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ORIGINAL RESEARCH

Lymphocyte-to-C Reactive Protein Ratio is an Independent Predictor of Survival Benefits for Hepatocellular Carcinoma Patients Receiving Radiotherapy

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Background: Stereotactic body radiotherapy (SBRT) has emerged as an alternative approach for patients with hepatocellular carcinoma (HCC), and we aim to find potential prognostic biomarkers for HCC patients who received SBRT.

Methods: In this study, we retrospectively analyzed HCC patients who underwent SBRT in our institution from January 2018 to December 2022. The inflammatory parameters, along with baseline patients' characteristics were collected to elucidate the potential relationship with survival benefits and liver toxicities.

Results: Overall, 35 patients were enrolled in our study. For the efficacy population (25 patients who underwent SBRT for primary liver lesions), the objective response rate (ORR) and disease control rate (DCR) were 60% and 100%, respectively. The median progression-free survival (PFS) was 9.9 months [95% confidence interval (CI) 5.6–14.1 months], and the median overall survival (OS) was 18.5 months (95% CI 14.2–22.8 months). We further confirmed that higher baseline lymphocyte-C-reactive protein ratio (LCR) (≥2361.11) was positively related to both longer PFS (12.0 vs 4.3 months, $P = 0.002$) and OS (21.9 vs 11.4 months, $P = 0.022$). Moreover, patients with diabetes and higher alpha-fetoprotein (AFP) (≥400 ng/mL) were also found to be associated with worse OS. The most common hepatotoxicity was elevated gamma-glutamyl transferase (GGT) (84.0%).

Conclusion: In conclusion, for patients with inoperable HCC, SBRT resulted in satisfactory local control, survival benefits, and acceptable liver toxicity. Pre-radiotherapy LCR might be an independent and readily available predictor for survival, which facilitates us to find the most appropriate treatment options.

Keywords: hepatocellular carcinoma, stereotactic body radiotherapy, lymphocyte-C-reactive protein ratio, survival, liver toxicity

Introduction

Liver cancer represents the sixth most common malignancy and third lethal cancer-related mortality worldwide,[1] with an estimated 1.4 million new cases and 1.3 million deaths in 2040,[2] in which, hepatocellular carcinoma (HCC) is the most common form. Notably, the aetiology, diagnosis, treatment, and survival have changed during the past decade.[3] Surgical resection, liver transplantation, and local radiofrequency ablation (RFA) are the preferred treatment regimens for early-stage HCC patients. The following locoregional therapies, such as transarterial chemoembolization (TACE), hepatic artery infusion chemotherapy (HAIC), and external beam radiotherapy (EBRT) have become the mainstays for intermediate HCC cases. Additionally, systemic targeted therapy and immunotherapy have shown promising antitumor

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activity for those who were not candidate for surgery or locoregional interventions.[4] Dual immune-checkpoint inhibitors were also confirmed to be effective and well-tolerance.[5] More recently, camrelizumab (an anti-programmed cell death protein-1 [PD-1] antibody) plus rivoceranib (an anti-angiogenic tyrosine-kinase inhibitor) showed encouraging survival benefits for unresectable HCC.[6]

Currently, EBRT, especially for stereotactic body radiotherapy (SBRT), has emerged as an alternative approach to intermediate and advanced HCC, with the advantage of higher precision of radiation delivery, and less toxicity to the surrounding normal tissues,[7] even for those who diagnosed with Barcelona clinical liver cancer (BCLC) stage-C, palliative SBRT is an effective and safe treatment modality.[8] Previous studies have demonstrated the high efficacy and well-tolerance of SBRT alone for the treatment of primary liver cancer, as well as extrahepatic metastases.[9,10] In addition, the Phase 3 clinical trial of NRG/RTOG 1112 reported that SBRT followed by sorafenib prolonged the survival benefits for HCC patients.[11] More recently, Chen et al found that SBRT plus sintilimab (the PD-1 inhibitor) achieved outstanding progression-free survival (PFS) and objective response rate (ORR) for patients with recurrent or oligometastatic HCC.[12] However, there are no convenient and effective biomarkers to predict the efficacy and safety of HCC patients receiving radiotherapy until now.

Cancer-related inflammation is now regarded as a hallmark of cancer and is known to promote the occurrence, development, and progression of cancers. Radiotherapy has been shown to transform immunologically "cold" tumors into "hot" by stimulating the release of inflammatory mediators, increasing immune cell infiltration, and promoting immunogenicity.[13] Currently, various inflammatory indicators are found to be associated with the inflammation status, and the efficacy and safety of anti-cancer treatment.[14,15] To our knowledge, there is currently a lack of studies on the potential prognostic indicators for HCC patients who underwent SBRT. Therefore, we conducted this retrospective study to confirm the efficacy and safety of SBRT in patients with moderate and advanced-stage HCC, and further evaluated the relationship between the peripheral blood indicators and treatment outcomes.

Patients and Methods

Patients

This was a retrospective study of HCC patients receiving radiotherapy from January 2018 to December 2022 at our institution. All procedures were conducted with the approval of the Ethics Committee of Nanjing Drum Tower Hospital and following the Declaration of Helsinki. Only patients who signed the consent and met the following criteria were included in this study: Age ≥ 18 years; pathologically or clinically diagnosed with HCC; Child-Pugh class A or B; BCLC stage of B-C; SBRT for primary liver lesions or metastatic bone lesions; Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0–1; no prior radiotherapy to the liver; sufficient liver, renal, cardiac, hematologic, and coagulation function; had at least one measurable lesion; underwent imaging assessments both before and after the administration of radiotherapy. The exclusion criteria were as follows: multiple extrahepatic metastases; abnormal liver or renal function; discontinued therapy; serious comorbidity; without imaging examinations; lack of baseline clinico-pathological data; or cessation of follow-up.

Clinical Data

The following laboratory data, including neutrophil count, lymphocyte count, platelet count, monocyte count, serum C-reactive protein, and albumin levels were collected. The platelet-to-lymphocyte ratio (PLR, platelet count/lymphocyte count), neutrophil-to-lymphocyte ratio (NLR, neutrophil count/lymphocyte count), lymphocyte-to-C reactive protein ratio [LCR, lymphocyte count ($10^{\wedge}9$/L) × $10^{\wedge}4$ /CRP (mg/L)], lymphocyte-to-monocyte ratio (LMR, lymphocyte count/monocyte count), C-reactive protein-to-albumin ratio [CAR, CRP (mg/L)/albumin (g/L)], and systemic immune-inflammation index (SII, platelet count × neutrophil count/lymphocyte count) were then calculated according to former data. The related data on liver function were also retrieved before and after radiotherapy.

Radiotherapy

For patients without extrahepatic metastasis, the gross tumor volume (GTV) was regarded as the primary tumor lesion and the vascular tumor thrombus according to each phase of computed tomography (CT) and/or magnetic resonance imaging (MRI), the clinical target volume (CTV) was set by the expansion of 3–5 mm margin around the intrahepatic GTV, considering the subclinical disease extension, the planning target volume (PTV) was created by the CTV + 5 mm, depending on the setup error, respiration control, and organ motion. Additionally, we created the planning gross tumor volume (PGTV) as the GTV with a 3 mm uniform expansion to deliver higher radiation doses to tumor lesions. The target doses to PTV were 24–30 Gy/8-10 fractions, and the doses to PGTV were increased to 40–50 Gy/8-10 fractions. The surrounding normal organs and uninvolved liver dose constraints were determined according to the ASTRO guideline.[7] Patients with bone metastases were treated based on previous reports.[16,17]

Evaluation and Follow-Up

Tumor response was evaluated with enhanced CT and/or MRI before and one month after radiotherapy, and then followed every three months according to the response evaluation criteria in solid tumors (RECIST) version 1.1, including complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). Survival benefits were assessed by PFS and overall survival (OS). Liver toxicities were evaluated by the Common Terminology Criteria of Adverse Events (CTCAE) version 5.0.

Statistical Analysis

All statistical analyses were performed with SPSS software version 22.0 and the R programs. The optimal cutoff values for PLR, NLR, LCR, LMR, CAR, and SII were determined using R software and the receiver operating characteristic (ROC) curve. The Wilcoxon signed-rank test was used to compare the changes in inflammatory parameters before and after radiotherapy. The relationships between peripheral blood markers and tumor response were assessed by the chi-square test and Fisher's exact test. PFS and OS were estimated using the Kaplan–Meier method. Univariate and multivariate Cox regression analyses were performed to find the independent factors for survival and adverse events, the results were presented as hazard ratio (HR) and 95% confidence interval (CI). $P < 0.05$ was considered significant.

Results

Patient Characteristics

The flow diagram of this study is shown in Figure 1. From January 2018 to December 2022, 588 patients with primary liver cancer underwent treatment at our institution, of which, 416 patients were diagnosed with HCC. Among HCC patients, 90 received radiotherapy, and 25 patients who underwent SBRT for primary liver lesions were included in the efficacy population. Table 1 shows the baseline characteristics of the study population. The median duration of follow-up was 16.0 months (range 4.6–66.9 months). Of the 35 patients, 25 received radiotherapy for intrahepatic lesions, and another 10 received palliative radiotherapy for bone. The median age of our study population was 58 years (range 33–77 years). Twenty-nine patients (82.9%) were male. Twenty-one patients had an ECOG PS of 0. Most patients were diagnosed with chronic hepatitis B virus infection (91.4%) and cirrhosis (60.0%). Six and twelve patients had diabetes and hypertension, respectively. Portal vein thrombosis (PVT) was found in 11 patients. Alpha-fetoprotein (AFP) ≥ 400 ng/mL was observed in 16 patients (45.7%). About 60.0% of patients had a larger tumor size (≥5.0 cm) when they underwent SBRT for primary liver lesions. In this study, 10 patients were categorized as BCLC stage B, while 25 patients were categorized as BCLC stage C. Among the efficacy population who received SBRT for primary liver lesions, 15 out of 25 patients (60.0%) had advanced-stage disease (BCLC class C).

Changes in Inflammatory Markers

Changes in PLR, NLR, LMR, LCR, CAR, and SII between pre- and post-radiotherapy are shown in Supplementary Figure 1. PLR was significantly increased ($P < 0.0001$) in patients who underwent radiotherapy for primary liver lesions, and similar results were also observed in NLR and SII. Furthermore, LCR and LMR were significantly reduced compared to pre-radiotherapy (LCR:

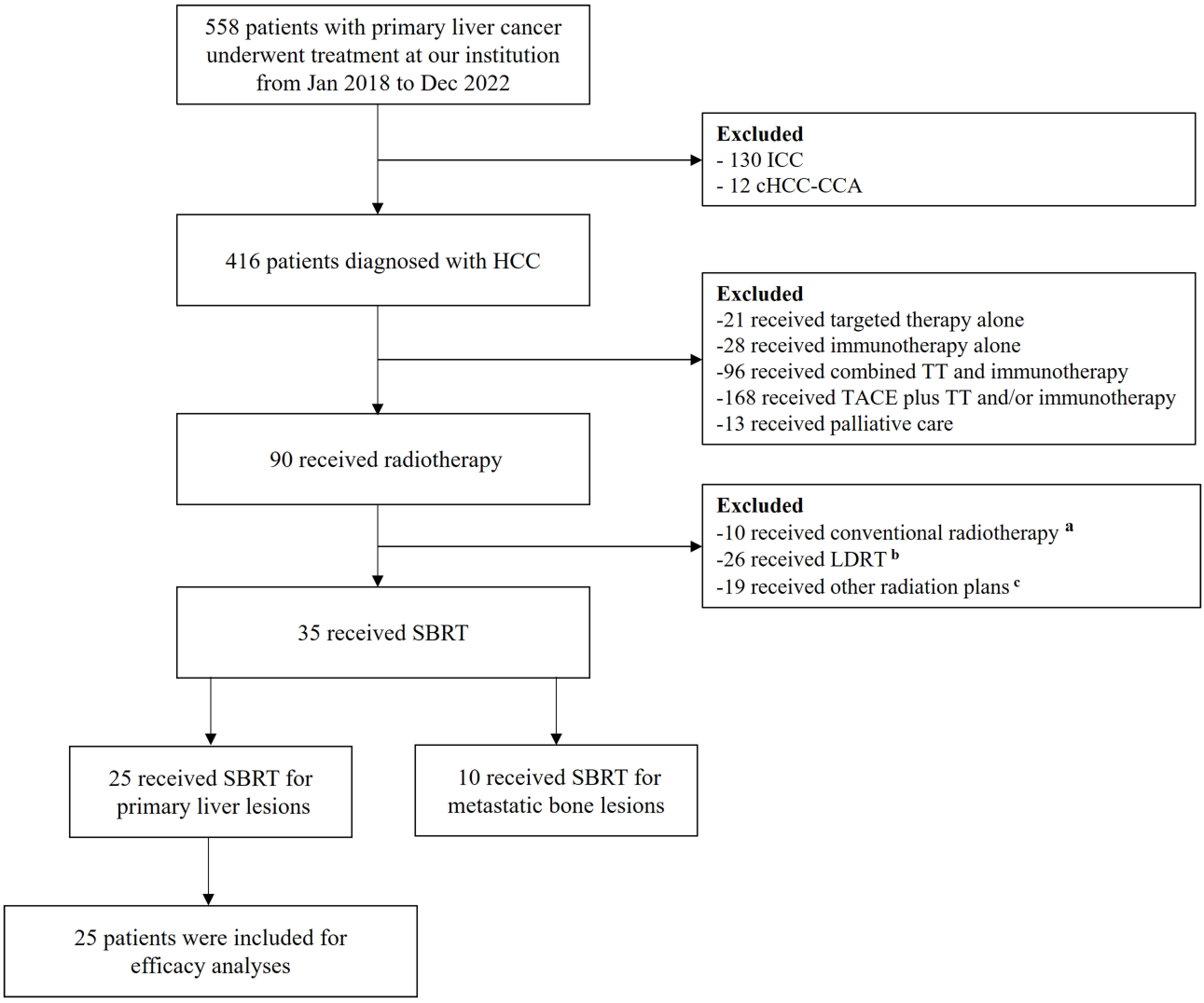

Figure 1 Flowchart of the recruitment process. [a]PTV 50 Gy in 25 fractions, five consecutive days per week; [b]PTV 15–24 Gy in 3 fractions, three consecutive days; [c]PTV 18 Gy/6 fractions, or 45 Gy/3 fractions.

Abbreviations: ICC, intrahepatic cholangiocarcinoma; cHCC-CCA, combined hepatocellular-cholangiocarcinoma; HCC, hepatocellular carcinoma; TT, targeted therapy; TACE, transarterial chemoembolization; LDRT, low-dose radiotherapy; SBRT, stereotactic body radiation therapy; PTV, planning target volume; PGTV, planning gross tumor volume.

$P = 0.001$; LMR: $P < 0.0001$). In addition, we analyzed the parameter changes in HCC patients with bone metastases who received radiotherapy, and found that the previous inflammatory indices (PLR, NLR, LMR, LCR, and SII) had no significant difference after radiotherapy, only the CAR decreased significantly ($P = 0.043$) (Supplementary Figure 2). To better identify the valuable parameter, we calculated the optimal cut-off values of the biomarkers using ROC curves. As shown in Supplementary Figure 3, the cut-off values for PLR, NLR, LCR, LMR, CAR, and SII were set to 97.34, 1.95, 2361.11, 4.74, 0.10, and 348.87, respectively. The area under the curve (AUC) values for NLR and LCR were higher than other indicators (NLR: 0.750; LCR: 0.733).

Analysis of PFS by Inflammatory Markers

Of the 35 HCC patients included in our study, 10 patients were excluded because their targeted bone lesions were not measurable according to RECIST 1.1 criteria, and an additional 25 patients with measurable intrahepatic lesions were included in the efficacy population. As shown in Figure 2, the median PFS was 9.9 months (95% CI 5.6–14.1 months). By the univariate and multivariate analysis, we confirmed that patient suffering from higher LCR (≥2361.11) was an independent predictor for PFS (12.0 vs 4.3 months, HR = 0.229, 95% CI 0.088–0.595, $P = 0.002$) (Table 2 and Figure 2).

Table 1 Patient Baseline Characteristics

	Total (N=35, %)	RT for Primary Liver Lesions (N=25, %)	RT for Metastatic Bone Lesions (N=10, %)
Age (years)			
Median (range)	58 (33–77)	62 (34–77)	54 (33–77)
<65	23 (65.7)	14 (56.0)	9 (90.0)
≥65	12 (34.3)	11 (44.0)	1 (10.0)
Sex			
Male	29 (82.9)	21 (84.0)	8 (80.0)
Female	6 (17.1)	4 (16.0)	2 (20.0)
ECOG PS			
0	21 (60.0)	19 (76.0)	2 (20.0)
1	14 (40.0)	6 (24.0)	8 (80.0)
Cirrhosis			
Yes	21 (60.0)	16 (64.0)	5 (50.0)
No	14 (40.0)	9 (36.0)	5 (50.0)
Viral infection			
Hepatitis B	32 (91.4)	23 (92.0)	9 (90.0)
Hepatitis C	3 (8.6)	2 (8.0)	1 (10.0)
Hypertension			
Yes	12 (34.3)	9 (36.0)	3 (30.0)
No	23 (65.7)	16 (64.0)	7 (30.0)
Diabetes			
Yes	6 (17.1)	4 (16.0)	2 (20.0)
No	29 (82.9)	21 (84.0)	8 (80.0)
BCLC class			
B	10 (28.6)	10 (40.0)	0 (0)
C	25 (71.4)	15 (60.0)	10 (100.0)
PVT			
Yes	11 (31.4)	11 (44.0)	0 (0)
No	24 (68.6)	14 (56.0)	10 (100.0)
Tumor size (cm)			
<5.0	10 (28.6)	10 (40.0)	–
≥5.0	15 (42.9)	15 (60.0)	–
AFP (ng/mL)			
<400	19 (54.3)	14 (56.0)	5 (50.0)
≥400	16 (45.7)	11 (44.0)	5 (50.0)

Abbreviations: RT, radiotherapy; ECOG PS, Eastern Cooperative Oncology Group Performance Status; BCLC, Barcelona clinical liver cancer; PVT, portal vein thrombosis; AFP, alpha-fetoprotein.

Analysis of OS by Inflammatory Markers

In the efficacy population, the median OS was 18.5 months (95% CI 14.2–22.8 months), and 6 patients were alive at the last follow-up (Figure 3A). We then analyzed the association between inflammatory factors and overall survival benefit (Table 3). By univariate Cox regression analysis, we found that the following characteristics, including diabetes, AFP ≥ 400 ng/mL, LCR < 2361.11, LMR < 4.74, and without cirrhosis were negative prognostic predictors for OS. Furthermore, the multivariate analysis was performed, and the results suggested that patients with higher LCR (≥2361.11) achieved longer OS compared with the lower LCR group (21.9 vs 11.4 months, HR 0.310, 95% CI 0.114–0.844, $P = 0.022$). Two years after treatment, there were 1 (10.0%) and 6 (40.0%) patients were still alive in the lower and higher LCR group, respectively. Furthermore, elevated AFP (≥400 ng/mL) was significantly associated with worse OS (15.8 vs 28.3 months, HR 4.148, 95% CI 1.336–12.878, $P = 0.014$), and patients with diabetes also had a shorter survival time (10.5 vs 21.9 months, HR 4.258, 95% CI 1.273–14.245, $P = 0.019$) (Figure 3B–D).

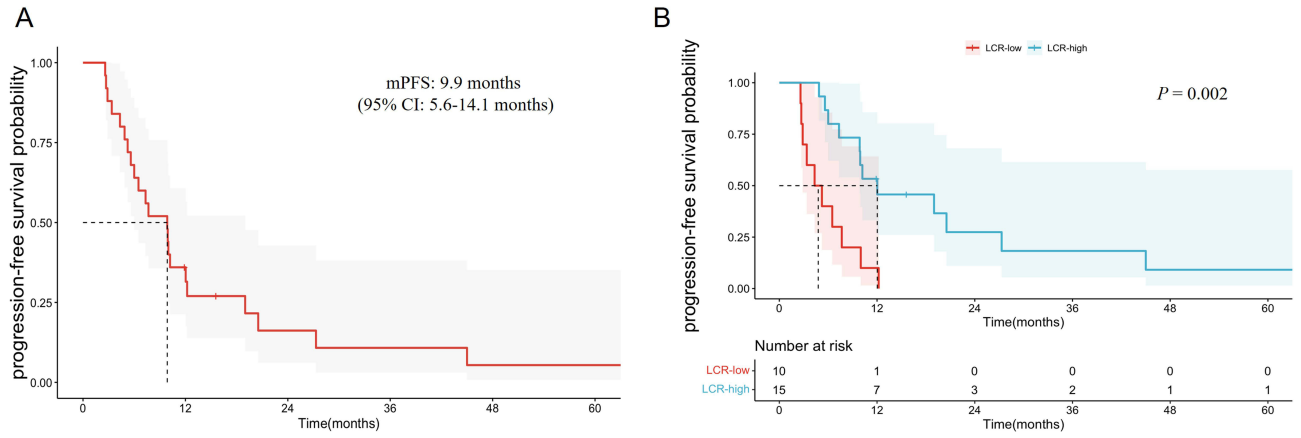

Figure 2 Kaplan–Meier curves for PFS (**A**), and stratified by LCR (**B**).
Abbreviations: PFS, progression-free survival; LCR, lymphocyte-to-C reactive protein ratio.

Tumor Response

As shown in Supplementary Table 1 and Supplementary Figure 4, 15 patients achieved the radiologic partial response, and 10 had stable disease on treatment with radiotherapy. The ORR and DCR were 60.0% and 100%, respectively. Patients with higher PLR, LCR, LMR, and lower CAR achieved better objective response rates compared to the control group (PLR: 69.2% vs 50.0%, $P = 0.428$; LCR: 66.7% vs 50.0%, $P = 0.442$; LMR: 66.7% vs 56.3%, $P = 0.691$; CAR: 66.7% vs 53.8%, $P = 0.688$), although no statistical significance was observed.

Table 2 Uni- and Multivariate Analyses for PFS

Characteristics		Univariate Analysis			Multivariate Analysis		
		HR	95% CI	P	HR	95% CI	P
Age, years	<65	1.0		0.851			NA
	≥65	1.084	0.465–2.527				
Sex	Male	1.0		0.761			NA
	Female	1.188	0.392–3.595				
ECOG PS	0	1.0		0.066			NA
	1	2.518	0.942–6.729				
Cirrhosis	No	1.0		**0.048**	1.0		0.124
	Yes	0.397	0.158–0.993		0.374	0.107–1.309	
Hypertension	No	1.0		0.208			NA
	Yes	0.545	0.212–1.402				
Diabetes	No	1.0		0.078			NA
	Yes	2.775	0.898–8.576				
BCLC class	B	1.0		0.366			NA
	C	1.527	0.610–3.820				
PVT	No	1.0		0.788			NA
	Yes	1.126	0.475–2.672				
Tumor size, cm	<5.0	1.0		0.396			NA
	≥5.0	1.483	0.597–3.686				
AFP	<400	1.0		**0.034**	1.0		0.297
	≥400	2.742	1.078–6.974		1.955	0.555–6.887	
PLR	<97.34	1.0		0.945			NA
	≥97.34	1.030	0.444–2.390				

(*Continued*)

Table 2 (Continued).

Characteristics		Univariate Analysis			Multivariate Analysis		
		HR	95% CI	*P*	HR	95% CI	*P*
NLR	<1.95	1.0		0.298			NA
	≥1.95	1.592	0.663–3.823				
LCR	<2361.11	1.0		**0.002**	1.0		**0.000**
	≥2361.11	0.229	0.088–0.595		0.154	0.054–0.439	
LMR	<4.74	1.0		0.504			NA
	≥4.74	0.388	0.148–1.016				
CAR	<0.10	1.0		0.061			NA
	≥0.10	2.311	0.962–5.552				
SII	<348.87	1.0		0.711			NA
	≥348.87	1.188	0.478–2.955				

Notes: *P* value in bold indicated a statistically significant difference in the univariate or multivariate Cox regression analyses ($P<0.05$).
Abbreviations: PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group Performance Status; BCLC, Barcelona clinical liver cancer; PVT, portal vein thrombosis; AFP, alpha-fetoprotein; PLR, platelet-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; LCR, lymphocyte-to-C reactive protein ratio; LMR, lymphocyte-to-monocyte ratio; CAR, C-reactive protein-to-albumin ratio; SII, systemic immune-inflammation index.

Liver Toxicity

Overall, there were no treatment-related deaths or radiation-induced liver disease (RILD) in the three months following radiation therapy. The most common hepatotoxicities were an increase in gamma-glutamyl transferase (GGT) (84.0%) and a decrease in albumin (44.0%). Nine patients (40.0%) showed an elevated alanine aminotransferase (ALT). In addition, the main severe toxicity (grade ≥ 3) was the higher GGT value (Supplementary Table 2). All hepatic toxicities were well tolerated and improved with symptomatic treatment. We further assessed the relationship between inflammatory biomarkers and liver toxicity, but there were no independent predictors for the adverse events (Supplementary Figure 5).

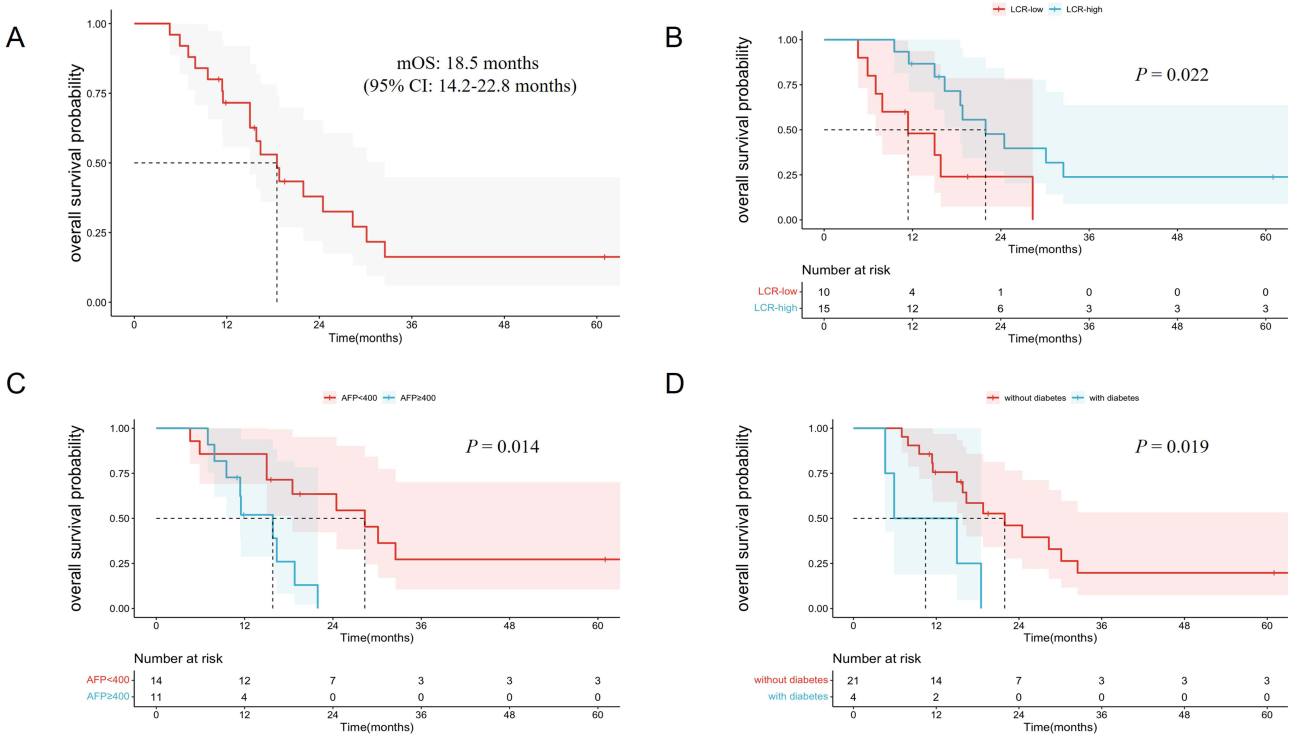

Figure 3 Kaplan–Meier curves for OS (**A**), and stratified by LCR (**B**), AFP (**C**), and diabetes (**D**).
Abbreviations: OS, overall survival; LCR, lymphocyte-to-C reactive protein ratio; AFP, alpha-fetoprotein.

Table 3 Uni- and Multivariate Analyses for OS

Characteristics		Univariate Analysis			Multivariate Analysis		
		HR	95% CI	*P*	HR	95% CI	*P*
Age, years	<65	1.0		0.655			NA
	≥65	0.806	0.314–2.071				
Sex	Male	1.0		0.235			NA
	Female	2.029	0.631–6.531				
ECOG PS	0	1.0		0.119			NA
	1	2.397	0.798–7.196				
Cirrhosis	No	1.0		**0.037**	1.0		0.363
	Yes	0.358	0.136–0.942		0.531	0.136–2.076	
Hypertension	No	1.0		0.473			NA
	Yes	0.684	0.243–1.929				
Diabetes	No	1.0		**0.019**	1.0		**0.000**
	Yes	4.258	1.273–14.245		1156.287	10.179–2399.684	
BCLC class	B	1.0		0.358			NA
	C	1.577	0.597–4.166				
PVT	No	1.0		0.897			NA
	Yes	1.061	0.430–2.621				
Tumor size, cm	<5.0	1.0		0.603			NA
	≥5.0	1.295	0.488–3.434				
AFP	<400	1.0		**0.014**	1.0		**0.001**
	≥400	4.148	1.336–12.878		42.078	4.184–423.210	
PLR	<97.34	1.0		0.664			NA
	≥97.34	1.223	0.493–3.038				
NLR	<1.95	1.0		0.344			NA
	≥1.95	1.563	0.620–3.940				
LCR	<2361.11	1.0		**0.022**	1.0		**0.013**
	≥2361.11	0.310	0.114–0.844		0.182	0.048–0.695	
LMR	<4.74	1.0		**0.041**	1.0		0.143
	≥4.74	0.330	0.114–0.958		0.382	0.105–1.385	
CAR	<0.10	1.0		0.069			NA
	≥0.10	2.414	0.935–6.234				
SII	<348.87	1.0		0.710			NA
	≥348.87	1.208	0.446–3.270				

Notes: *P* value in bold indicated a statistically significant difference in the univariate or multivariate Cox regression analyses ($P<0.05$).
Abbreviations: OS, overall survival; HR, hazard ratio; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group Performance Status; BCLC, Barcelona clinical liver cancer; PVT, portal vein thrombosis; AFP, alpha-fetoprotein; PLR, platelet-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; LCR, lymphocyte-to-C reactive protein ratio; LMR, lymphocyte-to-monocyte ratio; CAR, C-reactive protein-to-albumin ratio; SII, systemic immune-inflammation index.

Discussion

This study presents the promising tumor response, survival benefits, and tolerable toxicity of radiotherapy in patients with intermediate and advanced-stage HCC. Additionally, it identified LCR as a significant independent prognostic factor for HCC patients undergoing radiotherapy for the first time.

As one of the most lethal malignancies, HCC results in poor survival due to the lack of effective treatment regimens. Either surgery or radiofrequency is only available for early-stage liver cancer. TACE and HAIC are now effective locoregional therapies for patients with intermediate-stage HCC.[18] The RATIONALE-301 study demonstrated that single-agent tislelizumab had better and durable treatment responses compared to sorafenib as the initial treatment for HCC.[19] Combining immunotherapy with targeted therapy has also emerged as a promising approach.[20] As reported by the IMbrave150 clinical trial,[21] atezolizumab plus bevacizumab resulted in superior survival benefits compared to sorafenib for unresectable HCC patients (median OS: 19.2 vs 3.4 months, descriptive $P < 0.001$; median PFS: 6.9 vs

4.3 months, descriptive $P < 0.001$). Another phase 3 study, CARES-310, revealed that the combination of camrelizumab and rivoceranib significantly improved the median PFS (5.6 vs 3.7 months) and OS (22.1 vs 15.2 months) versus sorafenib alone,[6] these findings provided more novel and effective treatment modalities for HCC patients. However, local recurrences after curative treatment and distant metastasis to bone, lung, and lymph nodes are the main reasons for treatment failure.[4,22] SBRT is a safe and effective alternative treatment regimen compared to TACE for HCC patients with either 1–2 tumors[23] or medium-sized (3–8 cm) tumors.[24] A single-arm, Phase 2 study showed that sequential TACE and SBRT followed by an anti-programmed cell death ligand-1 (PD-L1) drug achieved promising outcomes for patients with locally advanced HCC. The ORR was 67%, and the DCR was 70%. Additionally, the rates of local control at 6, 12, and 24 months were 98%, 92%, and 92%, respectively.[25] SBRT was also confirmed to be associated with lower recurrence rates than RFA in unresectable Asian HCC patients (20.1% vs 27.9%, $P < 0.001$).[26] The STRSPH trial demonstrated acceptable toxicities and promising survival benefits of SBRT for previously untreated solitary HCC that is not amenable to curative treatment options.[27] Our previous study also showed a high local control rate of 100% and survival rate of 43% at 2 years with hypofractionated radiotherapy (PTV 50 Gy/10 fractions) using helical tomotherapy.[28] In the current study, 25 patients underwent radiotherapy with a PTV dose of 24–30 Gy/8-10 fractions and a PGTV dose of 40–50 Gy/8-10 fractions to the primary liver lesions, and all patients achieved disease control, and no severe liver toxicity occurred during treatment, even for patients with poorer baseline liver function of Child-Pugh class B, who were reported to have a higher risk of RILD,[29] further confirming the high efficacy and safety of SBRT with our radiation treatment plan.

The development of HCC is often related to chronic inflammation and subsequent liver cirrhosis caused by persistent hepatitis B virus (HBV) or hepatitis C virus (HCV) infection. Shalapour e reported that chronic inflammation induced the accumulation of immunoglobulin-A-producing (IgA^+) cells, that directly inhibited the activation of CD8+ T lymphocytes (CTLs), and further promoted the development of HCC.[30] Inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) and interleukin (IL)-6, as well as their downstream targets, have been shown to mediate the inflammation-associated HCC.[31] Accumulating evidence suggests that inflammation-based markers are closely associated with the treatment response and adverse events for different treatment regimens, including HCC.[32–34] In which, CRP is widely used to reflect the inflammatory status of cancers, peripheral lymphocytes play a vital role in host cell-mediated cytotoxic immunity against infection and tumors. The combination of CRP levels along with lymphocyte count, both LCR and CLR have also been reported to correlate with prognosis in several cancers, such as colorectal and gastric cancer.[35,36] In terms of HCC, high LCR was found to be a predictor for better overall survival, as well as recurrence-free survival after liver resection.[37] Recently, Lo et al found that pre-treatment NLR could be a valuable marker to predict the survival and hepatotoxicity in HCC patients treated with stereotactic ablative radiation therapy (SART).[34] However, no related study about the relationship between LCR and radiotherapy for HCC has been reported yet. In the current study, we first observed a significant decrease in LCR after radiotherapy compared with baseline (median: 3448.28 vs 1538.46, $P = 0.001$), and found that high LCR was associated with prolonged PFS (12.0 vs 4.3 months, $P = 0.002$) and OS (21.9 vs 11.4 months, $P = 0.022$), the Cox regression analyses further demonstrated its role as an independent prognostic predictor for HCC patients receiving radiotherapy.

Diabetes is a risk factor for the development of HCC, it has been validated to activate inflammatory cascades through the generation of pro-inflammatory cytokines and reactive oxygen species, leading to genomic instability, cell proliferation, and inhibition of cell apoptosis, thereby promoting hepatocarcinogenesis.[38] In our results, it is interesting to note that the history of diabetes was negatively related to the OS, whereas no significance was observed about the PFS. As one of the most common tumor markers, AFP-positive HCC (APHC) accounts for about 75%, of those who had less cytotoxic T cells and more suppressive tumor immune microenvironment (TIME).[39] In our study, over 40% of patients experienced elevated levels of AFP (≥400 ng/mL), they had worse PFS and OS compared to lower AFP group (mPFS: 5.6 vs 10.2 months, $P = 0.028$; mOS: 15.8 vs 28.3 months, $P = 0.014$), the multivariate Cox regression analysis further confirmed AFP was an independent prognostic factor for OS, which was consistent with previous findings.[40]

In terms of radiotherapy safety, the most common liver toxicity was the elevated GGT (84.0%), and only one patient had severe elevated GGT, there was no death or treatment interruption during radiotherapy, which might be partially associated with the residual normal liver volume was above 700 mL in our radiation plan. We further analyzed the

relationship between inflammatory indices and liver toxicity, and found no statistical significance, which reminds us to explore more potential markers to predict the adverse events.

This study has several limitations. Firstly, it was a single-center, retrospective study, which could lead to selection bias. Secondly, the sample size was small, and the conclusion needs to be further confirmed by larger cohorts. Thirdly, some confounding factors, such as medication usage, immune system status, and comorbidities, could potentially impact the results of the inflammatory index. In addition, the heterogeneity of treatment regimens prior to radiotherapy might be associated with the outcome.

In conclusion, our study confirmed the high efficacy and good tolerability of radiotherapy in patients with intermediate and advanced-stage HCC and, for the first time, demonstrated the association between LCR and survival benefit after SBRT. The predictive and prognostic potential of LCR should be further confirmed by prospective studies with larger sample sizes in the future.

Abbreviations

HCC, hepatocellular carcinoma; SBRT, stereotactic body radiotherapy; LCR, lymphocyte-to-C reactive protein ratio; PLR, platelet-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; CAR, C-reactive protein-to-albumin ratio; SII, systemic immune-inflammation index; PFS, progression-free survival; OS, overall survival.

Data Sharing Statement

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Statement

All procedures performed in this study involving human participants were in accordance with the guidelines of the Ethics Committee of Nanjing Drum Tower Hospital and with the 1964 Helsinki Declaration. Patients treated in our hospital will be informed of the potential research use of personal information. Only patients who agreed with and signed the consent were included in our study.

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Disclosure

All authors declare no conflicts of interest related to this manuscript.

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