ImmunoTargets and Therapy

Dovepress
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ORIGINAL RESEARCH

Clinical Outcomes and Hepatic Toxicity of Combined Intensity Modulated Radiotherapy and PD-1 Inhibitors in Child-Pugh Class B Advanced Hepatocellular Carcinoma

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Purpose: There is limited research data on the management of hepatocellular carcinoma (HCC) patients with Child-Pugh class B (CP-B). This study aimed to evaluate the clinical outcomes and radiation-induced hepatic toxicity (RIHT) of combined intensity modulated radiotherapy (IMRT) and programmed cell death protein 1 (PD-1) inhibitors in advanced HCC patients with CP-B.

Patients and Methods: This retrospective study screened 232 CP-B advanced HCC patients who had undergone IMRT, and the irradiation scopes were intrahepatic tumor lesions and/or venous tumor thrombosis. The propensity matching method (PSM) was used to reduce selection bias between the radiotherapy (RT) and RT+PD-1 groups. The primary endpoints were overall survival (OS) and progression-free survival (PFS), and the secondary endpoints included local progression-free survival (LPFS), out-of-field progression-free survival (outPFS), objective response rate (ORR), disease control rate (DCR), and RIHT.

Results: 50 and 39 patients with CP-B advanced HCC were included in the RT+PD-1 and RT groups. After PSM, 39 patients from each group were matched. The median follow-up duration was 15.53 months (95% CI, 13.83–17.22). The median OS and median PFS of RT+PD-1 group were significantly prolonged than RT group (OS:14.27 months [95% CI, 10.53–not estimable] vs 7.57 months [95% CI, 6.57–10.00], HR = 0.284; 95% CI, 0.153–0.526; $p < 0.001$), (PFS:9.00 months [95% CI, 5.00–not estimable] vs 4.50 months [95% CI, 3.10–6.00], HR = 0.349; 95% CI, 0.188–0.648; $p < 0.001$). The ORR of RT+PD-1 group was improved than RT group, 43.6% (95% CI, 27.3–59.9) vs 28.2% (95% CI, 13.4–43.0) ($p = 0.157$). The incidence of RIHT did not differ between the groups except the RT+PD-1 group experienced increased total bilirubin (≥grade 1) more frequently ($p = 0.021$).

Conclusion: Combined IMRT and PD-1 inhibitors improved clinical outcomes with a comparable incidence of RIHT to radiotherapy alone in advanced HCC patients with CP-B. The individual combined IMRT and PD-1 inhibitors for CP-B could be cautiously applied weighing the survival benefits and the RIHT risks.

Keywords: Child-Pugh B, hepatocellular carcinoma, PD-1 inhibitors, hepatic toxicity, radiotherapy, immunotherapy

Background

Hepatocellular carcinoma (HCC) is a leading form of primary liver cancer that is often associated with cirrhosis and chronic liver disease.[1,2] Managing patients with Child-Pugh class B (CP-B) advanced HCC remains challenging because of reduced hepatic reserve function. Liver function for tolerance and potential benefits in HCC patients with CP-B should be carefully assessed to strategize effective therapeutic approaches.[3] Comprehensive research on the optimal treatment options for HCC patients with CP-B are lacking.

Radiotherapy (RT) remains the mainstay treatment for HCC;[4,5] however, it is commonly associated with radiation-induced hepatic toxicity (RIHT).[6] Defining RIHT can be challenging; it is generally indicated by an increase in CP score ≥ 1, or ≥ 2, or an increase in liver enzymes > grade 3 within 3–6 months after RT completion.[7–9]A prospective study revealed that the median

Received: 7 May 2025
Accepted: 30 August 2025
Published: 12 September 2025

overall survival (mOS) was 7.9 months for CP-B or C advanced HCC patients who underwent stereotactic body radiation therapy (SBRT).[7] In addition, Korean and Chinese studies have demonstrated significant efficacy and manageable RIHT in HCC patients with CP-B receiving fractionated conformal radiotherapy or intensity-modulated radiotherapy (IMRT).[10,11] A study in our center revealed that the mOS of HCC patients with CP-B who received IMRT was 9.0 and 24.2 months for patients with and without RIHT, respectively, and 12.2 months for all patients.[11]

Programmed cell death protein 1 or ligand 1 (PD-1 or PD-L1) immune checkpoint inhibitors (ICIs) are now the standard treatment for advanced HCC, with objective response rates (ORR) ranging from 14% to 17% when used as single agents.[12–14] For CP-B advanced HCC, first-line treatment with nivolumab resulted in a 55% disease control rate (DCR) and 4% treatment interruption rate due to toxicities, confirming its effectiveness and acceptable toxicity in this patient population.[15] Furthermore, a recent meta-analysis demonstrated ICIs are highly effective in CP-B HCC, with no significant increase in toxic effects compared with those in patients with CP-A HCC.[16]

The combination of RT and PD-1 inhibitors has been effective in advanced HCC patients,[17–21] with a median survival of 20.9 months without an increase in treatment side effects.[21] PD-1 inhibitors and RT may have a synergistic therapeutic benefit. Studies have demonstrated that RT for HCC can modify the tumor immune microenvironment, via increasing PD-L1, which suppresses CD8+ T-cell activity and promotes tumor cells' immunological escape. The immunosuppressive state caused by RT can be counteracted by PD-1 inhibitors and can also cause the regression of tumors outside the RT area, resulting in distal effects.[22,23] RT combined with PD-1 inhibitors improved survival and had fewer severe toxic effects compared to traditional therapy with sorafenib.[18] Because most patients in these studies had HCC with CP-A, the effectiveness and hepatic toxicity of combining RT and PD-1 inhibitors in patients with CP-B advanced HCC remain unclear. Therefore, this study aimed to evaluate the clinical outcomes and RIHT of combined IMRT and PD-1 inhibitors in advanced HCC patients with CP-B.

Materials and Methods

Patients

This retrospective study included 232 patients with CP-B HCC who received RT at Guangxi Medical University Cancer Hospital between September 2014 and December 2023. The main inclusion criteria were, (1) advanced HCC diagnosed by clinical imaging or pathology, (2) CP-B liver function before RT, (3) combined with macrovascular tumor thrombosis or extrahepatic metastasis, that was Barcelona Clinic Liver Cancer (BCLC) stage C, (4) treatment with RT alone or combined with PD-1 inhibitors, and (5) Eastern Cooperative Oncology Group (ECOG) performance score of 0–2. Patients with both HCC and intrahepatic cholangiocarcinoma; primary site of radiation was for extrahepatic metastasis; concurrent treatment with anti-angiogenic targeted therapy; those who received less than four cycles of PD-1 inhibitors therapy, and the interval time between the start of PD-1 inhibitors therapy and the start or end of RT is more than 8 weeks; local treatments, such as hepatectomy, radiofrequency, or interventions, are performed within 3 months after RT; hepatic toxicity from local treatments prior to RT, such as radiofrequency, or intervention, have not recovered to grade 1 or below; and those with missing laboratory indicators or radiological dosimetric data or follow-up data, were excluded. Ultimately, 89 patients, including 50 received RT alone (RT group) and 39 received RT combined with PD-1 inhibitors (RT+PD-1 group), were included in this study (Figure 1). This study was approved by the Guangxi Medical University Cancer Hospital (ethic no. KY2024878).

Radiotherapy Technique

For IMRT planning, the patient was in a supine position and the thermoplastic mold was cooled and set to fix the position. The patient was breathing spontaneously and a contrast-enhanced computed tomography (CT) (with a slice thickness of 2.5–3 mm) was performed for simulated positioning. The target area and organs at risk (OARs) were delineated using the MIM 6.8 system (MIM, USA), and the positioning CT images were fused with the diagnostic enhanced magnetic resonance images (MRI) before IMRT. Delineate the tumor target area on the fused image. Abdominal compression technique was adopted to reduce respiratory movements. IMRT plans were developed using Pinnacle 3 system (Philips, Netherlands) or Monaco treatment planning system (version 5.1), and IMRT was performed

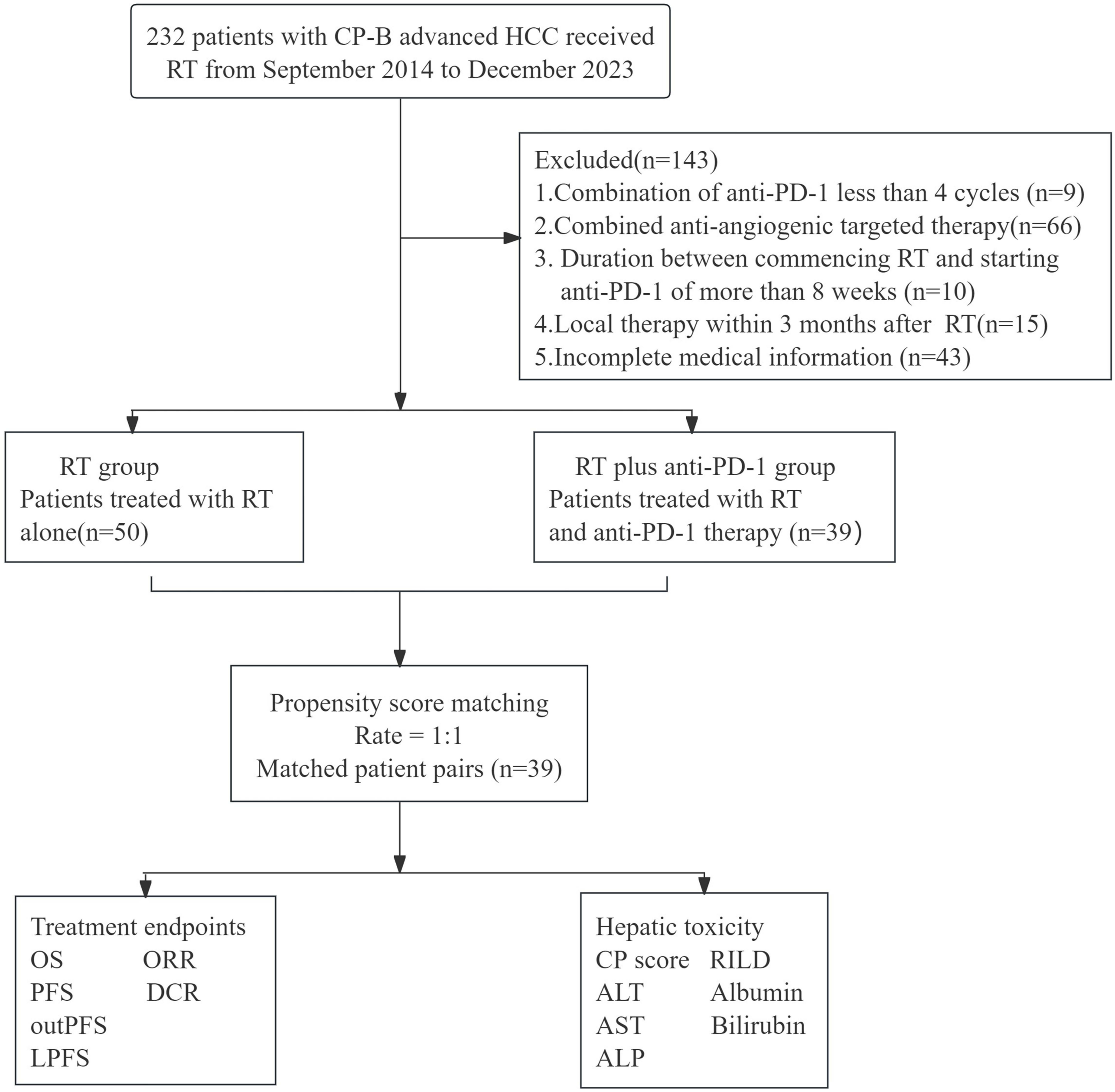

Figure 1 Flowchart of patient selection.

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; Anti-PD-1, antibodies against programmed cell death protein 1; AST, aspartate aminotransferase; CP, Child-Pugh; CP-B, Child-Pugh class B; DCR, disease control rate; HCC, hepatocellular carcinoma; LPFS, local progression-free survival; ORR, objective response rate; OutPFS, out-of-field progression-free survival; OS, overall survival; PFS; progression-free survival; RILD, radiation-induced liver disease; RT, radiotherapy.

using a 6 MV X-ray linear accelerator (ELEKTA Synergy, Sweden). Gross tumor volume (GTV) was programmed to include volume of the intrahepatic tumor thrombosis or intrahepatic tumor lesions enhanced on contrast-CT and CT-MRI fusion. Clinical target volume (CTV) was defined as a 4–5-mm margin outside GTV. The CTV and 5–10-mm buffer were included in the planned target volume to reduce the positioning uncertainty and the impact of breathing movement. A dose-volume histogram (DVH) analysis was conducted to assess the radiation strategy, which determined that OARs were adequately protected. Normal liver volume (NLV) was subtracted from the whole liver volume. The mean dose to normal liver was less than 23 Gy, with V20 ≤ 48%. For the kidneys, the mean dose to right kidney was less than 15 Gy and V20 < 32% of the volume, the mean dose to left kidney was less than 8 Gy and V20 < 10% of the volume. For the

https://doi.org/10.2147/ITT.S538796

spinal cord, the maximum dose is less than 35 Gy. For the esophagus, stomach, small intestine, and duodenum, the maximum dose is less than 40 Gy. For the heart, V30 < 10%.

The radiation doses were calculated using the fractionation method of 2.5 to 4.0 Gy per fraction. Patients received IMRT for 5 days a week, with a median fractionation rate of 3.0 Gy (range: 2.5–4.0 Gy) and a median total dose of 51.0 Gy (range: 47.0–60.0 Gy).

PD-1 Inhibitors Therapy

PD-1 inhibitors therapy were administered to patients in the RT+PD-1 group, either concurrently or sequentially. The PD-1 inhibitors included sintilimab (Innovent Biologics Co. Ltd., Suzhou, China), toripalimab (Junshi Biosciences Co. Ltd., Shanghai, China), tislelizumab (BeiGene Biosciences Co. Ltd., Shanghai, China), camrelizumab (HengRui Medicine Co. Ltd., Jiangsu, China), and nivolumab (Bristol Myers Squibb Pharma Co. Ltd., Princeton, America). The administration technique, dosage, and duration adhered to the manufacturer's recommendations.

Evaluation of efficacy and hepatic Toxicity

All patients received laboratory testing and magnetic resonance imaging (MRI) or contrast-enhanced CT to assess tumor response and hepatic toxicity before the initiation of RT and every 6–8 weeks thereafter. Two investigators assessed the tumor responses in target and non-target areas in line with modified Response Evaluation Criteria In Solid Tumors (mRECIST). The time interval from the start of RT to the date of death from any cause was defined as the overall survival (OS). The period of time between the onset of RT and the progression of the disease, the last follow-up, or death from any reason was called progression-free survival (PFS). Local progression-free survival (LPFS) refers to local control or irradiation in-field control rate. The length of time that the disease has progressed or recurred outside the irradiation lesion is referred to as out-of-field progression-free survival (outPFS). For the whole-body targeted lesions, the total of the partial and complete responses was designated as the objective response rate (ORR). The rate of stable state, partial response, or complete response was referred to as disease control rate (DCR). ORR and DCR were assessed for all target lesions (per mRECIST). For the evaluation of portal vein tumor thrombosis (PVTT) or hepatic vein tumor thrombosis (HVTT), any downstaging in Cheng's PVTT classification or a noticeable return of blood flow in the portal vein were considered PR for PVTT examination, whereas any upstaging was considered PD. Otherwise, the effects were classified as SD.[24]

RIHT was Evaluated Within 3 months After IMRT Completion Using the Common Terminology

Criteria for Adverse Events version 5.0 (CTCAE 5.0) and the CP score system. The CP score increased after IMRT completion (≥ 1 or ≥ 2) is a useful tool for assessing RIHT. Radiation-induced liver disease (RILD) is described as severe RIHT. RILD is frequently assessed within 3 months after completion of RT, exclude tumor growth or hepatitis B virus (HBV) reactivation, which is defined as a 10-fold or higher increase in HBV DNA levels. Two types of RILD have been identified: non-classic RILD (ncRILD) and classic RILD (cRILD). A level of serum alkaline phosphatase (ALP) greater than two times of upper limit of standard or baseline values (CTCAE 5.0 grade 2), anicteric hepatomegaly and ascites are associated with cRILD. A rise in CP score≥ 2, or a rise in the liver transaminase levels of no less than 5 times upper limit of baseline or standard value (CTCAE 5.0 grade 3), is associated with ncRILD.

Statistical Analysis

The "Matchlt" package in the R software was used for propensity score matching (PSM). PSM approach for patients in the two groups was to reduce selection bias and between-group heterogeneity. We chose the optimal matching method to keep the sample size to the maximum, the matching ratio is 1:1, and the caliper value was not set. Paired McNemar's test for categorical variables and paired *t*-test/Wilcoxon for continuous variables were adopted for post-PSM (1:1) comparisons between groups. The p-values and standardized mean difference (SMD) were used to assess covariate balance between groups. Age, hepatitis B virus infection (HBV), transcatheter chemoembolization (TACE) before RT, hepatectomy before RT, NLV, V10, V15, and V20, V25, V30, and V35 were among the factors that contributed to the propensity score of the study. Quantitative variables were evaluated for normality of the distribution using histograms and the Shapiro–Wilk test. The medians and interquartile ranges were used to describe continuous variables with abnormal distributions. Normally distributed continuous variables were presented as the mean ± standard deviation. Categorical variables were described as frequencies and percentages. An independent sample Student's *t*-test and Mann–Whitney *U*-test were used to compare quantitative variables between the two groups, and the chi-square test or Fisher's exact test were used to compare categorical variables before PSM. Cox regression analysis, both univariate and multivariate, was performed on variables exhibiting significant differences ($p < 0.05$). The Kaplan–Meier method and Log rank test were used to compare the PFS, OS, and outPFS between the two groups.

Results

Patient Characteristics

The patients' baseline characteristics, including clinical features, liver function factors before RT, and dosimetry factors before and after PSM, are summarized in Table 1. Of the 232 patients, 89 (comprising 86 men [96.63%]) were selected, 50 in RT group, 39 in RT+PD-1 group. Following PD-1 inhibitors were administered: camrelizumab (n = 16), tislelizumab (n = 10), nivolumab (n = 2), sintilimab (n = 7), and toripalimab (n = 3). Hepatitis B infection was present in 73 patients (82.02%). Intrahepatic tumors number more than 4 and max tumor size (which represents the largest single lesion) larger than 10 cm were identified in 47 (52.82%) and 40 (44.94%) patients, respectively. PVTT or HVTT were identified in 70 (78.65%). 36 (40.45%) patients had metastatic lesions, including 12 patients with separate abdominal lymph node metastases, 10 patients with separate lung metastases, 4 patients with separate bone metastases, and 10 patients had multiple lymph node and distant organ metastases. After PSM, there were no discernible variations between the two groups' initial features ($p > 0.05$, SMD < 0.2). The percentage of CP-B7 patients was 79.49% (n = 31) in the RT group and 87.18% (n = 34) in the RT+PD-1 group.

Efficacy Outcomes

The overall median follow-up was 13.83 months for RT+PD-1 group, and 17.58 months for RT group, 15.53 months (95% confidence interval [CI], 13.83–17.22) for the total patients. After PSM, the median OS (mOS) of RT group was 7.57 months (95% CI, 6.57–10.00) and RT+PD-1 group was 14.27 months (95% CI, 10.53–not estimable). Compared with the RT group, mOS was significantly higher in the RT+PD-1 group (HR = 0.284, 95% CI, 0.153–0.526, $p < 0.001$) (Figure 2A). The survival rates of patients between RT+PD-1 and RT groups at 6, 9, and 12 months were 66.7% (95% CI, 51.2%–82.1%) vs 74.4% (95% CI, 60.0%–88.7%), p = 0.456, 48.7% (95% CI, 32.3%–65.1%) vs 35.9% (95% CI, 20.1%–51.7%), p = 0.252, and 28.5% (95% CI, 22.5%–55.4%) vs 12.8% (95% CI, 1.8%–52.3%, p = 0.010, respectively. Patients in the RT+PD-1 group who did not receive TACE before radiotherapy had a significantly higher mOS than those in the RT group (not reach [95% CI,10.53–not estimable] vs 7.12 months [95% CI,6.03–not estimable], HR = 0.160; 95% CI, 0.040–0.636; p = 0.003) (Figure Supplemental 1A). The subgroup analysis of OS indicated that RT+PD-1 improved survival outcomes across all examined subgroups (Figure Supplemental 3A).

The median PFS (mPFS) was significantly higher in the RT+PD-1 group than in the RT group (9.00 months [95% CI, 5.00–not estimable] vs 4.50 months [95% CI, 3.10–6.00], HR = 0.349; 95% CI, 0.188–0.648; $p < 0.001$) (Figure 2B). The mPFS of patients who did not receive TACE before radiotherapy was higher in the RT+PD-1 group than in the RT group (7.0 months [95% CI, 5.0–not estimable] vs 4.5 months [95% CI, 1.50–not estimable], HR = 0.283; 95% CI, 0.085–0.946; p = 0.025) (Figure Supplemental 1B). The median outPFS was significantly higher in the RT+PD-1 group than in the RT group (11.0 months [95% CI, 7.00–not estimable] vs 5.0 months [95% CI, 4.50–6.00], HR = 0.244; 95% CI, 0.120–0.496; $p < 0.001$) (Figure Supplemental 2). The 6-month local progression-free survival (LPFS) of patients in the RT+PD-1 and RT groups was 51.3% (95% CI, 34.9%–67.7%) and 30.8% (95% CI, 15.6%–45.9%), respectively, p = 0.066. At 9 months, the RT+PD-1 group showed a significantly higher LPFS than the RT group: 33.3% (95% CI, 17.9%–48.8%) vs 5.1% (95% CI, 2.1%–12.4%), p = 0.002. The subgroup analysis of PFS indicates that the RT+PD-1 group benefited across all examined subgroups (Figure Supplemental 3B).

https://doi.org/10.2147/ITT.S538796

Table 1 Patient Baseline Clinical, Dosimetric Characteristics

Variable	Before PSM				After PSM			
	RT (n = 50)	RT+PD-1 (n = 39)	P Value	SMD	RT (n = 39)	RT+PD-1 (n = 39)	P Value	SMD
Age, Mean ± SD	50.30 ± 10.12	54.56 ± 9.40	**0.045**	0.453	50.85 ± 10.24	54.56 ± 9.40	0.099	0.195
Sex, n (%)			1.000				1.000	
Female	2 (4.0)	1 (2.6)		−0.091	2 (5.1)	1 (2.6)		−0.162
Male	48 (96.0)	38 (97.4)		0.091	37 (94.9)	38 (97.4)		0.162
Hepatitis B virus infection, n(%)			0.094				0.329	
Negative	12 (24.0)	4 (10.3)		−0.453	7 (17.9)	4 (10.3)		−0.154
Positive	38 (76.0)	35 (89.7)		0.453	32 (82.1)	35 (89.7)		0.154
Cirrhosis, n (%)			0.348				0.615	
Absent	11 (22.0)	12 (30.8)		0.190	10 (25.7)	12 (30.8)		0.111
Present	39 (78.0)	27 (69.2)		−0.190	29 (74.3)	27 (69.2)		−0.111
ECOG PS, n (%)			0.946				0.821	
0	24 (48.0)	19 (48.7)		0.014	18 (46.2)	19 (48.7)		0.051
1	26 (52.0)	20 (51.3)		−0.014	21 (53.8)	20 (51.3)		−0.051
Aspartate aminotransferase(U/L), M (Q_1, Q_3)	55.0 (40.2, 86.7)	59.0 (37.0, 82.5)	0.817	−0.033	56.0 (40.5, 91.0)	59.0 (37.0, 82.5)	0.579	−0.100
Alanine aminotransferase(U/L), M (Q_1, Q_3)	43.5 (22.0, 61.7)	38.0 (22.5, 65.5)	0.750	0.007	42.0 (22.0, 61.5)	38.0 (22.5, 65.5)	0.745	0.002
Alkaline phosphatase(U/L), M (Q_1, Q_3)	159.0 (107.5, 185.7)	150.0 (106.0, 237.0)	0.728	0.166	164.0 (106.0, 186.0)	150.0 (106.0, 237.0)	0.787	0.133
Prothrombin time (sec), Mean ± SD	13.4 ± 1.5	13.0 ± 1.9	0.237	0.237	13.4 ± 1.3	13.0 ± 1.9	0.248	−0.129
Platelet counts(10^9/L), M (Q_1, Q_3)	173.5 (122.2, 251.0)	171.0 (117.0, 223.0)	0.820	−0.070	175.0 (118.5, 267.4)	171.0 (117.0, 223.0)	0.614	−0.152
Child-Pugh score, n (%)			0.673				0.362	
7	42 (84.0)	34 (87.2)		0.095	31 (79.5)	34 (87.2)		0.130
8/9	8 (16.0)	5 (12.8)		−0.095	8 (20.5)	5 (12.8)		−0.130
ALBI score, Mean ± SD	−1.7 ± 0.3	−1.8 ± 0.3	0.338	−0.222	−1.7 ± 0.4	−1.8 ± 0.3	0.121	−0.186
Alpha fetoprotein (ng/mL), n (%)			0.759				0.821	
<400	24 (48.0)	20 (51.3)		0.066	19 (48.7)	20 (51.3)		0.051
≥400	26 (52.0)	19 (48.7)		−0.066	20 (51.3)	19 (48.7)		−0.051
Max tumor size(cm), n (%)			0.839				1.000	
≤10	28 (56.0)	21 (53.8)		−0.043	21 (53.8)	21 (53.8)		0.000
>10	22 (44.0)	18 (46.2)		0.043	18 (46.2)	18 (46.2)		0.000
Tumor number, n (%)			0.548				0.496	
<4	25 (50.0)	17 (43.6)		−0.129	20 (51.3)	17 (43.6)		−0.155
≥4	25 (50.0)	22 (56.4)		0.129	19 (48.7)	22 (56.4)		0.155
PVTT/HVTT, n (%)			0.383				0.262	
Absent	9 (18.0)	10 (25.6)		0.175	6 (15.4)	10 (25.6)		0.135
Present	41 (82.0)	29 (74.4)		−0.175	33 (84.6)	29 (74.4)		−0.135
Metastasis, n (%)			0.333				0.492	
Absent	32 (64.0)	21 (53.8)		−0.204	24 (61.5)	21 (53.8)		−0.154
Present	18 (36.0)	18 (46.2)		0.204	15 (38.5)	18 (46.2)		0.154

Gross tumor volume (cc), M (Q_1, Q_3)	751.1 (286.9, 999.7)	604.0 (190.5, 891.6)	0.435	−0.045	709.8 (204.1, 1175.5)	604.0 (190.5, 891.5)	0.542	−0.079
Normal liver volume (cc), M (Q_1, Q_3)	809.1 (659.7, 1073.3)	959.0 (788.7, 1113.1)	0.088	0.371	833.0 (664.1, 1058.2)	959.0 (788.7, 1113.1)	0.094	0.374
Dmean(cGy), Mean ± SD	1796.5 ± 482.8	1507.3 ± 462.9	**0.005**	−0.625	1713.8 ± 459.9	1507.3 ± 462.9	0.052	−0.146
BED10	72.77 ± 11.46	64.61 ± 12.48	0.020	−0.247	68.37 ± 11.88	64.61 ± 12.48	0.089	−0.125
EQD2[2](Gy), M (Q_1, Q_3)	72.0 (56.3, 75.0)	60.0 (56.3, 75.0)	0.237	−0.360	72.0 (56.3, 75.0)	60.0 (56.2, 75.0)	0.285	−0.163
V5(%), Mean ± SD	72.1 ± 16.4	68.1 ± 17.2	0.262	−0.235	70.2 ± 16.3	68.1 ± 17.2	0.581	−0.122
V7.5(%), M (Q_1, Q_3)	60.2 (46.4, 70.3)	49.5 (44.8, 68.3)	0.239	−0.269	57.1 (45.8, 67.3)	49.5 (44.8, 68.2)	0.516	−0.165
V10(%), M (Q_1, Q_3)	50.6 (37.8, 62.9)	45.5 (36.9, 56.8)	0.161	−0.353	48.8 (37.4, 60.1)	45.5 (36.9, 56.8)	0.396	−0.142
V15(%), M (Q_1, Q_3)	42.8 (28.1, 51.7)	31.7 (27.0, 39.1)	0.085	−0.337	36.7 (27.4, 48.9)	31.7 (27.0, 39.1)	0.280	−0.234
V20(%), M (Q_1, Q_3)	35.5 (23.3, 43.9)	26.3 (17.8, 33.5)	**0.048**	−0.297	29.9 (21.5, 42.8)	26.3 (17.8, 33.5)	0.154	−0.104
V25(%), M (Q_1, Q_3)	26.9 (21.0, 38.0)	23.2 (12.8, 28.9)	0.058	−0.240	24.8 (16.7, 37.1)	23.2 (12.8, 28.9)	0.153	−0.159
V30(%), M (Q_1, Q_3)	22.2 (17.3, 30.7)	19.5 (10.1, 23.9)	0.062	−0.195	21.9 (12.9, 30.1)	19.5 (10.1, 23.9)	0.147	−0.130
V35(%), M (Q_1, Q_3)	18.1 (12.5, 24.9)	15.5 (7.7, 19.3)	**0.037**	−0.200	18.1 (10.6, 22.3)	15.5 (7.7, 19.3)	0.108	−0.131
Prior therapy								
TACE, n (%)			**0.008**				0.050	
Absent	8 (16.0)	16 (41.0)		0.509	8 (20.5)	16 (41.0)		0.117
Present	42 (84.0)	23 (58.9)		−0.509	31 (79.5)	23 (58.9)		−0.117
Hepatectomy, n (%)			0.154				0.202	
Absent	40 (80.0)	26 (66.7)		−0.283	31 (79.5)	26 (66.7)		−0.172
Present	10 (20.0)	13 (33.3)		0.283	8 (20.5)	13 (33.3)		0.172
Ablation, n (%)			0.276				0.176	
Absent	46 (92.0)	32 (82.1)		−0.259	36 (92.3)	32 (82.1)		−0.167
Present	4 (8.0)	7 (17.9)		0.259	3 (7.7)	7 (17.9)		0.167
Therapy stage, n (%)			0.348				0.300	
Naive	39 (78.0)	27 (69.2)		−0.190	31 (79.5)	27 (69.2)		−0.122
Recurrent	11 (22.0)	12 (30.8)		0.190	8 (20.5)	12 (30.8)		0.122

Notes: Vx, the percentage of normal liver volume receiving>x Gy radiation (x=5, 7.5, 10, 15, 20, 25, 30, and 35, respectively). The bolded values indicates that pis less than 0.05, representing statistical significance.
Abbreviations: ALBI, albumin-bilirubin scores; Dmean, mean dose to the normal liver; BED10, biologically effective dose, α/β=10; ECOG PS, Eastern Cooperative Oncology Group-performance status; EQD2[2], equivalent dose in 2-Gy fractions;[2] using LQ model, α/β=2 Gy; HVTT, hepatic vein tumor thrombosis; PD-1, programmed cell death protein 1; PSM, propensity score matching; PVTT, portal vein tumor thrombosis; RT, radiotherapy; SMD, standardized mean difference; TACE, transcatheter chemoembolization; SD, standard deviation; M, Median; Q_1, 1st Quartile; Q_3, 3st Quartile.

https://doi.org/10.2147/ITT.S538796

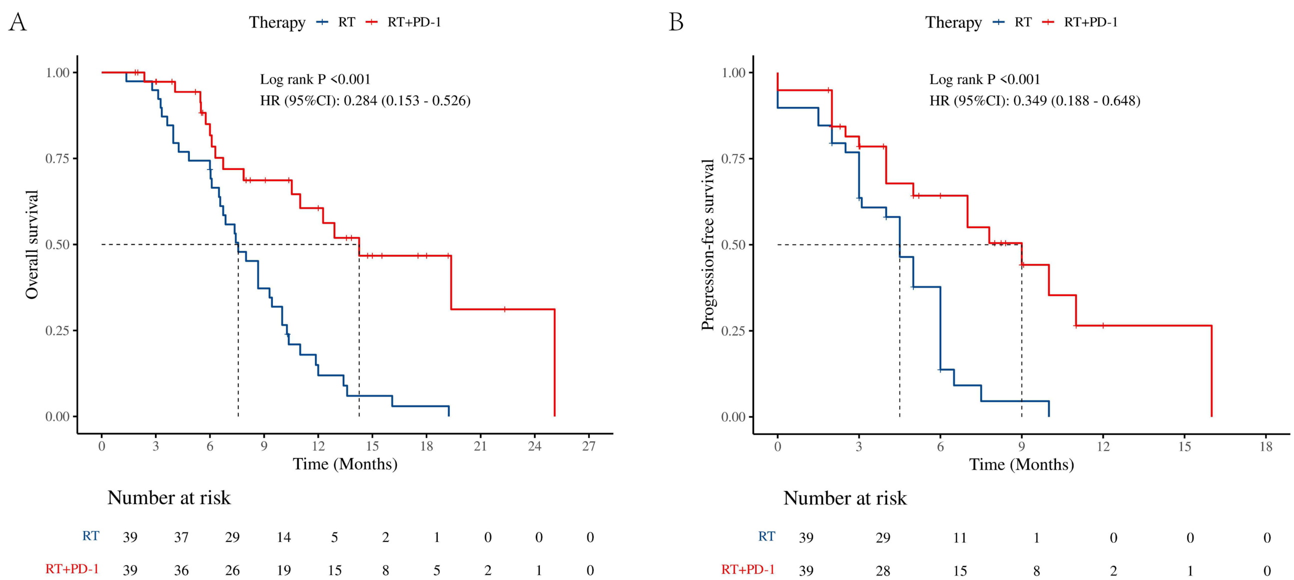

Figure 2 Kaplan–Meier curves for (**A**) overall survival and (**B**) progression-free survival.
Abbreviations: PD-1, programmed cell death protein 1; RT, radiotherapy; HR, hazard ratio; CI, confidence interval.

Pearson correlation analysis revealed multiple correlations (p > 0.8) among the radiotherapy dose-volume variables V5–V35 (Figure Supplemental 4). To eliminate multicollinearity of the variables, we selected V5 and V30 for COX regression analysis (Pearson correlation p = 0.45). Univariate and multivariate Cox analyses identified RT+PD-1 as an independent prognostic factor associated with improved OS and PFS (Table 2).

According to the mRECIST criteria, complete responses were observed in 4% (n = 2) and 10.3% (n = 4) of patients in the RT and RT+PD-1 groups, respectively. Partial response was observed in 26% (n = 13) and 33.3% (n = 13) of patients in the RT and RT+PD-1 groups, respectively. Progressive disease occurred in 10% (n = 5) and 5.1% (n = 2) of patients, respectively. After PSM, compared with the RT group, the RT+PD-1 group demonstrated a trend towards higher ORR (Table 3), although this difference was not statistically significant (43.6% vs 28.2%, p = 0.157). RT+PD-1 group showed similar rates of DCR (94.9% vs 89.7%, p = 0.671), CR (10.3% vs 5.1%, p = 0.671), PR (33.3% vs 23.1%, p = 0.314), SD (51.3% vs 61.5%, p = 0.361), and PD (5.1% vs 10.3%, p = 0.671) to RT group.

There were no statistical differences of those secondary outcomes between the two groups. This might be attributed to the limited sample size.

Evaluation and Incidence of RIHT

Among the 78 patients in the matched groups, the incidence of RILD was 30.8% (n = 24), including cRILD in 6.41% (n = 5) and ncRILD in 24.4% (n = 19). Between the two groups, there was no difference in the incidence of RILD, cRILD, or ncRILD (p = 1.000, p = 1.000, and p = 0.792, respectively). Within 3 months after RT finished, the increase of CP scores ≥ 1 and ≥ 2 were observed in 46.2% (n = 36) and 21.8% (n = 17) patients, respectively. AST increased to grade 3 and ALT increased to grade 3 were observed in 12.8% (n = 10) and 3.9% (n = 3) of patients, respectively. Moreover, ALP increased to grade 2, total bilirubin increased to grade 3, and albumin decreased to grade 2 were observed in 10.3% (n = 8), 11.5% (n = 9), and 56.4% (n = 44) patients, respectively. After PSM, there was no difference in the incidence of RIHT across the groups; nevertheless, the RT+PD1 group experienced increased total bilirubin (≥grade 1) more frequently (p = 0.021) (Table 4).

Discussion

Most existing studies have focused on CP-A HCC patients treated with RT and immunotherapy.[17,19,21] Given that only a little studies have investigated the therapy results of combined RT and PD-1 inhibitors in CP-B HCC patients. This study explored the efficacy and RIHT of combined RT and PD-1 inhibitors compared to RT for CP-B advanced HCC.

Table 2 Univariate and Multivariate Analysis of Overall Survival and Progression-Free Survival After PSM

For Matched Groups (n=78)	**Overall Survival**				**Progression-Free Survival**			
	Univariable Analysis		**Multivariable Analysis**		**Univariable Analysis**		**Multivariable Analysis**	
	HR (95% CI)	**p**	**HR (95% CI)**	**p**	**HR (95% CI)**	**p**	**HR (95% CI)**	**p**
Age	0.98 (0.95~ 1.01)	0.211			0.97 (0.94~ 1.00)	0.058		
Sex,male vs female	0.26 (0.08~ 0.86)	**0.028**	0.38 (0.11 ~ 1.28)	0.120	0.51 (0.12~ 2.16)	0.368		
Hepatitis B virus infection, positive vs negative	0.85 (0.38~ 1.91)	0.710			0.57 (0.26~ 1.25)	0.163		
Cirrhosis, present vs absent	1.07 (0.59~ 1.94)	0.817			1.11 (0.59~ 2.05)	0.740		
ECOG PS,1 vs 0	1.07 (0.59 ~ 1.94)	0.817			1.26 (0.72~ 2.21)	0.402		
Aspartate aminotransferas(U/L)	1.00 (0.99 ~ 1.01)	0.238			1.00 (0.99~ 1.01)	0.630		
Alanine aminotransferase(U/L)	1.00 (0.99 ~ 1.01)	0.153			1.00 (0.99~ 1.01)	0.108		
Alkaline phosphatase(U/L)	1.00 (0.99 ~ 1.00)	0.746			1.00 (0.99~ 1.00)	0.898		
Prothrombin time (sec)	1.02 (0.88 ~ 1.18)	0.747			1.02 (0.87~ 1.21)	0.734		
Platelet counts(10^9/L)	1.00 (0.99 ~ 1.00)	0.248			1.00 (0.99~ 1.00)	0.450		
Child-Pugh score,8/9 vs 7	1.51 (0.75 ~ 3.03)	0.246			1.74 (0.83~ 3.65)	0.140		
ALBI score	1.17 (0.56 ~ 2.46)	0.664			0.96 (0.44~ 2.12)	0.937		
Alpha fetoprotein(ng/mL), ≥400 vs <400	1.48 (0.85 ~ 2.57)	0.165			1.11 (0.64~ 1.92)	0.706		
Max tumor size(cm), >10 vs ≤10	1.40 (0.81 ~ 2.41)	0.219			1.10 (0.63~ 1.91)	0.735		
Tumor number,≥4 vs <4	1.28 (0.74 ~ 2.21)	0.367			1.14 (0.65~ 1.98)	0.638		
PVTT/HVTT, present vs absent	1.64 (0.80 ~ 3.36)	0.176			1.79 (0.84~ 3.82)	0.130		
Metastasis, present vs absent	1.52 (0.88 ~ 2.63)	0.133			1.15 (0.66 ~ 2.03)	0.608		
Gross tumor volume(cc)	1.00 (1.00 ~ 1.00)	0.587			1.00 (1.00~ 1.00)	0.554		
Normal liver volume(cc)	1.00 (0.99 ~ 1.00)	0.379			1.00 (0.99~ 1.00)	0.506		
Dmean(cGy)	1.00 (1.00 ~ 1.00)	**0.015**	1.00 (1.00 ~ 1.00)	0.783	1.00 (1.00~ 1.00)	**0.031**	1.00 (1.00~1.00)	0.220
EQD2[2](Gy)	1.00 (0.98 ~ 1.01)	0.956			0.99 (0.98~ 1.01)	0.941		
V5(%)	1.00 (0.99 ~ 1.02)	0.435			1.00 (0.98~ 1.02)	0.531		
V30(%)	1.01 (1.00 ~ 1.03)	**0.035**	1.02 (0.99 ~ 1.05)	0.142	1.01 (0.99~ 1.03)	0.068		
Prior therapy								
TACE, present vs absent	1.54 (0.81 ~ 2.94)	0.185			1.13 (0.61~ 2.10)	0.684		
Hepatectomy, present vs absent	0.64 (0.33 ~ 1.22)	0.178			0.68 (0.35~ 1.35)	0.278		
Ablation, present vs absent	0.51 (0.20 ~ 1.30)	0.161			0.50 (0.20~ 1.28)	0.154		
Therapy stage, recurrent vs naive	0.54 (0.28~ 1.04)	0.069			0.50 (0.25~ 0.99)	**0.047**	0.55 (0.27~ 1.08)	0.084
RT+PD-1 vs RT	0.28 (0.15 ~ 0.52)	**<0.001**	0.29 (0.14 ~ 0.57)	**<0.001**	0.34 (0.18~ 0.64)	**<0.001**	0.38 (0.20 ~ 0.73)	**0.004**

Notes: Vx, the percentage of normal liver volume receiving>x Gy radiation (x=5, 7.5, 10, 15, 20, 25, 30, and 35, respectively). The bolded values indicates that p is less than 0.05, representing statistical significance.
Abbreviations: ALBI, albumin-bilirubin scores; Dmean, mean dose to the normal liver; ECOG PS, Eastern Cooperative Oncology Group-performance status; EQD2[2], equivalent dose in 2-Gy fractions,[2] using LQ model, α/β=2Gy; HVTT, hepatic vein tumor thrombosis; PD-1, programmed cell death protein 1; PSM, propensity score matching; PVTT, portal vein tumor thrombosis; RT, radiotherapy; TACE, transcatheter chemoembolization; HR, Hazard Ratio; CI, Confidence Interval.

Table 3 Therapeutic Efficacy

Therapeutic Response Assessment	Before PSM			After PSM		
	RT (n = 50)	RT+PD-1 (n = 39)	P Value	RT (n = 39)	RT+PD-1 (n = 39)	P Value
ORR, no.(%;95% CI)	15 (30.0;16.8–43.2)	17 (43.59;27.3–59.9)	0.185	11 (28.2;13.4–43.0)	17 (43.6;27.3–59.9)	0.157
DCR, no.(%;95% CI)	45 (90.0;81.4–98.6)	37 (94.9;87.6–100.0)	0.652	35 (89.7;79.8–99.7)	37 (94.9;87.6–100.0)	0.671
Best overall response						
CR, no. (%)	2 (4.0)	4 (10.3)	0.458	2 (5.1)	4 (10.3)	0.671
PR, no. (%)	13 (26.0)	13 (33.3)	0.450	9 (23.1)	13 (33.3)	0.314
SD, no. (%)	30 (60.0)	20 (51.3)	0.411	24 (61.5)	20 (51.3)	0.361
PD, no. (%)	5 (10.0)	2 (5.1)	0.652	4 (10.3)	2 (5.1)	0.671

Abbreviations: CR, complete response; DCR, disease control rate; ORR, objective response rate; PD, progressive disease; PD-1, programmed cell death protein 1; PR, partial response; PSM, propensity score matching; RT, radiotherapy; SD, stable disease.

Table 4 Evaluation and Incidence of RIHT After PSM

Hepatotoxicity Metrics	RT (n = 39)	RT+PD-1 (n = 39)	P Value
CTCAE 5.0 laboratory toxicities			
Increased AST, ≥grade1	24 (61.5)	27 (69.2)	0.475
Increased AST, ≥grade2	8 (20.5)	6 (15.4)	0.555
Increased AST, grade3	6 (15.4)	4 (10.3)	0.498
Increased ALT, ≥grade1	17 (43.6)	17 (43.6)	1.000
Increased ALT, ≥grade2	2 (5.1)	4 (10.3)	0.671
Increased ALT, grade3	1 (2.6)	2 (5.1)	1.000
Increased ALP, ≥grade1	19 (48.7)	19 (48.7)	1.000
Increased ALP, grade 2	3 (7.7)	5 (12.8)	0.709
Increased total bilirubin, ≥grade1	18 (46.2)	28 (71.8)	**0.021**
Increased total bilirubin, ≥grade 2	16 (41.0)	12 (30.8)	0.345
Increased total bilirubin, grade3	5 (12.8)	4 (10.3)	1.000
Decreased albumin, ≥grade1	33 (84.6)	35 (89.7)	0.498
Decreased albumin, grade 2	25 (64.1)	19 (48.7)	0.171
Liver function metrics			
Increased Child-Pugh score, ≥1	17 (43.6)	19 (48.7)	0.650
Increased Child-Pugh score, ≥2	7 (17.9)	10 (25.6)	0.411
Radiation-induced liver disease	12 (30.8)	12 (30.8)	1.000
Classic radiation-induced liver disease	2 (5.2)	3 (7.7)	1.000
Non-classic radiation-induced liver disease	10 (25.6)	9 (23.1)	0.792

Notes: The bolded values indicates that p is less than 0.05, representing statistical significance.
Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTCAE 5.0, the Common Terminology Criteria for Adverse Events v5.0; PD-1, programmed cell death protein 1; PSM, propensity score matching; RT, radiotherapy; RIHT, radiation-induced hepatic toxicity; RT, radiotherapy.

Our findings highlighted combined RT and PD-1 inhibitors therapy can improve survival outcomes in CP-B advanced HCC patients. Furthermore, when compared to RT alone, this combination did not raise the incidence of RIHT.

Compared with RT alone treatment, combined RT and PD-1 inhibitors resulted in significantly longer OS and PFS in patients with CP-B advanced HCC who had not previously received treatment or had a recurrence. The mOS in HCC patients was 9.9 months for CP-B7 liver function and 2.8 months for CP-B ≥ 8 liver function after stereotactic body radiotherapy (SBRT).[7] In another study, patients with advanced HCC were divided into CP-A, CP-B, and CP-C groups. Among CP-B HCC patients, those who underwent accelerated hypofractionated RT or SBRT experienced a median survival of 11.8 months with a local control rate of > 90% and manageable radiological hepatotoxicity.[25] Additionally, according to a Korean study, CP-B HCC patients treated with fractionated conformal RT had a mOS of 9.4 months. The percentages of 6-month OS, LPFS rates were 70.8% and 39.8%, the 1-year OS, LPFS rates were 78.0% and 58.9%, respectively.[10] These findings emphasize that RT is effective for treating patients with CP-B advanced HCC. Our findings indicated that mOS was uniformly longer in RT+PD-1 regimen than in RT regimen (14.27 vs 7.57 months, $p < 0.001$) and a significantly higher 12-month OS (28.5% vs 12.8%, $p = 0.01$). The mPFS and outPFS in the RT+PD-1 group were 9 and 11 months, respectively, with a higher rate of 9-month LPFS (33.3% vs 5.1%, $p = 0.002$) than that observed in the RT group. The patients in our study had BCLC-C stage with large tumors (44% tumor size >10 cm), and most patients had portal or hepatic vein thrombosis (82%), and impaired liver function, indicating a poor prognosis. The mOS and mPFS rates were relatively poor in the RT group.

The remarkable efficiency and manageable toxicity of PD-1 in CP-B HCC have been previously documented.[15,26,27] A recent meta-analysis on ICIs for CP-B advanced HCC, including the 699 patients, reported an ORR of 14% and a DCR of 46% after receiving ICIs, with a median PFS of 2.68 months and an OS of 5.49 months.[16] Their findings indicate the efficacy of ICIs with manageable side effects, even in patients with advanced HCC and impaired liver function. RT has the ability to converted the tumor microenvironment, characterized by low immunogenicity or inadequate infiltration of immune cell, to one featuring a robust immunological response. RT combined with ICIs can disrupt immune escape and produce a more potent antitumor effect.[28–30] Sequential RT after progression during anti-PD1 therapy in advanced HCC resulted in an mPFS of 7.4 months and an mOS of 18.8 months. The DCR and ORR rates were 72.2% and 38.9%, respectively.[31] Our study showed that the RT+PD-1 group had a better median outPFS than that of the RT group (11 vs 5 months, $p < 0.001$). This could offer more information on the mechanism underlying the synergistic or systemic treatment enhanced by RT ("STAR") effects when ICIs and RT are combined.[30,32] Among the clinical, liver functional, and dosimetric characteristics, combined RT and PD-1 inhibitors therapy regimen is an independent prognostic factor for better OS and PFS. It was particularly noted that compared with RT alone, combined RT and PD-1 inhibitors therapy was related to a higher ORR (43.6% vs 28.2%). But there were no statistical differences of ORR, DCR, PR, CR, and SD between the two groups. This might be attributed to the limited sample size. Further multicenter studies and prospective cohorts with larger sample sizes will be conducted to verify the effectiveness of RT plus PD-1 inhibitors to HCC patients with CP-B.

Our previous research findings have elucidated that the treatment regimen of RT plus PD-1 inhibitors has encouraging effectiveness and a favorable safety profile when employed as an innovative treatment approach in patients with advanced HCC, offering prospective therapeutic options for these patients.[17–19] The ORR of SBRT with camrelizumab for advanced HCC was 52.4%, and the mPFS and OS were 5.8 and 14.2 months, respectively.[17] Du et al reported that RT plus PD-1 inhibitors improved mOS and mPFS in patients with advanced HCC, the mOS in the RT plus PD-1 inhibitors cohort was 20.9 months in compared to 11.2 months in the PD-1 cohort, the mPFS was 5.7 months in compared to 2.9 months.[21] Chiang et al reported that SBRT combined with ICIs demonstrate impressive tumor control in patients with large tumors of advanced HCC, the mPFS was 14.9 months, 1-year local control and OS rate were both 100%.[33] The OS and PFS in our study were comparable with those of previous studies, highlighting the efficacy of RT plus PD-1 inhibitors in improving survival outcomes in CP-B HCC patients. Recently, a Ib prospective study about TACE combined with pembrolizumab for HCC showed that the mPFS was 8.95 months, and the mOS was as long as 33.5 months.[34] However, all the included patients were BCLC-A and BCLC-B, and CP-A class. Another Phase II prospective study demonstrated that the combination of TACE and sintilimab to patients with intermediate-stage HCC achieved an ORR of 30% and a DCR of 95%.[35] These results confirmed the efficacy of local treatment combined with PD-1 inhibitors immunotherapy in the multidisciplinary approaches of HCC.

HCC patients with CP-B are at high risk for RIHT. A study utilizing 45 Gy in 18 fractions or 50 Gy in five fractions of SBRT or AHRT, 28% CP-A or CP-B7 liver function, and 35% CP-B8 or CP-B9 liver function had a 2-point worsening of the CP score.[25] A three-dimensional conformal radiation therapy (3DCRT) study found that 22% (2 of 11) CP-B patients developed grade 4 liver function damage after receiving 66 Gy of radiation therapy delivered in 33 sections.[36] In a hypofractionated 3DCRT trial, 60% (12 of 20) CP-B patients had experienced classic or non-classic RILD using a fraction of 4–8 Gy with total dose 40–60 Gy, whereas only seven of 108 patients (6%) with CP-A experienced this condition.[37] Our earlier research compared the hepatic toxicity of RT plus PD-1 inhibitors and RT in HCC, regardless of the CP grade, not a single patient experienced cRILD. In the RT plus PD-1 inhibitors group, the rates of ncRILD was 23.3%, and the rates of CP score ≥ 1 or ≥ 2 were 38.3%, 18.3%, respectively. There were no noticeable variations in the hepatotoxicity markers among the two groups.[19] This study shows, cRILD was reported in 6.4% of patients, and the incidence of ncRILD (24.4%), CP score ≥ 1 (46.2%), or ≥ 2 (21.8%), and AST increased to grade 3 (12.8%) of RT plus PD-1 inhibitors were slightly higher than our earlier research. Hepatic toxicity was acceptable and similar between the

RT plus PD-1 inhibitors and RT groups in CP-B advanced HCC patients. Moreover, RT plus PD-1 inhibitors therapy did not increase hepatic toxicity. These findings suggest that for CP-B advanced HCC patients, the treatment regimen of RT plus PD-1 inhibitors is the preferred treatment option over RT alone.

Our study had certain limitations. First, this was a single-center, retrospective study with a smaller sample size, with potential for selection bias with respect to the various PD-1 therapy regimens based on the patients' preferences, financial status, and health insurance coverage. Nevertheless, PSM was employed to counteract disparities between the two groups. Second, most patients were classified as CP-B7 (85.4%), with moderate liver impairment and preserved liver function than those who were classified as CP-B8 or CP-B9. Additionally, extending the follow-up period may facilitate a better assessment of the benefits of combination therapy on survival outcomes.

Conclusions

This study initially explored the clinical outcomes and hepatic toxicity of RT plus PD-1 inhibitors in patients with CP-B advanced HCC. Combined IMRT and PD-1 inhibitors improved clinical outcomes with a comparable incidence of RIHT to radiotherapy alone in advanced HCC patients with CP-B. The individual combined IMRT and PD-1 inhibitors for CP-B could be cautiously applied weighing the survival benefits and the RIHT risks. This study provides evidence that IMRT plus PD-1 inhibitors may be an appropriate treatment option for patients with CP-B advanced HCC.

Abbreviations

ALP, alkaline phosphatase; ALT, alanine aminotransferase; Anti-PD-1, antibodies against programmed cell death protein 1; AST, aspartate aminotransferase; CP, Child-Pugh; CP-B, Child-Pugh classification B; CP-C, Child-Pugh classification C; CI, confidence interval; CR, complete response; cRILD, classic RILD; CT, computed tomography; CTV, clinical target volume; Dmean, mean dose to the normal liver; ECOG PS, Eastern Cooperative Oncology Group-performance status DVH, dose-volume histogram; DCR, disease control rate; GTV, gross tumor volume; IMRT, intensity-modulated radiation therapy; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HR, hazard ratio; HVTT, hepatic vein tumor thrombus; LPFS, local progression-free survival; mOS, median overall survival; mPFS, median progression-free survival; ncRILD, non-classic RILD; OAR, organs at risk; ORR, objective response rate; outPFS, out-of-field progression-free survival; OS, overall survival; PD-1, monoclonal antibody against programmed cell death protein 1; PFS; progression-free survival; PSM, propensity score matching; RILD, radiation-induced liver disease; RIHT, radiation-induced hepatotoxicity; RT, radiotherapy; TACE, transcatheter chemoembolization; Vx, percentage of normal liver volume receiving >x Gy radiation; 3DCRT, three-dimensional conformal radiation therapy.

Data Sharing Statement

The data of this article will be made available by the corresponding author Shixiong Liang.

Ethics Approval and Consent to Participate

This study was approved by the ethical review committee of Guangxi Medical University Cancer Hospital (ethic no. KY2024878). The study were conducted in accordance with the local legislation and institutional requirements. Since the patients' data could not be recognized, the informed consent requirement was dropped. We will strictly keep patients' medical data confidential. The Declaration of Helsinki was followed in the execution of this study plan.

Acknowledgments

Thanks to all the patients who participated in this study from Guangxi Medical University Cancer Hospital.

Author Contributions

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.

Funding

This study was funded by the Development and Application Project for the Appropriate Technology of Health of Guangxi Province (No. S2024086). Promoting Project of Basic Capacity for Young and Middle-aged University Teachers in Guangxi (2022KY0079).

Disclosure

The authors report no conflicts of interest in this work.

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