confirmed that only the higher NLR level (HR=1.066, 95% CI: 1.006–1.130) and mALBI grade (HR=1.896, 95% CI: 1.220–2.949) were independent risk factors for shorter PFS (Table 7 and Figure 4).

Discussion

Despite breakthroughs achieved with the combination of PD-1/PD-L1 inhibitors and targeted therapy, its overall response rate (ORR) was still unsatisfactory, advanced hepatocellular carcinoma (HCC) continues to pose a substantial therapeutic challenge on global health systems.[5–8] Exploring other therapeutic strategies that can improve the local control in advanced HCC remains urgently needed. In contrast to the systemic therapy alone, in this study, we investigate the integration of radiotherapy with PD-1 inhibitors and targeted therapy, evaluating the efficacy and safety of this triple regimen combining locoregional and systemic therapy.

Overall, the triple therapy had a favorable mOS of 19.0 months (95% CI: 17.8–23.4 months) and a mPFS of 7.2 months (95% CI: 5.5–10.9 months), comparable to the established first-line benchmarks of 19.2 months reported in the

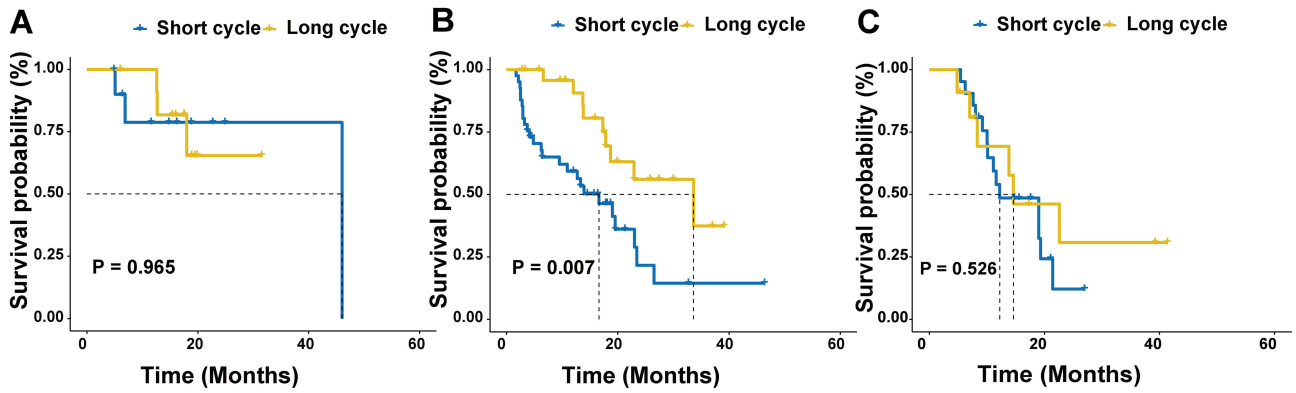

Figure 3 Kaplan–Meier plots of overall survival between short immunotherapy cycle group and long immunotherapy cycle group within PR+CR patients (**A**), SD patients (**B**) and PD patients (**C**).
Abbreviations: PR, partial response; CR, complete response; SD, stable disease; PD, progressive disease; HR, hazard ratio; 95% CI, 95% confidence interval.

IMbrave150 trail and 22.1 months in the CARES-310 trail.[6,26] However, the ORR of 18.85% (95% CI: 12.34%–26.93%) is still limited. This may be attributed to the potential selection bias, as substantial proportions of patients with PVTT and extrahepatic metastases were enrolled in our study.[18] Typically, it is crucial to note that 42.6% of patients in our study had received prior therapy. Given that an mOS of 13.5 months and an mPFS of 5.7 months reported in similar second-line or refractory settings (RESCUE),[8] as well as standard TKIs in RESORCE and CELESTIAL typically yield an mOS of only 10.2–10.6 months,[27,28] the mOS and mPFS in our study remained considerable. The addition of radiotherapy may confer a synergistic survival benefit for system therapy. Moreover, the cohort yielded a high disease control rate of 73.78%, which hinted effective disease stabilization and long-lasting anti-tumor activity of this triple regimen. Previous studies

Table 7 Univariate and Multivariate Analysis of Progression-Free Survival

Characteristics	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Gender (male vs female)	0.965 (0.482, 1.929)	0.919		
Age	1.021 (1.002, 1.041)	0.033		
HBV (no vs yes)	0.471 (0.242, 0.920)	0.028		
Baseline laboratory data				
AFP (>100ng/mL vs <=100ng/mL)	1.535 (0.994, 2.371)	0.053		
NLR	1.085 (1.029, 1.144)	0.003	1.066 (1.006, 1.130)	0.030
PLR	1.001 (0.999, 1.003)	0.069		
PNI	0.966 (0.938, 0.996)	0.025		
TB	1.008 (0.998, 1.018)	0.118		
ALB	0.969 (0.936, 1.002)	0.064		
PLT	1.000 (0.998, 1.002)	0.973		
PT	1.113 (0.986, 1.255)	0.083		
Maximum tumor size	1.007 (0.961, 1.056)	0.760		
Tumor number (solitary vs multiple)	0.923 (0.631, 1.469)	0.861		
Child-Pugh (A vs B/C)	1.169 (0.742, 1.843)	0.501		
mALBI (1/2a vs 2b/3)	2.061 (1.337, 3.176)	0.001	1.896 (1.220, 2.949)	0.004
BCLC (A vs B/C)	1.028 (0.564, 1.874)	0.928		
Radiotherapy dose (Gy)	1.003 (0.995, 1.011)	0.468		

Abbreviations: HBV, hepatitis B virus; AFP, alpha-fetoprotein; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; PNI, prognostic nutritional index; TB, total bilirubin; ALB, albumin; PLT, platelet; PT, prothrombin time; mALBI grade, modified albumin-bilirubin grade; BCLC, Barcelona clinic liver cancer; mRECIST, modified response evaluation criteria in solid tumors; HR, hazard ratio; 95% CI, 95% confidence interval.

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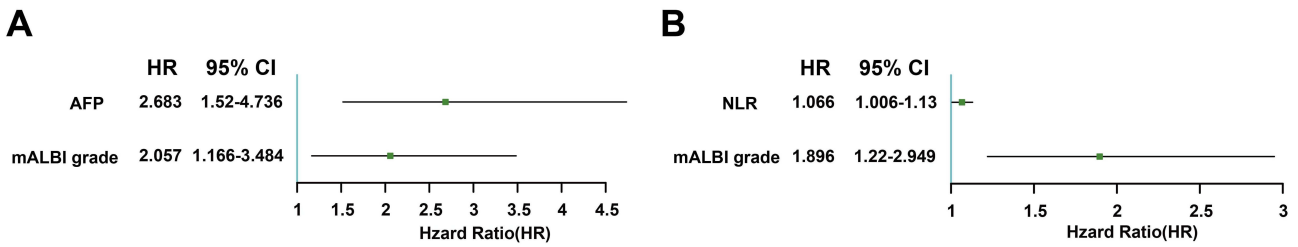

Figure 4 Independent risk factors for OS (**A**) and PFS (**B**).
Abbreviations: AFP, alpha-fetoprotein; PR, partial response; CR, complete response; SD, stable disease; PD, progressive disease; HR, hazard ratio; 95% CI, 95% confidence interval; OS, overall survival; PFS, progression-free survival.

have demonstrated radiotherapy not only induces immunogenic death but also promotes infiltration of anti-tumor T cells into the tumor microenvironment, while upregulating the expression of immune checkpoint molecules (PD-1, PD-L1) and VEGF.[16,29] In addition, anti-angiogenic therapy facilitates normalization of vessel formation, which in turn enhances the efficacy of radiotherapy and stimulates immune infiltration.[30,31] Thus, the synergistic triple-combination strategy contributed to improved anti-tumor efficacy, which eventually translated into the observed long-term survival benefit.

The safety of this triple regimen was consistent with known toxicity profiles. In the LEAP-012 trail, grade 3 or higher TRAEs were observed in 32% of patients receiving TACE plus lenvatinib and pembrolizumab.[32] Chi et al reported 41.9% of patients with uHCC experienced grade 3–4 TRAEs when treated with lenvatinib plus anti-PD-1 antibodies together with TACE or HAIC.[33] Moreover, in a retrospective study that enrolled 16 advanced HCC receiving PD-1/PD-L1 inhibitors plus anti-angiogenic therapy and RT, grade 3–4 TRAEs were observed in 25% of patients.[34] In our study, grade 3 or 4 TRAEs occurred in 32.79% of patients, primarily manifested as abnormal laboratory parameters. Importantly, strict adherence to dose-volume constraints for organs at risk (OARs) ensured that radiotherapy-related toxicities were minimal. All AEs were tolerable and manageable, and no treatment-related deaths were observed. In general, the combination of radiotherapy with immunotherapy and targeted therapy demonstrated an acceptable safety profile.

Furthermore, we investigated potential risk status influencing disease progression and overall survival. Consistent with established prognostic models, an AFP level ≥100 ng/mL and higher mALBI grade were identified as independent risk factors for shorter OS. As high AFP level significantly associated with aggressive tumor behavior, vascular invasion and VEGF overexpression, these results further reinforcing the importance of lower baseline AFP level in achieving better outcomes.[35–37] Regarding liver function assessment, the mALBI grade emerged as a robust predictor for both OS and PFS in our cohort. Different from traditional Child-Pugh score, the mALBI grade was calculated by albumin and bilirubin levels, which enable it as an objective measure for liver function reserve.[38–41] Since radiotherapy, TKIs, and ICIs all require adequate hepatic reserve for metabolism or tolerance, patients with poorer mALBI grades (2b or 3) are more prone to treatment interruptions or liver decompensation, thereby compromising survival outcomes.[42,43] In addition to mALBI, higher baseline neutrophil-to-lymphocyte ratio (NLR) was identified as an independent risk factor for early disease progression. As a system immune-inflammation index, elevated NLR indicated a dominance of pro-tumorigenic inflammation over anti-tumor immune response, which promotes immunosuppressive microenvironment that may render tumor resistant to immune checkpoint blockade.[44,45] Beyond these baseline prognostic stratifiers, we performed an exploratory analysis regarding treatment exposure. We observed that patients who received more cycles of immunotherapy had better survival outcomes. Specifically, subgroup analysis revealed that this survival benefit was most pronounced in patients achieving stable disease (SD). As the delayed changes and persistent therapeutic effect,[46,47] the sustained immune activation may be necessary to convert radiological disease stabilization into long-term survival.

There are several limitations need to be acknowledged. First, selection bias may present for retrospective design of this study. Secondly, although this represents the largest data collected from multiple centers thus far, the sample size remains relatively small. Specifically, due to the retrospective nature of data extraction, granular details such as sub-classification of PVTT and precise breakdown of all irradiation sites were not uniformly available. In addition, variations existed in the specific radiotherapy technologies, PD-1 antibodies, and targeted agents employed, even though all patients

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followed a triple-therapy framework. Finally, the lack of a standard-treatment control group prevented a comparative assessment against conventional regimens. Prospective randomized controlled trials with larger cohorts and standardized protocols are necessary to confirm these results and establish causality.

Conclusion

With encouraging survival benefits and manageable safety profile, the triple therapy that combined radiotherapy plus PD-1 inhibitors and targeted agents provides a promising treatment option for uHCC. According to baseline AFP level, mALB grade and NLR level, prognosis evaluation is available. Further prospective validation is warranted for this therapeutic combination.

Abbreviations

uHCC, unresectable hepatocellular carcinoma; RT, radiotherapy; PD-1, programmed death-1; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; TRAEs, treatment related adverse events; PFS, progression-free survival; OS, overall survival; PVTT, portal vein tumor thrombosis; AFP, alpha-fetoprotein; HBV, hepatitis B virus; AFP, alpha-fetoprotein; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; PNI, prognostic nutritional index; TB, total bilirubin; ALB, albumin; PLT, platelet; PT, prothrombin time; mALBI grade, modified albumin-bilirubin grade; BCLC, Barcelona clinic liver cancer; IMRT, Intensity-modulated radiation therapy; SBRT, Stereotactic Body radiation therapy; mRECIST, modified response evaluation criteria in solid tumors; ORR, objective response rate; DCR, disease control rate; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HR, hazard ratio; 95% CI, 95% confidence interval.

Data Sharing Statement

The original anonymous dataset is available on request from the corresponding author at cxiongzpc@fjmu.edu.cn.

Ethics Approval and Informed Consent

The studies involving humans were approved by Institutional Review Board of the Mengchao Hepatobiliary Hospital of Fujian Medical University (ID: 2023_143_03). The studies were conducted in accordance with the local legislation and institutional requirements. The Hospital Ethics Committee at the three medical centers granted approval for this study and exempted the requirement of written informed consent for accessing medical records due to its retrospective nature. All clinical data used in this study were anonymous and were obtained after each patient agreed to treatment by written consent.

Consent for Publication

All authors have reviewed and approved the final version of the manuscript and consent to its publication. They confirm that they have been shown all content, including any images, videos, or recordings, to be included in the article.

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Author Contributions

Xu WX, Gao SM and Zheng PC designed and performed the research and drafted the manuscript; Lu LB designed the research and supervised and reviewed the report; Chen X supervised and reviewed the report and provided funding acquisition; Chen JL, Guo XY and Li C designed the research and contributed to the analysis; Chen XL, Tang SN and Nie YY collected data and provided methodology.

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically

reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The author(s) report no conflicts of interest in this work.

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