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ORIGINAL RESEARCH

Radiotherapy with Targeted Therapy or Immune Checkpoint Inhibitors for Hepatocellular Carcinoma with Hepatic Vein and/or Inferior Vena Cava Tumor Thrombi

Zhuoran Li[1,*], Yirui Zhai[1,*], Fan Wu[2,*], Dayong Cao[2,*], Feng Ye[3,*], Yan Song[4], Shulian Wang[1], Yueping Liu[1], Yongwen Song[1], Yuan Tang[1], Hao Jing[1], Hui Fang[1], Shunan Qi[1], Ningning Lu[1], Ye-Xiong Li[1], Jianxiong Wu[2], Bo Chen[1]

[1]State Key Laboratory of Molecular Oncology, Department of Radiation Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences (CAMS) and Peking Union Medical College (PUMC), Beijing, People's Republic of China; [2]Department of Hepatobiliary Surgery, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences (CAMS) and Peking Union Medical College (PUMC), Beijing, People's Republic of China; [3]Department of Radiology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences (CAMS) and Peking Union Medical College (PUMC), Beijing, People's Republic of China; [4]Department of Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences (CAMS) and Peking Union Medical College (PUMC), Beijing, People's Republic of China

*These authors contributed equally to this work

Correspondence: Bo Chen, State Key Laboratory of Molecular Oncology, Department of Radiation Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences (CAMS) and Peking Union Medical College (PUMC), Beijing, People's Republic of China, Tel +86-10-87788280, Email chenboo@outlook.com; Jianxiong Wu, Department of Hepatobiliary Surgery, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences (CAMS) and Peking Union Medical College (PUMC), Beijing, People's Republic of China, Tel +86-10-87781700, Email Dr_wujx@163.com

Purpose: This study evaluated the clinical outcomes of patients with hepatocellular carcinoma (HCC) with hepatic vein tumor thrombus (HVTT) and/or inferior vena cava tumor thrombus (IVCTT) receiving radiotherapy (RT) combined with systemic therapies.

Patients and Methods: Patients with HCC with HVTT and/or IVCTT who received RT were identified at our institution. The prescription doses were 30–65 Gy for planning target volume and 40–65 Gy for the gross tumor volume. Targeted therapy and immune checkpoint inhibitors were used concurrently if patients were at a high risk of or already had distant metastasis. After RT completion, follow-up was performed at 1, 3, 6, and 12 months, and 3 to 6 months thereafter. The objective response rate (ORR), overall survival (OS), progression-free survival (PFS) and toxicity were recorded.

Results: Thirty-four patients were retrospectively enrolled between January 2016 and September 2021. Most patients received concurrent targeted therapy (70.6%) and/or post-RT (79.4%). The in-field ORR and disease control rates were 79.4% and 97.1%, respectively. The OS rates were 77.6% at 1 year and 36.3% at 2 years (median OS, 15.8 months). The median PFS and median in-field PFS were 4.2 months and not reached, respectively. The PFS and in-field PFS rates were 24.6% and 79.2% at 1 year, 19.7% and 72.0% at 2 years, respectively. An alpha-fetoprotein level >1000 ng/mL was a significant prognostic factor for worse OS (HR, 5.674; 95% CI, 1.588–20.276; p=0.008); in-field complete/partial response was a significant prognostic factor for better OS (HR, 0.116; 95% CI, 0.027–0.499; p=0.004). The most common site of first failure was the lungs (13/34 patients, 38.2%), followed by the liver (7/34 patients, 20.6%). No patients developed radiation-induced liver disease or pulmonary embolism during follow-up.

Conclusion: Combining RT and systemic therapy was safe and effective in treating patients with HCC with HVTT and IVCTT.

Keywords: liver cancer, immunotherapy, systemic therapy, radiation therapy

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Introduction

Liver cancer is the seventh most common malignancy and the second leading cause of cancer-related deaths worldwide.[1] It is also the third-leading cause of cancer-related mortality in China.[2] Hepatocellular carcinoma (HCC) accounts for approximately 80% of all liver cancers and frequently involves the vasculature.[1,3] Although hepatic vein and/or inferior vena cava tumor thrombi (IVCTT) only exist in approximately 6% of all HCC cases, it can cause Budd–Chiari syndrome, which significantly shortens patient survival.[4] According to a recent study, the median survival of patients with hepatic vein tumor thrombus (HVTT) is only 6.5 months.[5]

Currently, atezolizumab plus bevacizumab is the first-line treatment for patients with HCC.[6–8] However, when treating HCC patients with main trunk and/or contralateral portal vein invasion, atezolizumab plus bevacizumab did not show an overall survival (OS) or progression-free survival (PFS) benefit compared to sorafenib.[9] Hence, there is no convincing evidence of the effectiveness of systemic therapy for HVTT. In the East, more aggressive local treatments such as surgery and transcatheter arterial chemoembolization (TACE) are recommended for these patients.[10–14] Improvements in techniques such as intensity-modulated radiotherapy (IMRT) and volumetric-modulated arc therapy (VMAT) have increased the use of radiotherapy (RT) in treating tumor thrombi in HCC. A recent meta-analysis showed that external beam radiation therapy can be well-tolerated in HCC patients with HVTT/IVC involvement. The objective response rate (ORR) rate was 33.3–81.8% and the 1-year OS rate was 53.6%.[15] However, few studies have reported the effectiveness of RT with targeted therapy or immune checkpoint inhibitors (ICIs) in patients with HCC with HVTT or IVC tumor thrombi. Hence, the present study evaluated the treatment response and survival outcomes of patients with HCC with HVTT and/or IVC involvement receiving RT using modern RT techniques combined with other multimodality therapies.

Materials and Methods

Patients

The inclusion criteria for this retrospective study were as follows: pathologically diagnosed HCC or clinically diagnosed HCC based on the Chinese standardization for diagnosis and treatment of hepatocellular carcinoma (2022 edition),[16] HVTT and/or IVCTT confirmed via magnetic resonance imaging (MRI) or computed tomography (CT) before receiving RT, Eastern Cooperative Oncology Group performance status 0–2, and the RT field included at least the main primary lesions and tumor thrombus. Demographic and clinical data were extracted from medical records. The study protocol was approved and an exemption for written informed consent was granted by the Ethics Committee of our hospital since patient data extracted for data analysis were anonymized and maintained with confidentiality. This study was compliance with the Declaration of Helsinki. (Approval Number: 22/094-3295. Board Name: National GCP Center for Anticancer Drugs, The Independent Ethics Committee. Board Affiliation: National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College).

Between January 2016 and September 2021, 570 patients with HCC who received RT were referred to our hospital. Among them, 35 were diagnosed with HVTT or IVCTT. One patient with a history of RT for HCC was excluded, and the remaining 34 patients were eligible for the present study.

Radiotherapy

All the patients were treated with VMAT or IMRT. Examinations before RT included chest-abdominal CT, liver MRI, complete blood count, blood biochemistry, and alpha-fetoprotein (AFP) level determination. All patients were immobilized using customized devices in the supine position with both arms raised above the head. A 4-dimensional (4D) CT scan simulation with a 5-mm slice thickness was routinely performed. A simulated MRI with a 5-mm slice thickness was also performed. The CT and MRI images were transferred to a planning system and merged to determine the target volume. Gross tumor volume (GTV) was defined as the gross tumor volume, HVTT/IVCTT, and metastatic regional lymph nodes identified on MRI. Thrombi and primary tumors of the liver were included in the GTV. However, if there were multiple lesions in the liver and some were far from the gross primary tumor, these lesions were not included in the GTV. The clinical target volume (CTV) was defined as the GTV plus a 0.5-cm margin in all directions for intrahepatic tumors and 1.0-cm margins along the

major vessels for thrombi. The right atrium was included in the CTV if it was affected by a thrombus. The planning target volume (PTV) was contoured by expanding a 0.5-cm margin to the CTV in the anterior-posterior and left-right directions and a 1.0–1.5-cm margin in the cranial-caudal direction according to the 4D-CT. Before 2019, the prescribed dose for 95% of the PTV was planned to be 48–56 Gy in 22–28 fractions over 5–6 weeks. After 2019, a simultaneous integrated boost was administered to 95% of the GTV at 55–65 Gy, except in one patient; prescription doses of 40 Gy and 30 Gy in 10 fractions were administered to the GTV and PTV of this patient. The dose constraints for the organ at risk were as follows: whole liver, mean dose ≤24 Gy; stomach and duodenum, maximum dose ≤54 Gy, V50 ≤10 mL; colon, maximum dose ≤55 Gy, V52 ≤10 mL; spinal cord planning risk volume, maximum dose ≤40 Gy; left kidney, V20 ≤20%, right kidney, V20 <30%. The UK consensus on normal tissue dose constraints was followed.[17]

Systemic Treatment

After 2017, targeted therapies, including sorafenib, lenvatinib, and regorafenib, were used concurrently with RT if the patients could tolerate it. After 2021, ICIs, including camrelizumab and sintilimab, were considered to be used concurrently with targeted therapy and RT if patients had distant metastases before RT or if their tumors could not be entirely included in the RT field. Targeted therapy and ICIs were considered after RT if the patients already had distant metastases or were at a high risk of distant metastases.

Follow-Up and Outcomes

After RT was completed, chest-abdominal CT and liver MRI were performed at 1, 3, 6, and 12 months, and 3 to 6 months thereafter. The primary endpoint of this study was OS. The secondary endpoints were ORR, in-field ORR, PFS, in-field PFS, and toxicity. Treatment response was defined as the best response in 3 months after RT. ORR was defined as the percentage of patients who met the complete response (CR) or partial response (PR) criteria as defined by the modified Response Evaluation Criteria in Solid Tumors (mRECIST) and RECIST 1.1.[18,19] PFS was defined as the time from the end of RT until tumor progression or death from any cause. OS was defined as the time from the end of RT to death from any cause. Toxicity was assessed and graded according to the Common Terminology Criteria for Adverse Events 5.0 (CTCAE 5.0).

Statistical Analyses

Survival analysis was performed using the Kaplan–Meier method. Differences in survival were analyzed using Log rank tests. Univariate and multivariate analyses of the prognostic factors for PFS and OS were performed using the Cox proportional hazards model. $p<0.05$ was considered statistically significant. All statistical analyses were performed using SPSS Statistics (v25.0; IBM, Armonk, NY, USA) and R software (v4.0.4; R Foundation, Vienna, Austria).

Results

Patient Characteristics

The baseline characteristics of the 34 patients included in the present study are summarized in Table 1. Most patients (30/34, 88.2%) were male, with a median age of 53.5 years (range, 30–71 years). All but one patient had hepatitis B (94.1%) or hepatitis C (2.9%). Seven (20.6%) patients had lymph node metastases. Ten (29.4%) patients had distant metastases before RT, including six patients with lung metastases. According to the Japanese classification of HVTT,[4] 12 (35.3%) patients had thrombi in the right, middle, or left hepatic veins (Vv2), and 22 (64.7%) patients had thrombi involving the IVC (Vv3), among which six patients had thrombi involving the right atrium. Nearly all tumor thrombi in the right or middle hepatic vein arose from HCC in the right lobe. Only one left-lobe HCC case involved the middle hepatic vein. Portal vein involvement was observed in 17 patients (50.0%).

Table 1 Demographic and Clinical Characteristics of Patients at Baseline

Characteristic (N=34)	No. of Patients (%)
Age (years), median (range)	53.5 (30–71)
Age group (years)	
≤60	23 (67.6)
>60	11 (37.9)
Gender	
Male	30 (88.2)
Female	4 (11.8)
Child-Pugh class	
A	31 (91.2)
B	3 (8.8)
Hepatitis	
HBV	32 (94.1)
HCV	1 (2.9)
No hepatitis	1 (2.9)
AFP (ng/mL), median (range)	1565 (3.0–283,633.0)
AFP group (ng/mL)	
≤1000	16 (47.1)
>1000	18 (52.9)
No. of primary tumors	
1	20 (58.8)
≥2	14 (41.2)
Tumor size (cm), median (range)	7.2 (1.4–14.7)
Tumor size group (cm)	
≤10	26 (76.5)
>10	8 (23.5)
Tumor location	
Left lobe	7 (20.6)
Right lobe	17 (50.0)
Both lobe	10 (29.4)
Tumor thrombus location	
Left hepatic vein	6 (17.6)
Middle hepatic vein	6 (17.6)
Right hepatic vein	22 (64.7)
IVC thrombus type	
Vv2	12 (35.3)
Vv3	22 (64.7)
Portal vein thrombus	
Yes	17 (50.0)
No	17 (50.0)
LN metastasis	
Absent	27 (79.4)
Present	7 (20.6)
Distant metastasis	
Absent	24 (70.6)
Present	10 (29.4)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; HCV, hepatitis C virus; AFP, alpha-fetoprotein; IVC, inferior vena cava; LN, lymph node; Vv1, invasion of (or tumor thrombus in) peripheral branches of the hepatic vein; Vv2, invasion of (or tumor thrombus in) the right, middle, or left hepatic vein, the inferior right hepatic vein, or the short hepatic vein; Vv3, invasion of (or tumor thrombus in) the inferior vena cava.

Radiotherapy and Concurrent Targeted Therapy and/or ICIs

RT was the initial local treatment in 24 patients (70.6%) after the diagnosis of tumor thrombi. Eight (23.5%) and two (5.9%) patients underwent TACE and radiofrequency ablation (RFA) before radiotherapy, respectively (Table 2). Among them, five and one patients had tumor thrombus progression after TACE and RFA, respectively. Fourteen (41.2%) received systemic therapy, including targeted therapy and ICIs. Five patients had tumor thrombus progression before RT, while the efficacy in two patients was unknown owing to a lack of clinical data. After careful evaluation, 27 (79.4%) patients received VMAT, and 7 (20.6%) received IMRT. The median RT dose for the PTV was 48.0 Gy (range, 30.0–56.0 Gy). Twenty (58.8%) patients underwent simultaneous integrated boost for GTV, and the median RT dose was 59.8 Gy (range, 40.0–65.0 Gy). Among them, one patient received hypofractionated radiotherapy with a prescription dose of 40 Gy and 30 Gy in 10 fractions to the GTV and PTV, respectively. In 20 (58.8%) patients, all lesions, including the HVTT/IVCTT, were included in the RT field, while in the other 14 (41.2%) patients, only the thrombi and lesions that continued with the thrombi were included in the RT field due to multiple lesions in the liver or distant metastasis. Twenty-one (61.8%) patients received concurrent targeted therapy (including sorafenib, lenvatinib, and regorafenib), three (8.8%) patients received concurrent targeted therapy and ICIs, and 10 (29.4%) patients received RT alone. Twenty (58.8%) and seven (20.6%) patients received targeted therapy or targeted therapy and ICIs respectively, after RT.

Treatment Response

Treatment responses are summarized in Table 3. Based on the RECIST standards, the ORR and DCR were 32.4% and 55.9%, respectively. Based on the mRECIST standards, the ORR and DCR were 47.1% and 61.8%, respectively. The ORR and DCR for in-field lesions were 52.9% and 97.1%, respectively, based on the RECIST criteria (Figure 1A), and 79.4% and 97.1%, respectively, based on the mRECIST criteria (Figure 1B). One patient achieved a CR for all lesions. Only one patient had in-field progression within 3 months after RT, while 12 patients had progression out of the RT field without in-field progression.

Table 2 Treatment Characteristics

Characteristic (N=34)	No. of Patients (%)
First local treatment before RT and after diagnosis of tumor thrombus	
No	24 (70.6)
TACE	8 (23.5)
RFA	2 (5.9)
Previous systemic treatment	
Yes	14 (41.2)
No	20 (58.8)
Concurrent treatment	
Targeted therapy	24 (70.6)
Immune therapy	3 (8.8)
Target therapy and immune therapy	3 (8.8)
No concurrent treatment	10 (29.4)
RT technique	
IMRT	7 (29.2)
VMAT	27 (79.4)
RT target	
All tumors and thrombus	20 (58.8)
Part of all tumors and thrombus	14 (41.2)
RT dose ($EQD_{10/2}$, Gy)	
Median (range)	57.0 (40.0–68.3)

Abbreviations: TACE, transcatheter arterial chemoembolization; RFA, radiofrequency ablation; RT, radiotherapy; IMRT, intensity modulated radiotherapy; VMAT, volumetric modulated arc therapy; $EQD_{10/2}$, equivalent dose in 2 Gy fractions, $\alpha/\beta=10$; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Table 3 Treatment Response Evaluated by RECIST or mRECIST

	RECIST				mRECIST			
Treatment Response	**Primary Lesions**	**Thrombus**	**In-field**	**All Lesions**	**Primary Lesions**	**Thrombus**	**In-field**	**All Lesions**
CR	0 (0)	1 (2.9)	0 (0)	0 (0)	1 (2.9)	2(5.9)	1 (2.9)	1 (2.9)
PR	11 (32.4)	20 (58.8)	18 (52.9)	11 (32.4)	27 (79.4)	25 (73.5)	26 (76.5)	15 (44.1)
SD	22 (64.7)	12 (35.3)	15 (44.1)	8 (23.5)	5 (14.7)	6 (17.6)	6 (17.6)	5 (14.7)
PD	1 (2.9)	1 (2.9)	1 (2.9)	15 (44.1)	1 (2.9)	1 (2.9)	1 (2.9)	13 (38.2)

Abbreviations: RECIST, Response Evaluation Criteria in Solid Tumors; Mrecist, modified Response Evaluation Criteria in Solid Tumors; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Survival Outcomes and Prognostic Factors

During a median follow-up of 13.0 months, 23 patients (67.6%) in the entire cohort experienced disease progression. The 1- and 2-year OS rates were 77.6% and 36.3%, respectively, with a median OS of 15.8 months. The median PFS was 4.2 months, and the 1- and 2-year PFS rates were 24.6% and 19.7%, respectively. (Figure 2).

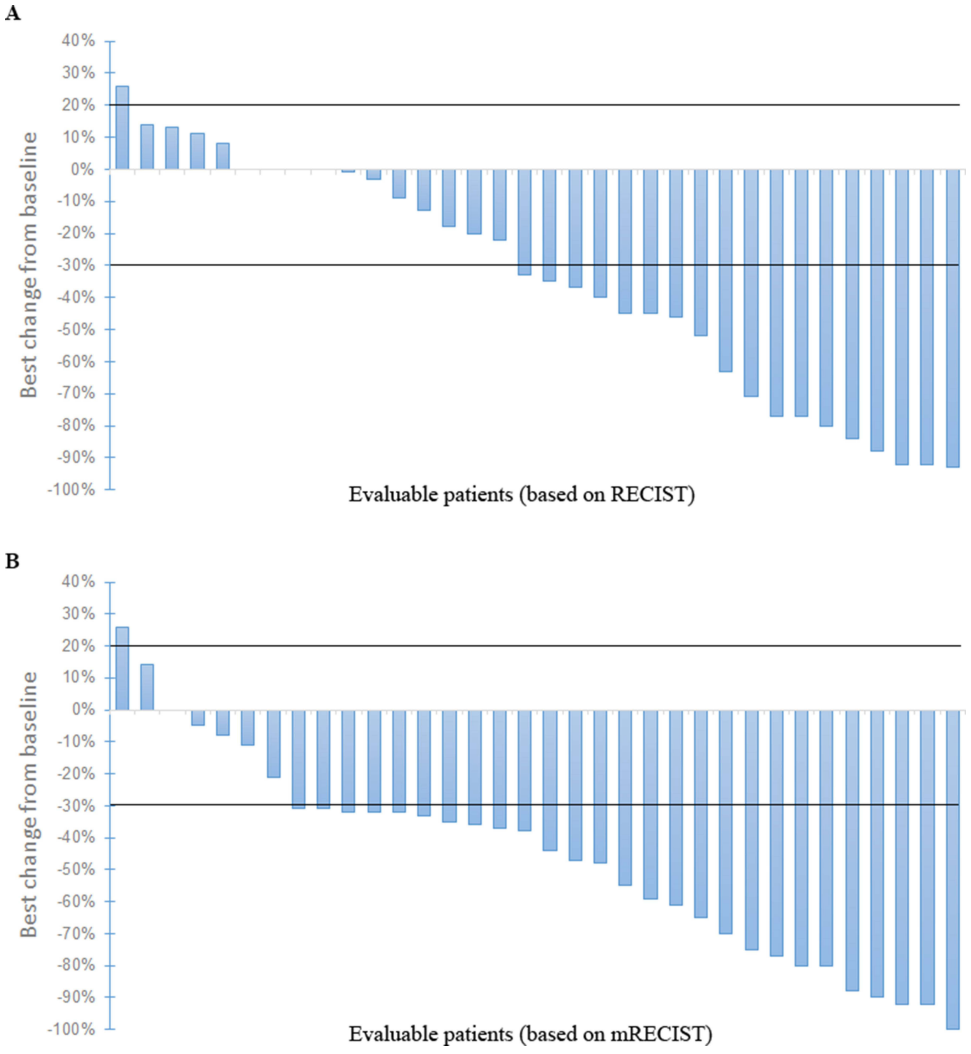

Figure 1 Evaluation of the short-term in-field therapeutic effect after radiotherapy. (**A**) Best change from baseline based on the RECIST criteria. (**B**) Best change from baseline based on the mRECIST criteria.
Abbreviations: RECIST, Response Evaluation Criteria in Solid Tumors; mRECIST, modified Response Evaluation Criteria in Solid Tumors.

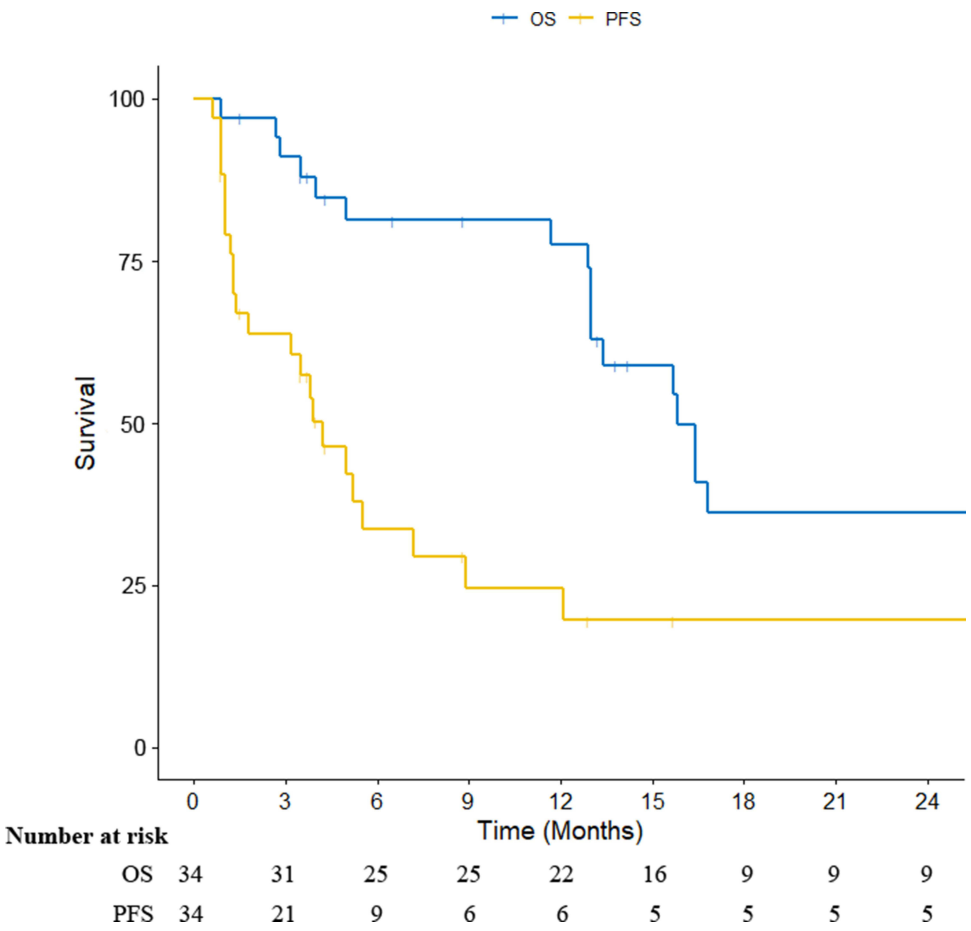

Figure 2 OS and PFS of all patients.
Abbreviations: OS, overall survival; PFS, progression-free survival.

In the univariate analysis, an AFP level >1000 ng/mL (HR, 3.432; 95% CI, 1.314–8.965; p=0.012; Figures 3A and 4A) was associated with worse OS, while in-field CR/PR (HR, 0.299; 95% CI, 0.104–0.864; p=0.026) was associated with better OS (Figures 3A and 4B). Although there was no significant difference in OS between Vv2 and Vv3 thrombi (p=0.091, (Figure 4C), the OS of Vv2 after 18 months was numerically superior to that of Vv3. The median OS of patients with Vv2 and Vv3 thrombi were 32.4 months and 15.7 months, respectively. This result was similar for OS between patients with and without PVTT. There was no significant difference in OS between patients without PVTT and those with PVTT (p=0.14, Figure 4D); however, the median OS of the former (25.4 months) was numerically superior to that of the latter (13.4 months). Lymph node, distant, and initial lung metastases before RT were not significant prognostic factors of OS or PFS (Figure 3A and B). In the multivariate analysis, an AFP level >1000 ng/mL was a significant prognostic factor for worse OS (HR, 5.674; 95% CI, 1.588–20.276; p=0.008), while in-field CR/PR was a significant prognostic factor for better OS (HR, 0.116; 95% CI, 0.027–0.499; p=0.004). No prognostic factors for PFS were identified in the multivariate analysis.

Pattern of Failure

The most common site of the first failure was the lungs (13/34 patients, 38.2%), followed by the liver (7/34 patients, 20.6%). Three patients (8.8%) experienced synchronous lung and liver disease progression. Six patients (17.6%) in the entire cohort showed progression in the RT field during follow-up. Only two thrombi in two patients progressed after radiotherapy. The median in-field PFS was not reached in the present study; the in-field PFS rates were 79.2% and 72.0% at one and two years, respectively.

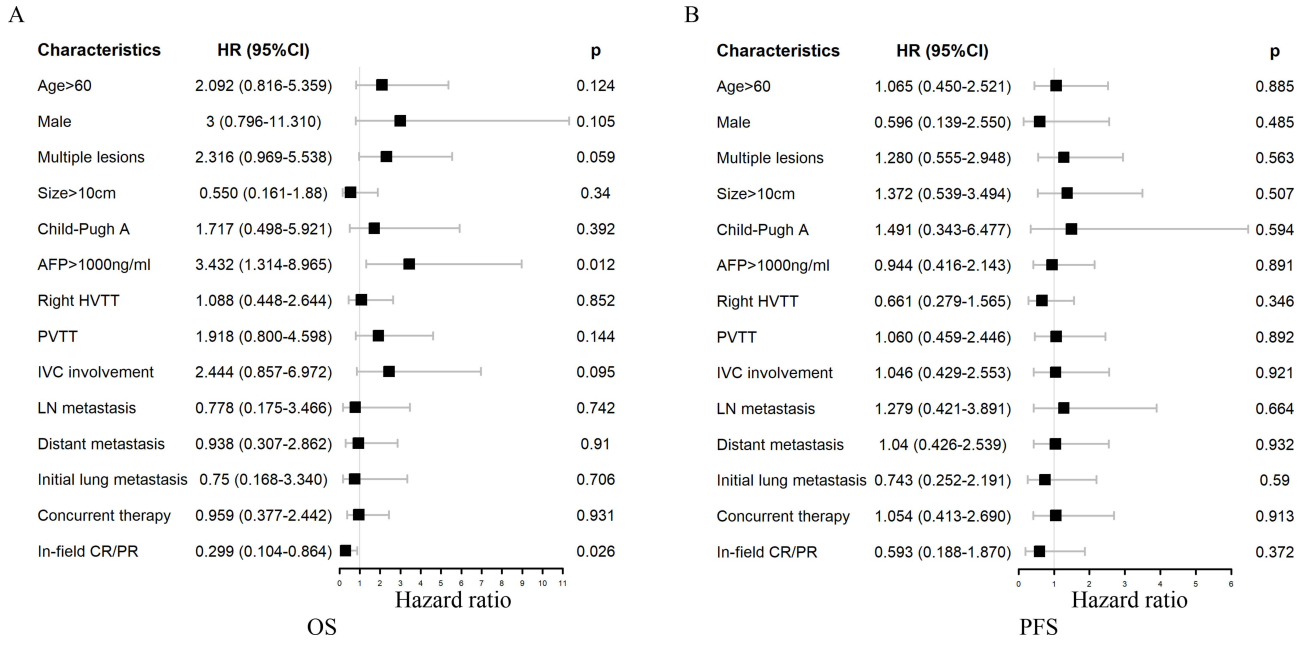

Figure 3 Univariate Cox analysis of prognostic factors in patients with HCC with HVTT/IVCTT. (**A**) Univariate Cox analysis of prognostic factors of OS. (**B**) Univariate Cox analysis of prognostic factors of PFS.

Abbreviations: AFP, alpha-fetoprotein; HVTT, hepatic vein tumor thrombus; PVTT, portal vein tumor thrombus; IVC, inferior vena cava; LN, lymph node; CR, complete response; PR, partial response; OS, overall survival; PFS, progression-free survival.

Toxicity

Common toxicities included leukemia (79.4%), gamma-glutamyl transpeptidase (GGT) elevation (79.4%), thrombocytopenia (73.5%), fatigue (70.6%), aminotransferase elevation (67.6%), and bilirubin elevation (55.9%). Most toxicities observed during RT were grade 1 or 2 (Table 4). Only one patient (2.9%) had grade 4 GGT elevation. This patient had a tumor measuring 11.40cm with tumor thrombi in the right hepatic vein, middle hepatic vein and main portal vein. The tumor thrombi were treated with radiotherapy at a dose of 59.8 Gy in 23 fractions, concurrently with Sorafenib 400mg twice daily. This patient also had grade 2 alanine/aspartate aminotransferase (ALT/AST) and bilirubin elevation. Two months after radiotherapy, the ALT/AST and GGT level recovered to grade 1 elevation and the bilirubin level recovered to normal. Ten patients (29.4%) had grade 1 or 2 radiation dermatitis, while none had radiation-induced liver disease or pulmonary embolism during follow-up.

Discussion

The present study revealed that HVTT and IVCTT are highly sensitive to RT. With 20.6% lymph node metastasis, 29.4% distant metastasis, and 64.7% Vv3 tumor thrombus, the median OS still reached 15.8 months. High-risk patients (70.6%) receiving concurrent systemic therapy had similar survival outcomes to those receiving RT alone. RT, targeted therapy, and ICIs can be safely administered to patients with HCC with HVTT/IVCTT if the RT plan is designed properly.

The incidence of HVTT and/or IVCTT in patients with HCC was 3.8–11.4%, according to the outcomes of surgery and TACE.[13,20] Macroscopic vascular invasion is considered one of the most important poor prognostic factors for HCC, with a median survival of only 3–5 months if left untreated.[21,22] Table 5 lists the previous studies on HVTT/IVCTT treatment in patients.[11–14,23–30] A previous study showed that the median OS of patients receiving RT as the primary treatment was 6.6–10.1 months,[26–28] shorter than that in the present study. One possible reason for this may be that the median RT dose was higher than that used in the previous studies. Alrashidi et al showed a better OS (18.3 months) than the current study (15.8 months), but more patients with Vv3 tumor thrombus were included in this study.[29]

A Japanese study showed that patients with HCC and HVTT who underwent liver resection had a better long-term prognosis than those who did not undergo surgery.[14] Chen et al also found that liver resection might improve recurrence-free survival and OS compared to IMRT.[25] However, these two studies included 30–50% of patients with HCC with

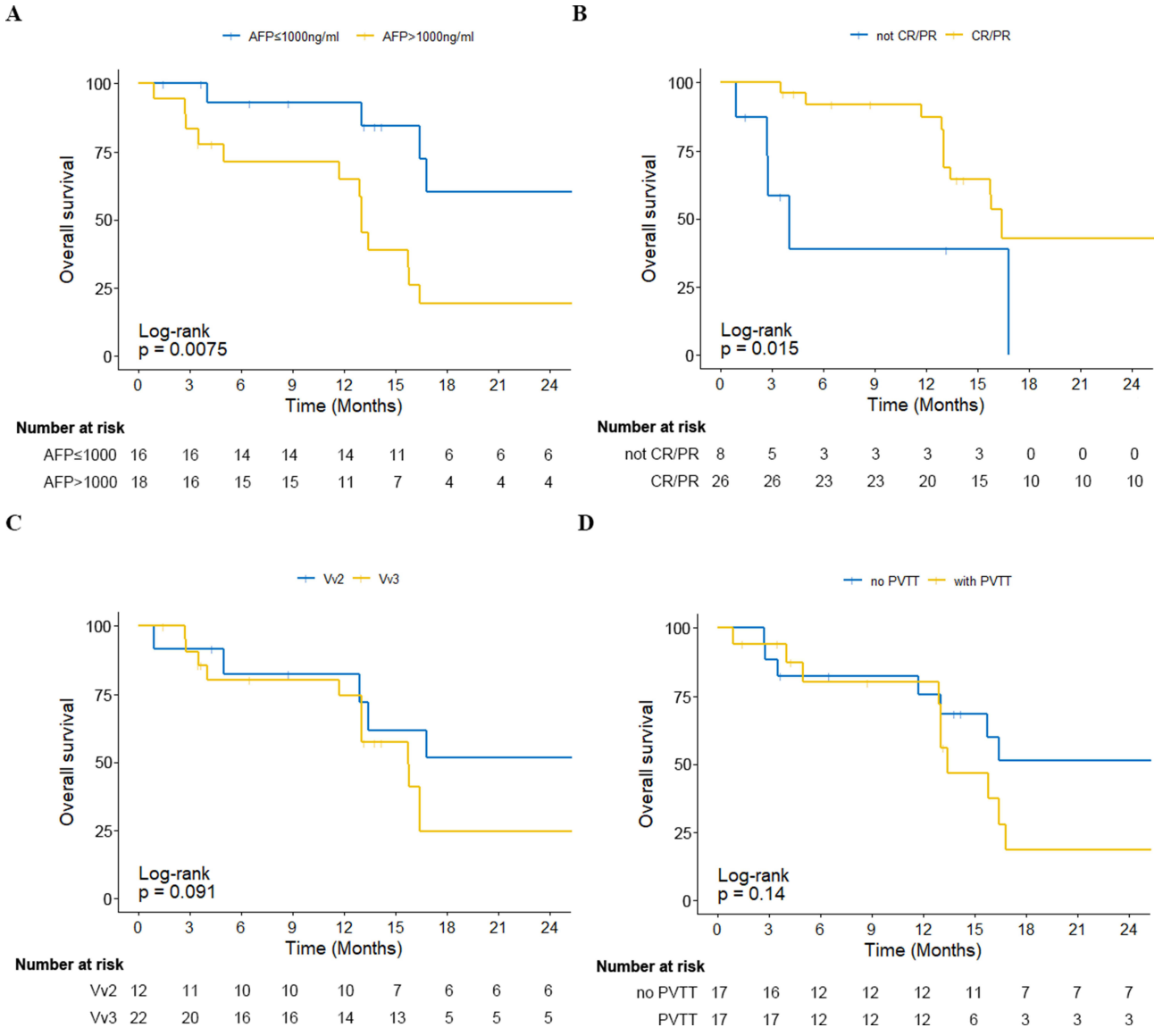

Figure 4 Overall survival according to (**A**) AFP level, (**B**) in-field response to radiotherapy, (**C**) HVTT type, and (**D**) portal vein involvement.
Abbreviations: HVTT, hepatic vein tumor thrombus; Vv2, invasion of (or tumor thrombus in) the right, middle, or left hepatic vein, the inferior right hepatic vein, or the short hepatic vein; Vv3, invasion of (or tumor thrombus in) the inferior vena cava; PVTT, portal vein tumor thrombus; AFP, alpha-fetoprotein; CR, complete response; PR, partial response.

peripheral HVTT and excluded patients with distant metastasis. This is in contrast with the present study, where all patients had major HVTT, and 10 (29.4%) patients had distant metastasis before RT. Moreover, in the present study, 17 (50.0%) patients had progression outside the RT field, which could not be radically resected via surgery. Previous evidence also showed that when undergoing liver resection, the prognosis of patients with IVC involvement (median OS, 16.7 months) was much worse than that of patients with HVTT alone (median OS, 47.4 months).[13] Wang et al indicated that when patients with Vv3 tumor thrombi underwent surgical resection, their 1-year survival rate was 68.0%, worse than that reported in the present study (77.6%). Therefore, surgery may not be the first choice for patients with HVTT/IVCTT, particularly when distant metastasis or IVC involvement is present. Therefore, RT should be considered preoperatively.

Univariate and multivariate analyses were conducted to identify possible prognostic factors. In contrast to other studies, an AFP level <1000 ng/mL and in-field CR/PR were associated with better OS in the univariate and multivariate analyses in the current study. This result indicates that RT should be considered as soon as possible if AFP levels continue to increase. PVTT, lymph node metastasis, and distant metastasis were not associated with OS or PFS. KROG 17–10, a multicenter retrospective

Table 4 Incidence of Treatment-Related Toxicities

Toxicities (N=34)	No. of Patients (%)			
	Grade 1	Grade 2	Grade 3	Grade 4
Leukemia	9 (26.5)	11 (32.4)	7 (20.6)	0 (0)
Thrombocytopenia	14 (41.2)	9 (26.5)	2 (5.9)	0 (0)
Anemia	7 (20.6)	0 (0)	0 (0)	0 (0)
ALT elevation	9 (26.5)	3 (8.8)	0 (0)	0 (0)
AST elevation	18 (52.9)	2 (5.9)	2 (5.9)	0 (0)
Bilirubin elevation	15 (44.1)	3 (8.8)	1 (2.9)	0 (0)
GGT elevation	18 (52.9)	6 (17.6)	2 (5.9)	1 (2.9)
Fatigue	20 (58.8)	4 (11.8)	0 (0)	0 (0)
Nausea	12 (35.3)	0 (0)	0 (0)	0 (0)
Vomiting	3 (8.8)	0 (0)	0 (0)	0 (0)
Radiation dermatitis	8 (23.5)	2 (5.9)	0 (0)	0 (0)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transpeptidase.

Table 5 Summary of Studies in Hepatocellular Carcinoma with HVTT/IVCTT

Author	Type of TT	Treatment	No.	LC	Median PFS/RFS, Month	Median OS, Month
Kokudo et al[13]	HVTT+IVCTT	Surgery	34	NA	4.9 for HVTT, 3.0 for IVCTT	47.4 for HVTT, 16.7 for IVCTT
Kokudo et al[14]	HVTT+IVCTT	Surgery vs no surgery	660	NA	NA	24.4 for HVTT, 13.9 for IVCTT
Kasai et al[23]	IVCTT	Surgery+HAIC	39	NA	5.3	15.2
Li et al[12]	IVCTT	Surgery vs RT	51 vs 57	NA	4.2 vs 5.0	14.5 vs 12.8
Komatsu et al[24]	IVCTT	Surgery vs particle RT	19 vs 31	NA	NA	3y: 14% vs 16%
Chen et al[25]	HVTT+IVCTT	Surgery vs RT	140 vs 167	NA	13.0 vs 9.7	21.0 vs 16.5
Wang et al[11]	IVCTT	Surgery vs TACE vs systemic therapy	25 vs 20 vs 11	NA	NA	19.0 vs 4.5 vs 5.0
Rim et al[26]	IVCTT	RT	49	2y 74.5%	4.0	10.1
Pao et al[27]	IVCTT	RT	42	NA	NA	6.6
Lee et al[28]	IVCTT	RT	19	89.4%	NA	9.4
Alrashidi et al[29]	HVTT+IVCTT	RT+TACE	79	NA	8.1	18.3
Duan et al[30]	IVCTT	RT+TACE	11	NA	NA	21.0
Our study	HVTT+IVCTT	RT	34	2y 72.0%	4.2	15.8

Abbreviations: TT, tumor thrombus; No, number of patients; LC, local control; PFS, progression-free survival; RFS, recurrence-free survival; OS, overall survival; HVTT, hepatic vein tumor thrombus; IVCTT, inferior vena cava tumor thrombus; RT, radiotherapy; TACE, transcatheter arterial chemoembolization; HAIC, hepatic arterial infusion chemotherapy; NA, not available; y, year.

study in Korea, reported that multiple lesions, an AFP level ≥300 ng/mL, and treatment in mid-volume medical centers were factors related to poor OS.[26] Two other similar retrospective studies showed that Child–Pugh class A, without lymph node or lung metastases, and RT dose ≥50 Gy were favorable prognostic factors.[27,28] In the present study, all except four patients received an RT dose ≥50 Gy to their primary lesions and tumor thrombus. Although extrahepatic metastasis, especially lung metastasis, was a worse prognostic factor for patients with HCC, the median OS in patients with distant metastases was approximately 12 months, much longer than that in patients with HVTT or IVCTT.[31] Therefore, we assumed that the local control of the tumor thrombus was the most crucial factor in prolonging patient survival. In fact, patients who achieved in-field CR or PR had a significantly longer OS, indicating that local control was important for patients with HVTT or IVCTT regardless of distant metastasis. Moreover, different from the surgical results for tumor thrombus, Vv2/Vv3 tumor thrombi were not associated with PFS or OS. The possible reasons may be as follows. Patients with Vv2 tumor thrombus can be directly resected, whereas surgical treatment of Vv3 requires thrombectomy from the inferior vena cava because the inferior vena cava cannot be removed. The procedure of thrombectomy has a higher probability of tumor cell shedding and lung metastasis than direct resection. Therefore, there is a large difference in the survival results of patients underwent surgical resection between Vv2 and Vv3. In contrast, radiotherapy is relatively less constrained by the extension of tumor thrombus. The local control is consistent for both Vv2 and Vv3 as long as they receive the same RT dosage. At the same time, tumor thrombus in inferior vena cava is far from stomach and duodenum, so the difficulty of

radiotherapy for Vv3 patients does not significantly increase compared to Vv2 patients. As a result, the difference in survival between Vv3 and Vv2 patients receiving radiotherapy is less than that observed with surgery.

Studies have explored multimodal therapies to treat HCC using HVTT and IVCTT. Most patients in the present study were treated using other local and systemic therapies before, during, or after RT. Two patients even underwent liver resection after tumor shrinkage induced by RT. Alrashidi et al showed that 31.6% of patients with HVTT or IVCTT in the TACE and RT groups achieved a CR.[29] PFS and OS were significantly longer in patients receiving TACE plus RT, especially in those with better liver function, higher AFP levels, larger or multiple tumors, and IVC/portal vein involvement. TACE is an effective therapy for primary lesions, but it cannot treat tumor thrombi inside major vessels. In some cases, tumor thrombi are even caused by failed RFA or TACE. Figure 5 shows the MRI images of two patients in the present study. Notably, even if the primary lesion responded to TACE, IVCTT progressed in patient 1 before receiving RT (Figure 5A and B), whereas IVCTT was well-controlled by RT in patient 2 (Figure 5C and D). These results indicated that other local treatments can be recommended with RT in patients with HVTT/IVCTT, but they should not be used without RT.

The IMbrave 150, ORIENT-32, and CARES-310 trials showed that ICIs plus targeted therapies improved the survival of patients with unresectable HCC over sorafenib, with a median PFS of 2.8–6.8 months.[32–34] Therefore, ICIs plus targeted therapy are the first-line treatment for unresectable HCC. However, no previous studies have focused on its efficacy in patients with HVTT/IVCTT. In a Phase II study, we explored the efficacy of concurrent RT and sorafenib in patients with HCC with portal vein thrombi and found that it was well-tolerated.[35] In the present study, most patients received targeted therapy with RT to control local and distant lesions. Seven patients in the present study received both ICIs and targeted therapy during or after RT, showing promising therapeutic effects and safety. Only one grade 4 toxicity was observed during follow-up. Bone marrow suppression, aminotransferase elevation, and gastrointestinal symptoms are the most common toxicities; however, they can be treated without long-term adverse effects.

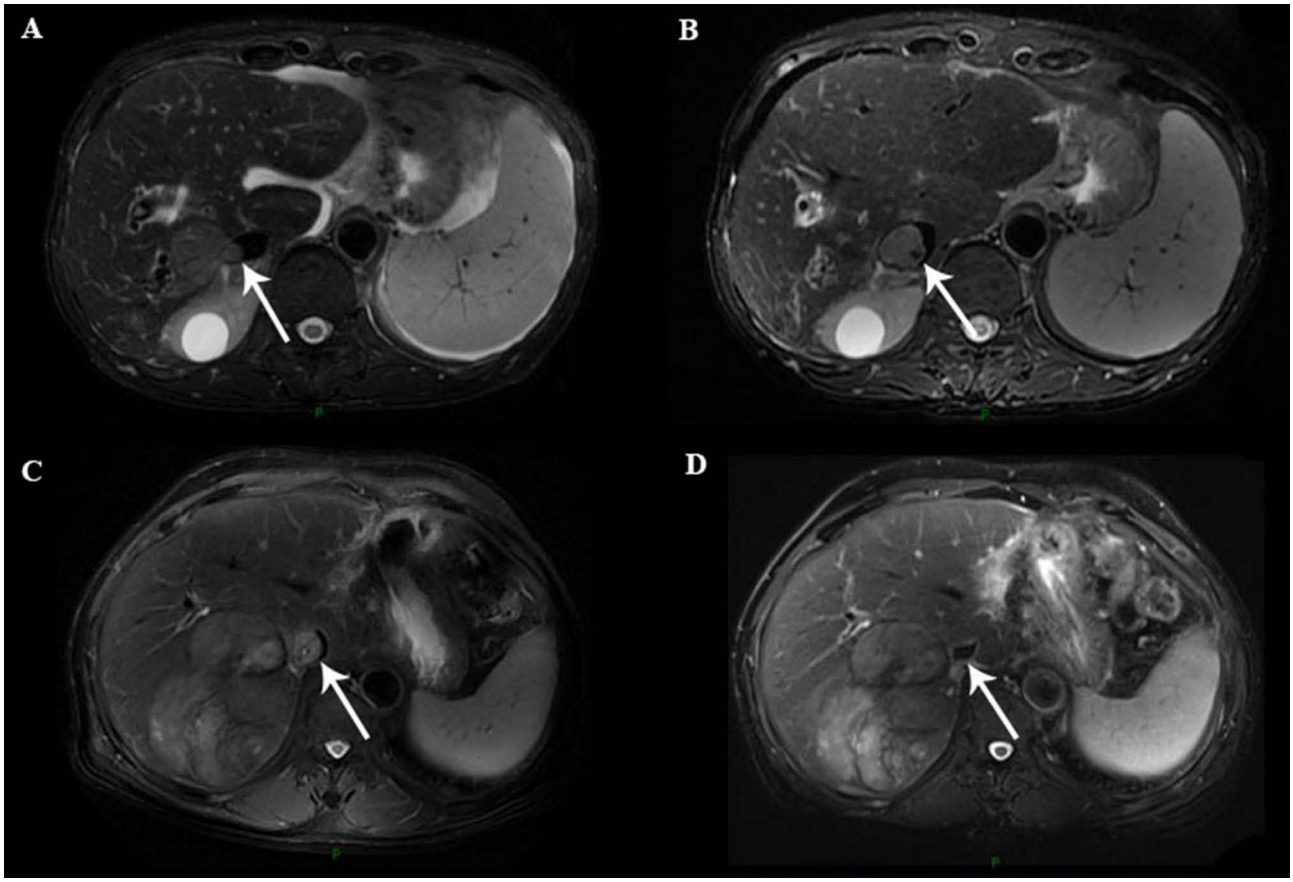

Figure 5 Patients with tumor thrombi who underwent TACE or radiotherapy. (**A** and **B**) MRI images of patient 1 before and after TACE therapy. (**C** and **D**) MRI images of patient 2 before and after radiotherapy. White arrows show the tumor thrombus.
Abbreviations: TACE, transcatheter arterial chemoembolization; MRI, magnetic resonance imaging.

This study had limitations. This was a single-center retrospective study with a small sample size because the incidence of HVTT and/or IVCTT in HCC is very low compared to that in PVTT. Hence, data on HVTT and IVCTT from multiple centers should be analyzed to generalize our results.

Conclusion

In conclusion, our study showed that HCC tumor thrombi are sensitive to RT. RT should be considered as soon as possible when HVTT/IVCTT is detected in patients with HCC.

Data Sharing Statement

Data are available on request due to restrictions of privacy.

Ethics Approval and Informed Consent

The study protocol was approved by the Institutional Ethics Committee of our hospital (22/094-3295). Board Name: National GCP Center for Anticancer Drugs, The Independent Ethics Committee. Board Affiliation: National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College.

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.

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Disclosure

The authors report no conflicts of interest in this work.

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