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Phase II study with sorafenib plus radiotherapy for advanced HCC with portal and/or hepatic vein tumor thrombosis

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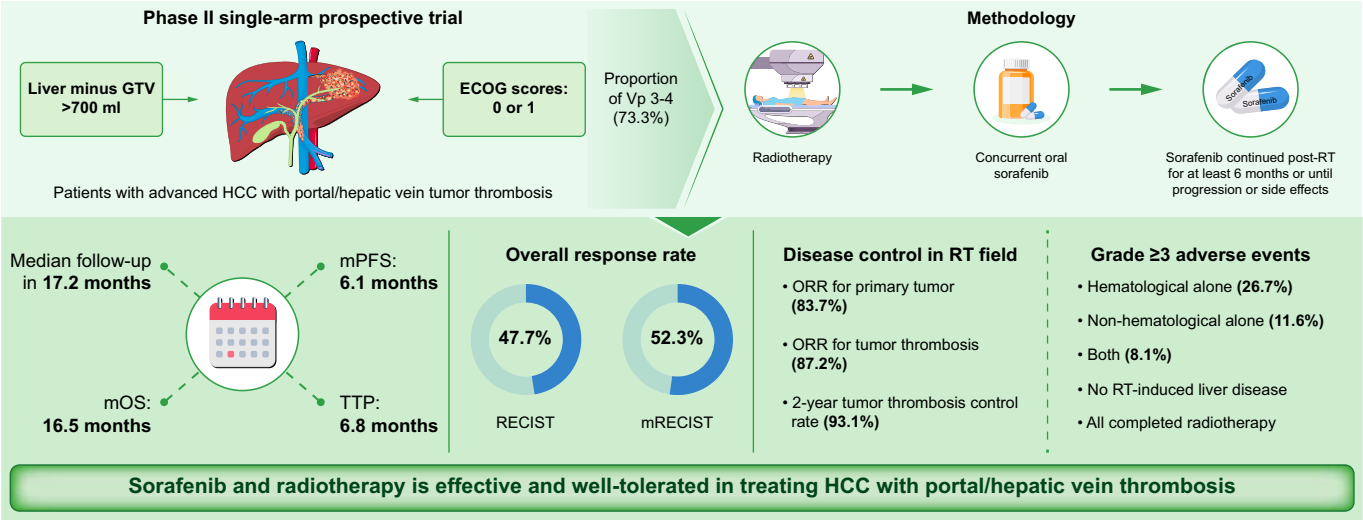
Graphical abstract



Highlights:

- Concurrent sorafenib and radiotherapy conferred favorable outcomes in HCC with venous thrombosis.
- Median OS of 16.5 months, PFS of 6.1 months, and TTP of 6.8 months were observed.
- The ORR was 47.7% (RECIST) and 52.3% (mRECIST), with an ORR (mRECIST) of 87.2% for the tumor thrombosis.
- The main grade ≥3 adverse events were thrombocytopenia (22.1%) and leukopenia (14.0%).

Impact and implications:

Treatment options for patients with hepatocellular carcinoma (HCC) and vascular tumor thrombus are limited. The efficacy and safety of concurrent sorafenib and radiation for HCC with portal or hepatic vein tumor thrombosis has not been elucidated. This phase II trial shows that concurrent sorafenib and radiotherapy is effective and well-tolerated in the treatment of advanced HCC with portal vein or hepatic vein tumor thrombosis.

https://doi.org/10.1016/j.jhepr.2024.101287

Research article

JHEP|Reports

Phase II study with sorafenib plus radiotherapy for advanced HCC with portal and/or hepatic vein tumor thrombosis

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JHEP Reports **2025**. vol. 7 | 1–10

Background & Aims: Portal and hepatic vein tumor thrombosis is associated with inferior outcomes in patients with hepatocellular carcinoma (HCC), and systemic treatment alone is often insufficient. This phase II trial evaluated the efficacy and safety of combining sorafenib with radiotherapy in advanced HCC with thrombosis.

Methods: Registered at ClinicalTrials.gov (NCT03535259), this phase II single-arm prospective trial targeted patients with HCC with portal or hepatic vein tumor thrombosis, liver minus gross tumor volume >700 ml, and Eastern Cooperative Oncology Group Performance Status scores of 0 or 1. Participants underwent 40–66 Gy radiotherapy for the hepatic primary tumor and vein tumor thrombosis, with concurrent oral sorafenib (400 mg twice daily) until disease progression or unacceptable adverse events. The primary endpoint was median overall survival (mOS) and the secondary endpoints included overall response rate (ORR) per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 and Modified Response Evaluation Criteria in Solid Tumors (mRECIST), median progression-free survival (mPFS), time to tumor progression (TTP), tumor thrombosis control, and grade ≥3 adverse events.

Results: Between May 2018 and January 2020, 86 patients were enrolled with a median radiotherapy dose of 54 Gy (40–65 Gy). At a median follow-up of 17.2 months, mOS, mPFS, and TTP stood at 16.5, 6.1, and 6.8 months, respectively. ORR reached 47.7% and 52.3% per RECIST and mRECIST, respectively. For the tumor thrombosis, 2-year control rates per mRECIST were 93.1%. No grade 5 adverse events were noted, whereas thrombocytopenia (22.1%) and leukopenia (14.0%) were the main grade 3 adverse events.

Conclusions: Concurrent sorafenib and radiotherapy is an effective and well-tolerated treatment for patients with HCC with portal or hepatic vein tumor thrombosis.

Clinical trials registration: This study is registered at ClinicalTrials.gov (NCT03535259).

Introduction

Hepatocellular carcinoma (HCC) is the most common pathological type accounting for 75–85% of liver cancers.[1] Portal vein tumor thrombosis (PVTT) and hepatic vein tumor thrombosis (HVTT) are observed in 16–50% and 2–13% of patients with HCC, respectively.[2–4] This occurrence increases to 44–70% at autopsy.[4] PVTT and HVTT significantly worsen patient survival owing to their tendency for intrahepatic spread, distant metastasis, and complications from increased portal pressure.[2,5] Untreated HCC patients with PVTT typically survive 2–4 months.[3] Despite various recommended treatments, the prognosis remains dismal.[4] Sorafenib, a classical multikinase inhibitor, was the predominantly available systemic therapy before 2018.[6] However, the outcomes remained poor, and survival time was 6.5–10.8 months in patients with macrovascular invasion.[7,8] Although IMbrave150 supports atezolizumab and bevacizumab as standard treatments in advanced HCC,[9] prolonged survival time was not observed in patients with main trunk portal vein invasion compared with those treated with sorafenib.[10] To date, no breakthrough treatment strategy has been reported. Prospective studies seldom target patients with PVTT/HVTT. Therefore, novel multimodal therapeutics still need to be explored to improve the outcomes of patients with PVTT/HVTT.

Technical advancements have enabled the safe delivery of radiotherapy to patients with larger tumors.[11] Theoretically, patients with PVTT/HVTT are presumably sensitive to radiotherapy owing to the sufficient blood supply to these sites. Clinical research reveals survival benefits for selected patients

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https://doi.org/10.1016/j.jhepr.2024.101287

with PVTT after radiotherapy.[12] Furthermore, sorafenib combined with irradiation exerts a schedule-dependent effect in HCC cells,[13] which has implications for the combination of sorafenib and radiotherapy for patients with HCC. However, no prospective results using combined sorafenib and radiation have been reported. Hence, we proposed this phase II study to evaluate the efficacy and safety of the concurrent combination of sorafenib and radiation in patients diagnosed with HCC and PVTT/HVTT.

Patients and methods

Ethics and registration

The study was conducted according to Good Clinical Practice Guidelines defined by the International Council for Harmonization and the principles of the 1975 Declaration of Helsinki. Trial protocol approval was obtained from the institutional ethics committee. Eligible patients provided written informed consent before study-related procedures. The trial was registered on the website of ClinicalTrials.gov (NCT03535259).

Participants

The inclusion criteria were clinically or pathologically confirmed HCC (clinical diagnosis required chronic hepatitis or liver cirrhosis, α-fetoprotein (AFP) increase, and enhancement pattern of early arterial enhancement with early washout if biopsy was not available); presence of PVTT/HVTT as identified by computed tomography (CT) and/or magnetic resonance imaging (MRI) based on the criteria of precious studies;[14,15] age 18–80 years; Eastern Cooperative Oncology Group performance status (ECOG PS) score of 0–1; measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.0, liver minus gross tumor volume (GTV) >700 ml, Child–Pugh score of A5-B8, neutrophil count ≥1.0 × 10^9/L, hemoglobin ≥80 g/L, blood platelet count ≥40 × 10^9/L, aspartate transaminase (AST) and alanine aminotransferase (ALT) ≤1.5 times the upper limit of normal (ULN) or ALT ≤ ULN and AST ≤6 times ULN excluding heart disease, and international normalized ratio ≤1.5 unless under anticoagulant therapy.

Exclusion criteria encompassed prior abdominal irradiation history, prior sorafenib administration, liver transplantation, significant myocardial disease, or sorafenib allergy. Further criteria are detailed in the protocol (Supplementary data).

Baseline evaluation

All patients received a baseline evaluation that included medical history; physical examination; and laboratory tests, including blood count, liver function, renal function, AFP, hepatitis virus, and coagulation function. The following tests were performed within 1 month before enrollment in the study: electrocardiography; chest, abdominal, and pelvic CT; and hepatic MRI.

Radiotherapy

GTV included the primary tumor and tumor thrombosis, with or without regional metastatic lymph nodes, in simulated CT and MRI. All intrahepatic sub-focal lesions near the primary tumor were included in the GTV unless the location of certain lesions was too far to be involved because of excess normal liver tissue. Clinical target volume (CTV) included GTV plus a 5-mm margin and 10 mm expanded from GTV in the direction of blood vessels with tumor thrombosis. The planning target volume (PTV) included CTV plus a 5-mm margin in the axial direction and CTV plus 10–15 mm in the cranial-caudal direction according to the movements defined by four-dimensional CT. A total dose of 40–60 Gy in 20–30 fractions, 2 Gy per fraction, and five fractions per week was prescribed for PTV with or without a simultaneous integrated boost to GTV with a dose of 54–66 Gy. The radiation dose mainly depends on the organs at risk (OAR) constraints, especially the dose constraints of normal liver (liver minus gross tumor volume, liver-GTV). The dose limitation of OAR was listed in the protocol (Supplementary data). Intensity-modulated radiotherapy was used in all patients. Radiotherapy quality assurance and control were performed by two senior physicists.

Sorafenib

Sorafenib was administered at 400 mg bid orally. Patients with PVTT/HVTT, who often progress rapidly, require prompt treatment. To prevent rapid lesion growth, oral sorafenib was allowed immediately after enrollment during simulated CT and MR scanning, target volume and normal tissue delineating, and radiotherapy treatment planning. It is imperative to initiate radiotherapy promptly to prevent alterations in the patient's clinical characteristics post-enrollment. The interval was not allowed to exceed 8 weeks after the commencement of sorafenib administration. During the radiation, sorafenib was prescribed concurrently. Post-radiation, sorafenib was continued for a minimum of 6 months or until disease progression, unacceptable side effects, patient consent withdrawal, or investigator determination.

Concomitant medications

Anti-virus treatment was recommended for patients with chronic viral hepatitis. Gastric mucosal protective agents were allowed for gastrointestinal symptoms.

Adverse events and treatment modifications

Adverse events (AEs) were evaluated every week during the treatment and at each follow-up, until the salvage therapy was delivered or up to 2 years after radiotherapy if the disease was still under control, according to the National Cancer Institute Common Toxicity Criteria of Adverse Events (NCI-CTCAE) Version 4.03.

Radiotherapy interruption was permitted for patients with any grade ≥4 toxicities or grade ≥3 non-hematological toxicities, and radiotherapy did not recommence until the toxicity had resolved to grade ≤2. If the Child–Pugh score increased to B9, radiation would be paused until it resolved to ≤B8.

Sorafenib modification was decided by two physicians together. The principles of sorafenib adjustment are depicted in protocol (Supplementary data).

Follow-up

During the concurrent therapy, symptoms, physical examinations, blood pressure and blood counts, coagulation function, and liver function were assessed once a week and at every follow-up. Neck, chest, abdominal, and pelvic CTs, hepatic

MRI, and AFP were assessed 1 and 3 months after treatment, every 3 months for 2 years, and thereafter every 6 months for 3 years. Follow-up examinations are provided in protocol (Supplementary data).

Statistical analysis

Survivals were calculated from the first day of radiation. The primary endpoint was the median overall survival time (mOS). The secondary endpoints included objective response rate (ORR, complete or partial response), tumor thrombosis response rate (complete or partial response of the tumor thrombosis), primary tumor response rate (complete or partial response of the primary tumor), time to progression (TTP, to the first documented disease progression during or after protocol-specified treatment), median progression-free survival (mPFS, to the first documented disease progression or death), in-radiation-field relapse-free survival (IRFS, to the first recorded in radiation field recurrence), out-radiation-field relapse-free survival (ORFS, to the first recorded out of radiation field recurrence), and grade ≥3 AEs. As primary tumor and tumor thrombosis were more life-threatening than other lesions, primary tumor response and control (PTC, to the first recorded primary tumor progression), and tumor thrombosis responses and control (TTC, to the first recorded tumor thrombosis progression) were also assessed separately. Tumor thrombosis target lesions were defined as their maximum lengths from the initiating portion of the tumor initiation to the end of the tumor thrombosis. Responses, progressions, and recurrences were confirmed by a senior radiologist and a senior radiation oncologist at every follow-up according to RECIST 1.1 and the modified Response Evaluation Criteria in Solid Tumors (mRECIST).[16] Where discrepancy occurred, another senior radiologist joined the evaluation and made the final decision. If the three doctors expressed three different opinions, the final decision was made by the multidisciplinary treatment team.

Previous studies reported that the mOS was 7–10 months after systemic therapies in the era of sorafenib as first-line therapy.[5,6] In our hypothesis, we posited that mOS would improve from 8.4 months with sorafenib alone to 12 months with combined radiotherapy and sorafenib. The estimated accrual period was 12 months, and the follow-up duration was projected to be 24 months. Assuming a statistical power of 80% and a two-sided type I error rate of 0.05, the required sample size was 78 patients. Accounting for an estimated 10% loss to follow-up, the total sample size was adjusted to 86 patients.

Tumor thrombosis subtypes were considered in univariate analysis using the log-rank test. PVTT was categorized into four groups, according to the Liver Cancer Study Group of Japan, as follows: Vp1, segmental portal vein invasion; Vp2, the second branch of portal vein invasion; Vp3, right or left portal vein invasion; and Vp4, main trunk portal vein invasion.[17] An anatomical classification for HVTT was proposed by a Japanese staging system as follows: Vv1, peripheral hepatic microvascular invasion; Vv2, right, middle, or left hepatic vein tumor invasion; and Vv3, inferior vena cava or heart atrium invasion.[17,18] We grouped the population with a similar prognosis and defined total vein tumor thrombosis (TVTT) as follows: TVTT1, Vp1 or Vv1; TVTT2, Vp2; TVTT3, Vp3 or Vv2; TVTT4, Vp4 or Vv3. Multivariate analysis of the prognosticators was

Table 1. Baseline demographic and clinical characteristics of patients receiving radiation plus sorafenib.

	n	%
Sex		
Male	81	94.2
Female	5	5.8
Age (years)		
≤60	60	69.8
>60	26	30.2
ECOG PS		
0	44	51.2
1	42	48.8
Diagnosis		
Pathological	80	93.0
Clinical	6	7.0
Child–Pugh		
5	77	89.5
6	7	8.1
7	2	2.3
ALBI grade		
Grade 1	50	58.1
Grade 2	35	40.7
Grade 3	1	1.2
AFP (ng/ml)		
≤1,000	48	55.8
>1,000	38	44.2
Hepatitis		
HBV	75	87.2
HCV	5	5.8
HBV + HCV	2	2.3
No	4	4.7
No. of IHL		
1	40	46.5
≥2	46	53.5
Tumor size (cm)		
≤5	25	29.1
5–10	42	48.8
>10	19	22.1
BCLC stage*		
A	11	12.8
B	7	8.1
C	68	79.1
T stage*		
T1	1	1.2
T2	1	1.2
T4	84	97.7
N stage*		
N0	75	87.2
N1	11	12.8
M stage*		
M0	80	93.0
M1	6	7.0
TNM stage*		
I	1	1.2
II	1	1.2
IIIB	68	79.1
IVA	10	11.6
IVB	6	7.0
Tumor thrombosis		
PVTT alone	69	80.2
HVTT alone	6	7.0
PVTT + HVTT	11	12.8
PVTT		
Vp0	6	7.0
Vp1	3	3.5
Vp2	14	16.3
Vp3	28	32.6
Vp4	35	40.7
Vv0	69	80.2

(*continued on next page*)

Table 1. (*continued*)

	n	%
Vv1	3	3.5
Vv2	6	7.0
Vv3	8	9.3
PVTT + HVTT		
TVTT1	1	1.2
TVTT2	12	14.0
TVTT3	30	34.9
TVTT4	43	50.0
Therapy line		
1	34	39.5
≥2	52	60.5
Previous therapy[†]		
Surgery	4	4.7
Surgery + TACE	2	2.3
Surgery + TACE + RFA	1	1.2
TACE + RFA	2	2.3
TACE	30	34.9
RFA	13	15.1
No	34	39.5

ALBI, albumin–bilirubin; AFP, α-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; ECOG PS, Eastern Cooperative Oncology Group Performance Status score; HVTT, hepatic vein tumor thrombosis; IHL, intrahepatic lesions; PVTT, Portal vein tumor thrombosis; RFA, radiofrequency ablation; TACE, transcatheter arterial chemoembolization; TVTT, total vein tumor thrombosis; Vp1, segmental portal vein invasion; Vp2, the second branch of portal vein invasion; Vp3, right or left portal vein invasion; Vp4, main trunk invasion; Vv1, peripheral hepatic microvascular invasion; Vv2, right, middle, or left hepatic vein invasion; Vv3, inferior vena cava or heart atrium invasion; TVTT1, Vp1 or Vv1; TVTT2, Vp2; TVTT3, Vp3 or Vv2; TVTT4, Vp4 or Vv3.
*Initial diagnosis stage (some patients were recurrent ones).
[†]All patients who received previous therapy had relapse or progression disease before enrollment.

calculated using the Cox proportional hazards model. All statistical analyses were conducted using the SPSS statistical software package version 22.0 (SPSS Inc., Chicago, IL) and R software (v4.0.4; R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient characteristics

From May 2018 to January 2020, a total of 96 patients were screened, and 86 met the enrollment criteria and were included in the analysis (Fig. S1). The patient baseline characteristics are shown in Table 1. There were 81 males (94.2%) and five females (5.8%). The median age was 56 years. Eighty patients (93.0%) were pathologically diagnosed. Most participants (95.3%) had viral hepatitis. Sixty-nine patients (80.2%) had PVTT alone, six (7.0%) had HVTT alone, and 11 (12.8%) had both. Half of these patients met the inclusion criteria for TVTT4. Forty-six patients (53.5%) had intrahepatic multi-foci. The number of intrahepatic tumor nodules ranged from 1 to 9. The mean diameter of primary tumors was 7.1 (range, 1.8–20.1) cm. Sixteen patients (18.6%) exhibited bilobar disease. Baseline AFP levels >1,000 ng/ml were recorded in 38 participants (44.2%) and the median AFP of the baseline was 422.9 ng/ml (range, 1.65–484,000 ng/ml). Distant metastasis was observed in six patients (7.0%), including three (3.5%) with distant lymph node metastasis, two (2.3%) with lung metastasis, and one (1.2%) with lung and adrenal metastasis. There were 77 patients (89.5%) with Child–Pugh A5 and others with A6-7. Fifty patients (58.1%) had albumin–bilirubin (ALBI) grade 1, 35 (40.7%) had ALBI grade 2, and 1 (1.2%) had ALBI grade 3.

Radiotherapy and sorafenib

All patients completed the full course of the planned radiation therapy. The median actual doses of radiotherapy to GTV and PTV were 54 Gy (range, 40–65 Gy) and 50 Gy (range, 40–56 Gy) in 25 fractions (20–28 fractions). All except seven patients, received radiation for all intrahepatic lesions, including those from which tumor thrombosis arose. The median interval between the first delivery of sorafenib and that of radiation was 1.5 (0–3.4) weeks. Suspension of radiotherapy was recorded in 14 patients (16.3%), and the median interruption time was 7 days. The reasons for radiation delay were infection (5/14), hematological AEs (4/14), elevated bilirubin and/or transaminase (4/14), and gastrointestinal hemorrhage (1/14). For these 14 patients, radiation restarted in all of them after proper treatment.

During the concurrent treatment, one patient (1.2%) discontinued sorafenib permanently because of grade 3 upper gastrointestinal hemorrhage after taking sorafenib for 5 days and receiving the second fraction of radiotherapy. This patient, however, completed the entire course of radiotherapy after receiving a blood transfusion. Additionally, 11 patients (12.8%) experienced a temporary interruption of sorafenib, with a median duration of 2 weeks (range: 0.7–3 weeks). The reasons for these interruptions included grade 3 skin rash in 1 patient, grade 3 hand-foot syndrome in 3, grade 3 radiation-induced dermatitis in 2, grade 3-4 transaminase elevation with or without grade 3-4 bilirubin elevation in 4, and grade 4 thrombocytopenia in 1. When sorafenib was resumed, it was initially prescribed at a reduced dose of 200 mg orally twice daily for all 11 patients during the first week. The full dose was restored in the second week for all but two patients, including one with skin rash and one with hand-foot syndrome; both continued on the reduced dose of 200 mg twice daily thereafter. Of the other four patients (4.7%) on a reduced of sorafenib dose during radiation, one had grade 3 diarrhea, and three had grade 3 hand-foot syndrome. After 2–3 weeks of dose reduction, three

Table 2. Summary of responses after radiation plus sorafenib.

	Total		Primary tumor		Tumor thrombosis*	
Evaluation	No.	%	No.	%	No.	%
RECIST						
CR	1	1.2	3	3.5	4	4.7
PR	40	46.5	59	68.6	56	65.1
SD	10	11.6	22	25.6	24	27.9
PD	35	40.7	2	2.3	2	2.3
ORR	41	47.7	62	72.1	60	69.8
DCR	51	59.3	84	97.7	84	97.7
mRECIST						
CR	22	25.6	25	29.1	30	34.9
PR	23	26.7	47	54.7	45	52.3
SD	6	7.0	12	14.0	9	10.5
PD	35	40.7	2	2.3	2	2.3
ORR	45	52.3	72	83.7	75	87.2
DCR	51	59.3	84	97.7	84	97.7

CR, complete response; DCR, disease control rate; mRECIST, modified Response Evaluation Criteria in Solid Tumors; ORR, overall response rate; PD, progression disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.
*Tumor thrombosis target lesions are defined as their maximum lengths from the initiating portion of the tumor initiation to the end of the tumor thrombosis.

patients resumed the full dose and the other one maintained 200 mg twice daily thereafter.

After radiation, one patient had frequent stomachaches and terminated sorafenib treatment. The other 85 patients continued sorafenib until disease progression. Among the 85 patients, sorafenib interruption was documented in four patients (4.7%), including one (1.2%) for grade 3 hand-foot syndrome, two (2.3%) for hematological AEs, and one (1.2%) for icterus. Sorafenib was restarted after treatment for these four patients. Only one patient (1.2%) received a sorafenib dose reduction for refractory thrombocytopenia, which also occurred during concurrent therapies.

Treatment responses

The ORRs were 47.7% and 52.3%, using RECIST and mRECIST criteria, respectively (Table 2). Although 35 patients (40.7%) were evaluated as having progression disease totally, 31 of these cases were because of the emergence of new lesions out of the radiation field. However, the lesions that were present before enrollment, especially the primary tumors and tumor thrombosis, were well controlled (Table 2). According to RECIST and mRECIST criteria, the ORRs of the tumor thrombosis were 69.8% and 87.2%, and ORRs of primary tumor were 72.1% and 83.7%, respectively. Overall, the total tumor burden was still decreasing or stable upon comprehensive evaluation. As a result, the AFP reduction rate reached 82.6%. The median AFP after treatment was 28.36 ng/ml (1.35–351,415 ng/ml). The changes of tumor diameters and AFP are plotted in Fig. 1A and B.

Survival

Median follow-up time was 17.2 months (range, 2.4–59.5 months; median follow-up for alive patients was 39.8 months). At the last follow-up, 64 patients died: 59 of tumor progression, three of other diseases, one of serious infection after salvage liver transplantation, and one of an unknown cause without tumor progression. Overall, 75 PFS events were recorded. The mOS and mPFS were 16.5 months (95% confidence interval [CI], 14.1–19.0 months) and 6.1 months (95% CI, 3.8–8.3 months) (Fig. 2A). Two-year and 3-year overall survival (OS) were 36.6% and 25.3%, respectively, and those for progression-free survival (PFS) were 19.0% and 13.1%, respectively. Salvage therapies included surgery (five patients), transcatheter arterial

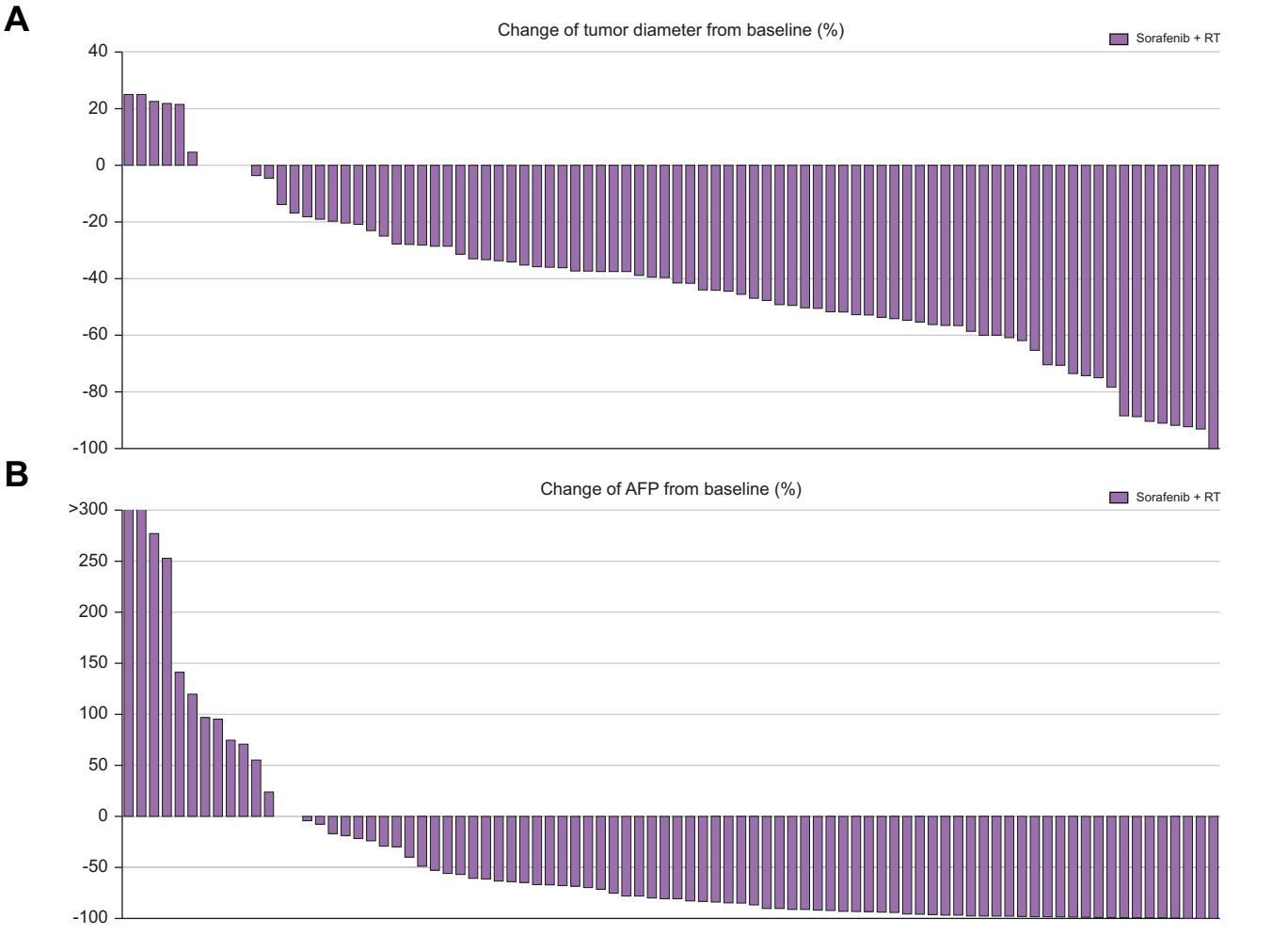

Fig. 1. Tumor diameter and AFP change. (A) Percent of tumor diameter change according RECIST criteria and (B) AFP change from the baseline. (The minimum value after treatment minus the value before treatment, and then divided by the value before treatment). Although 35 patients were evaluated as having progression disease, only six exhibited an increase in the total diameter of measurable lesions and 12 exhibit an increased AFP as a result of substantial regression of lesions within the radiation field. AFP, α-fetoprotein; RT, radiotherapy.

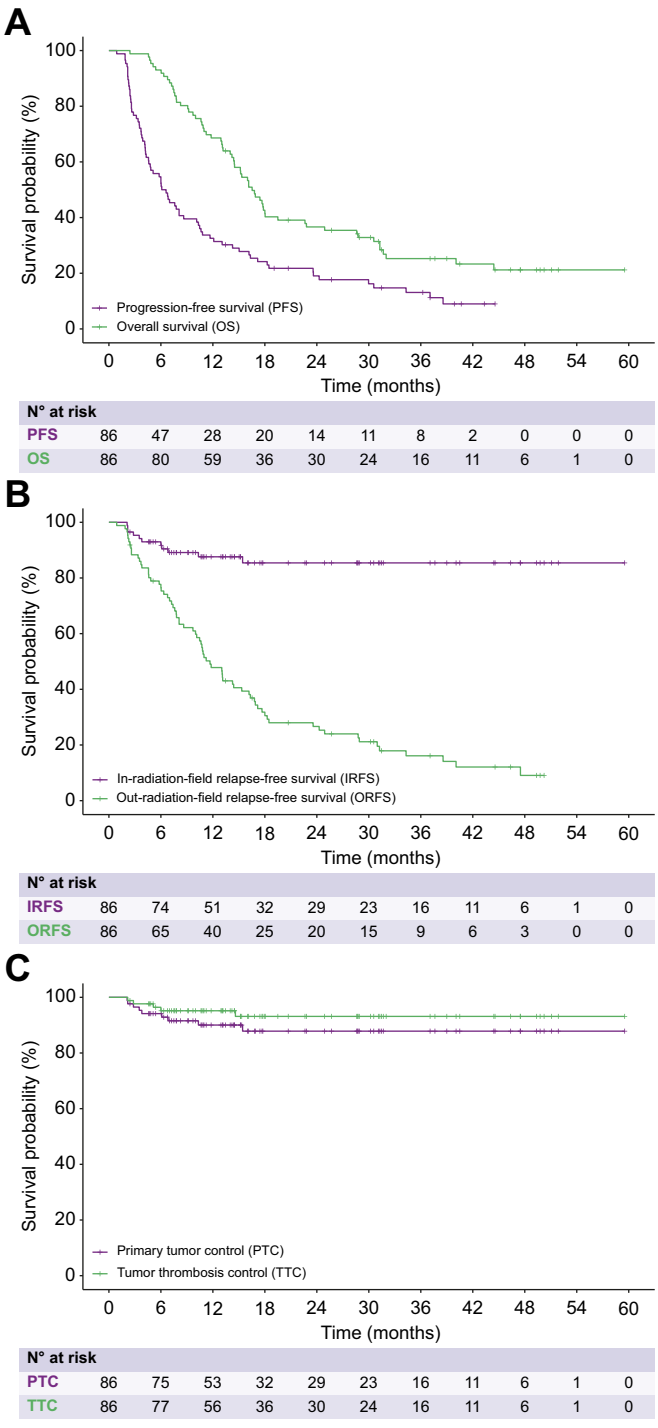

Fig. 2. Survival for concurrent sorafenib and radiotherapy for patients with hepatocellular carcinoma tumor thrombosis (using the Kaplan–Meier method). (A) OS and PFS; (B) IRFS and ORFS; (C) TTC and PTC. IRFS, in-radiation-field relapse-free survival; ORFS, out-radiation-field relapse-free survival; OS, overall survival; PFS, progression-free survival; PTC, primary tumor control; TTC, tumor thrombosis control.

chemoembolization (40 patients), radiofrequency ablation (four patients), other target therapies (27 patients), and immunotherapy (17 patients). Median TTP and 2- and 3-year tumor control were 6.8 months, 19.9%, and 13.1%, respectively. Eleven patients suffered from in-field recurrence, including six patients with primary tumor recurrence, two with tumor thrombus recurrence, and three with both. Outside of the radiation field, relapse was observed in 81 patients, including 32 with intrahepatic metastasis, 31 with extrahepatic metastasis, and 18 with both. Two- and 3-year IRFS were 85.4% and 85.4%, and 2- and 3-year ORFS were 26.3% and 16.1%, respectively (Fig. 2B). The long-term control within the radiation field was perfect either for primary tumors or tumor thrombosis. The 2-year and 3-year TTC were 93.1% and 93.1%, respectively, and 2-year and 3-year PTC were 87.8% and 87.8%, respectively (Fig. 2C).

Efficacy in different types of tumor thrombosis

Patients diagnosed with TVTT3 had similar mOS (32.0 months *vs.* 31.2 months, $p = 0.946$, Fig. 3A), mPFS (15.0 months *vs.*

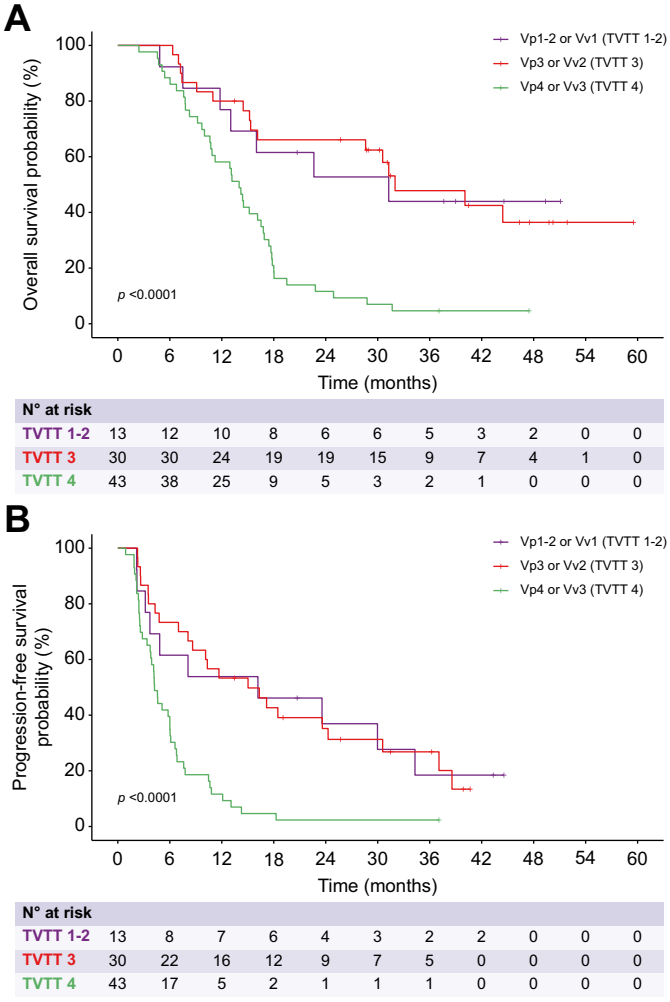

Fig. 3. Survival for different types of TVTT. (A) OS and (B) PFS between different types of TVTT, considering portal vein and/or hepatic vein tumor thrombosis. Levels of significance in OS: TVTT3 *vs.* TVTT1-2, $p = 0.946$; TVTT4 *vs.* TVTT3 $p < 0.001$ (Log-rank test). Levels of significance in PFS: TVTT3 *vs.* TVTT1-2, $p = 0.976$, TVTT4 *vs.* TVTT3 $p < 0.001$ (Log-rank test)] TVTT1, Vp1 (segmental portal vein tumor thrombosis) or Vv1 (peripheral hepatic microvascular tumor thrombosis); TVTT2, Vp2 (the second branch of portal vein tumor thrombosis); TVTT3, Vp3 (right or left portal vein tumor thrombosis) or Vv2 (right, middle, or left hepatic vein tumor thrombosis); TVTT4, Vp4 (main trunk portal tumor thrombosis) or Vv3 (inferior vena cava or heart atrium tumor thrombosis). Median PFS (15.0 months *vs.* 16.2 months, $p = 0.976$, [B]). OS, overall survival; PFS, progression-free survival; TVTT, total vein tumor thrombosis.

16.2 months, p = 0.976, Fig. 3B), TTP (15.0 months *vs.* 16.2 months, p = 0.832), IRFS (both not reached, p = 0.873), and ORFS (17.2 months *vs.* 16.2 months, p = 0.795), compared with those diagnosed with TVTT1–2. In contrast, prolonged mOS, mPFS, TTP, and ORFS were observed in patients with TVTT3 compared with those with TVTT4 (mOS 14.0 months, p <0.001, Fig. 3A; mPFS 4.2 months, p <0.001, Fig. 3B; TTP 4.6 months, p <0.001; ORFS 10.0 months, p <0.001).

Prognostic factors

Univariate analysis revealed that ECOG ≥1, multi-foci intrahepatic disease, and maximum diameter >10 cm were associated with worse OS, whereas radiation biological equivalent dose >60 Gy for GTV was associated with prolonged PFS (Table 3). Patients with ALBI grade 1 had better OS and PFS. In contrast, patients with TVTT4 disease had worse OS and PFS. Furthermore, the existence of out-of-radiation field intrahepatic lesions was a negative prognostic factor for both OS and PFS (Fig. 4A and B).

In multivariable analysis, TVTT4 was the only independent prognostic factor for both OS (p <0.001) and PFS (p <0.001). The existence of out-of-radiation field intrahepatic lesions was an independent prognostic factor for PFS (p = 0.006).

Adverse events

The AEs during or after combined sorafenib and radiotherapy were listed in Table 4. The typical specific AE was dermatitis within radiation field during concurrent radiation and sorafenib (Fig. S2). The dermatitis usually begins to appear at the 6th fraction (ranged from the 5th to the 9th fraction), becomes most severe between the 15th and 20th fraction of radiation, and then gradually subsides. Among all patients, 35 (40.7%), 12 (14.0%), and four (4.7%) experienced grade 1, grade 2, and grade 3 dermatitis, respectively. This type of dermatitis did not influence the radiotherapy, but in two patients, sorafenib was temporarily discontinued for 5–7 days for dermatitis before resuming the medication. The most common AE was leukopenia, followed by bilirubin increment and thrombocytopenia. Grade 4 AEs were observed in six patients (7.0%), comprising three (3.5%) with hematological and non-hematological AEs each. Grade 3 AEs were observed in 40 patients (46.5%), including 23 (26.7%) with grade 3 hematological AEs alone, 10 (11.6%) with non-hematological AEs, and seven (8.1%) with both. Patients who had grade 3–4 AEs were relieved after therapies, and no grade 5 AEs were recorded. All grade 3 or higher AEs were observed during radiation and within 6 months

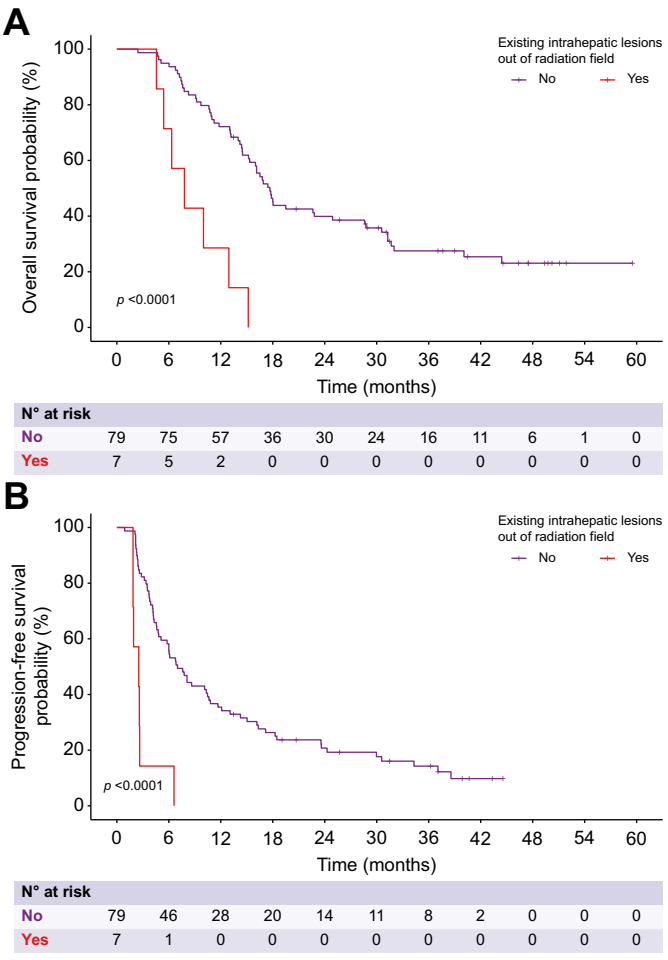

Fig. 4. Survival in patients with and without intrahepatic lesions out of the radiation field. (A) OS and (B) PFS in patients with and without intrahepatic lesions out of the radiation field. Levels of significance: OS: p <0.001; PFS: p <0.001; (Log-rank test). OS, overall survival; PFS, progression-free survival.

Table 3. Univariate analysis of the overall survival and progression-free survival.

	mOS (months)			mPFS (months)		
Prognostic factor	**Yes**	**No**	***p* value**	**Yes**	**No**	***p* value**
Male	16.5	31.7	0.480	6.0	8.1	0.297
Age >60 years	16.8	16.1	0.190	4.8	6.8	0.330
ECOG ≥1	14.5	17.8	0.036	4.8	10.5	0.165
Hepatitis	16.5	11.0	0.388	6.6	4.8	0.736
AFP ≥1,000 ng/ml	14.5	18.0	0.150	4.1	10.1	0.069
ALBI grade 1	28.6	14.0	0.002	8.6	4.2	0.011
Multi-foci	14.0	22.6	0.029	4.3	8.6	0.070
TVTT4	14.0	32.0	<0.001	4.2	16.2	<0.001
Dmax >10 cm	14.4	17.8	0.014	4.6	7.8	0.125
ORF lesion	7.8	17.7	<0.001	2.5	7.0	<0.001
BED >60 Gy	17.4	14.5	0.054	7.8	4.1	0.036
First line therapy	14.5	18.0	0.066	5.1	6.7	0.291

ALBI, albumin–bilirubin grade; AFP, α-fetoprotein; BED, biological equivalent dose for gross tumor volume (GTV); Dmax, the maximum diameter of tumor; ECOG, Eastern Cooperative Oncology Group Performance Status score; mPFS, median progression-free survival time; mOS, median overall survival time; ORF lesion, existing intrahepatic lesions out of radiation field; TVTT4, main portal trunk or inferior vena cava or heart atrium invasion.

Table 4. Adverse events from any cause.

	No. of patients (%)				
AEs	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Total**
Skin rash	9 (10.5)	4 (4.7)	3 (3.5)	–	16 (18.6)
Diarrhea	13 (15.1)	13 (15.1)	1 (1.2)	0 (0.0)	27 (31.4)
Hypertension	10 (11.6)	1 (1.2)	0 (0.0)	0 (0.0)	11 (12.8)
Dermatitis	35 (40.7)	12 (14.0)	4 (4.7)	0 (0.0)	51 (59.3)
Hand-foot syndrome	5 (5.8)	4 (4.7)	7 (8.1)	–	16 (18.6)
Anorexia	53 (61.6)	4 (4.7)	0 (0.0)	0 (0.0)	57 (66.3)
Nausea	9 (10.5)	0 (0.0)	0 (0.0)	–	9 (10.5)
Infection	0 (0.0)	5 (5.8)	0 (0.0)	0 (0.0)	5 (5.8)
GI hemorrhage	0 (0.0)	1 (1.2)	1 (1.2)	0 (0.0)	2 (2.3)
Leukopenia	30 (34.9)	25 (29.1)	12 (14.0)	2 (2.3)	69 (80.2)
Thrombocytopenia	15 (17.4)	22 (25.6)	19 (22.1)	1 (1.2)	57 (66.3)
Anemia	31 (36.0)	8 (9.3)	3 (3.5)	0 (0.0)	42 (48.8)
ALT increased	29 (33.7)	6 (7.0)	2 (2.3)	0 (0.0)	37 (43.0)
AST increased	41 (47.7)	5 (5.8)	8 (9.3)	1 (1.2)	55 (64.0)
Blood bilirubin increased	46 (53.5)	12 (14.0)	2 (2.3)	1 (1.2)	61 (70.9)
Hypoalbuminemia	43 (50.0)	7 (8.1)	3 (3.5)	1 (1.2)	54 (62.8)

AEs, adverse events; ALT, alanine aminotransferase; AST, aspartate transaminase; GI, gastrointestinal.

after radiation. No extra grade 3 or higher AE was observed after that time. After 6 months post-radiotherapy, common adverse effects induced by sorafenib, including rash in nine patients, hand-foot syndrome in six, and diarrhea in two, persisted throughout the duration of sorafenib administration.

Discussion

Our prospective study, the first one to examine concurrent radiotherapy and sorafenib for HCC patients with PVTT/HVTT, showed promising results. Focusing on OS as the primary endpoint, we demonstrated significant longevity, exceeding the prespecified goal. We found favorable ORR (52.3%) in both primary tumors (83.7%) and tumor thrombosis (87.2%) in the radiotherapy field. Moreover, we achieved sustained TTC over 3 years and favorable PFS despite including patients with Vp4, typically excluded from similar HCC studies.[19–21] We also observed that more than a half of the patients in our study received sorafenib and radiation as non-first-line therapy, and 7% of the patients had M1-stage disease. This indicates that concurrent sorafenib and radiation could be an effective and favorable treatment option for HCC patients with tumor thrombosis.

Our study achieved more promising ORR, prolonged mOS, and mPFS outcomes with concurrent radiation plus sorafenib in patients with PVTT/HVTT than with either single treatment. Studies using sorafenib alone showed 2–13.3% ORR, 4.2–15.2 months mOS, and 2.5–4.9 months mPFS.[6–26] Furthermore, several small studies used radiation alone in treating patients with PVTT, which resulted in 74–77.4% ORR in tumor thrombosis, 7–12.5 months mOS, and 3 months mPFS.[27–29] These comparative results strengthened the theoretical hypothesis that combined sorafenib and radiotherapy have enhanced efficacy against PVTT/HVTT. Until 2023, RTOG 1112 demonstrated that adding SBRT improved mOS (15.8 months) and mPFS (9.2 months) in patients with advanced HCC, compared with sorafenib alone, without the increment of AEs.[30] Our team also reported satisfactory mOS (15.8 months) and mPFS (4.2 months) after combining radiotherapy and systemic therapy in treating patients with HCC with hepatic vein and/or inferior vena cava tumor thrombosis.[31] This study was consistent with the previous two studies.[30,31] Meanwhile, typically favorable IRFS was reported in our study, representing satisfying sensitivities.

In the past 5 years, extensive evidence on emerging systemic treatment regimens for HCC has been accumulated. Compared with sorafenib, lenvatinib achieved a higher ORR and equivalent OS and PFS.[19] IMbrave150 showed that treatment with atezolizumab plus bevacizumab resulted in significantly better OS and PFS compared with sorafenib in advanced HCC.[9,32] Similar conclusions were drawn by CARES-310 and ORIENT-32.[25,26] The efficacy and survivals of systemic therapies are summarized in Table S1.[9,19–22,25,26,32–37] The percentages of tumor thrombosis reported in various clinical studies of systemic therapies ranges from 11 to 43%. Despite all patients having tumor thrombosis and 84.9% having Vp3–4 or Vv2–3, our study still showed better ORR, OS, and PFS compared with other systemic therapies. In terms of different subtypes of tumor thrombosis, the addition of radiation to sorafenib also demonstrated significant benefits. In our study, patients with TVTT3 exhibited optimal survival outcomes, with a mOS of 32.0 months and mPFS of 15.0 months. The mOS of TVTT4 was notably 14.0 months, better than those in historical reports. Even in the IMbrave 150 subgroup analysis, 48 patients designated as Vp4 who were treated with atezolizumab plus bevacizumab had an mOS of only 7.6 months.[10]

Radiation plus sorafenib effectively controlled the most lethal factors-tumor thrombosis, while achieving a lower bleeding rate of 2.3% by reducing portal pressures. Clinically, we observed that this combination effectively managed both the primary tumor and tumor thrombosis (Figs. S3A–D), in contrast to systemic therapies that addressed the primary tumor but not thrombosis usually (Figs. S3E–H). Therefore, for patients with Vp4/Vv3, combining radiation with sorafenib as an initial treatment, followed by other systemic therapies as the second line, warrants further investigation.

Meanwhile, combined radiation and sorafenib achieved more favorable ORR and OS and similar TTP compared with interventional therapies (ORR 5.0–53.1%, mOS 5.0–14.9 months, mPFS 2.0–2.3 months, and TTP 3.1–6.2 months).[24,38–41] A study using radiation plus HAIC reported a 50% response rate when evaluating tumor thrombosis alone.[42] Compared with that, the response rate of tumor thrombosis in

our study was more remarkable. We should also note that some of these studies eliminated patients with severe Vp4/Vv3.[41]

Modern intensity-modulated radiation technology allows safer radiotherapy for HCC patients with larger tumors in advanced stage.[43] The AE profile of combined radiotherapy and sorafenib in our study largely mirrored that of sorafenib alone in patients with HCC, showing no increment in grade 3 or higher AEs.[6,19] Our study reported any grade elevation of AST (64.0% *vs.* 17%) and increased bilirubin (70.9% *vs.* 13%) compared with those in patients who received sorafenib alone, but grade ≥3 AEs were not increased (elevated AST 10.5% *vs.* 8%, increased bilirubin 3.5% *vs.* 5%).[19] A significantly higher thrombocytopenia rate was observed in our study compared with historical report of sorafenib alone (66.3% *vs.* 12% for any grade; 23.3% *vs.* 3% for grade ≥3), attributed partly to baseline thrombocytopenia (27.9% for any grade, 3.5% for grade ≥3) linked to HCC with macrovascular invasion. Dermatitis was consistent with prior evidence on radiation plus sorafenib-induced AEs, but higher than radiation alone for potential enhanced radiosensitivity by sorafenib.[27] Hepatic grade 3–4 AEs (10.5%) in our study was not increased than that using radiation alone (14.1%),[29] probably because we controlled the normal liver dose more strictly (Supplementary data). Most of the patients had good baseline liver function, which might have contributed to the limited AEs.

The trial exhibited some limitations: the lack of a control group undermined its evidence level; variable timing between radiotherapy and systemic therapy obscured conclusions on optimal combination and timing. Despite radiation's efficacy in controlling tumor thrombosis locally, relapses outside the radiation field are a critical issue.

The study was initiated in 2018, identifying sorafenib as the only systemic treatment for HCC. However, current therapies, including lenvatinib, atezolizumab, and bevacizumab, offer superior survival. Given the frequent out-of-field relapse and positive outcomes in IMbrave150 and REFLECT, integrating immunotherapy or lenvatinib need to be considered.[19,32] Consequently, we proposed a phase II trial on concurrent lenvatinib and radiotherapy for advanced HCC (NCT04791176) and a phase III trial comparing radiotherapy plus toripalimab to sorafenib in HCC with PVTT (NCT04709380), potentially benefiting HCC patients.

Conclusions

The addition of radiation to sorafenib in an advanced population of HCC with macrovascular invasion showed favorable responses, OS, PFS, tumor thrombosis control, and tolerable AEs.

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Abbreviations

AEs, adverse events; ALBI, albumin–bilirubin; ALT, alanine aminotransferase; AFP, α-fetoprotein; AST, aspartate transaminase; CT, computed tomography; CTV, clinical target volume; ECOG PS, Eastern Cooperative Oncology Group performance status; GTV, gross tumor volume; HCC, hepatocellular carcinoma; HVTT, hepatic vein tumor thrombosis; IRFS, in-radiation-field relapse-free survival; mPFS, median progression-free survival; mRECIST, modified Response Evaluation Criteria in Solid Tumors; MRI, magnetic resonance imaging; OAR, organs at risk; ORFS, out-radiation-field relapse-free survival; ORR, overall response rate; OS, overall survival time; PFS, progression-free survival; PTC, primary tumor control; PTV, planning target volume; PVTT, portal vein tumor thrombosis; RECIST, Response Evaluation Criteria in Solid Tumors; TTC, tumor thrombosis responses and control; TTP, time to tumor progression; TVTT, total vein tumor thrombosis; ULN, upper limit of normal; Vp1, segmental portal vein invasion; Vp2, the second branch of portal vein invasion; Vp3, right or left portal vein invasion; Vp4, main trunk portal vein invasion; Vv1, hepatic microvascular invasion; Vv2, right, middle or left hepatic vein invasion; Vv3, inferior vena cava or heart atrium invasion.

Financial support

This work was supported by the Beijing Natural Science Foundation (grant number 7222151), National Key Research and Development Program of China (grant number 2017YFC0112103), CAMS Innovation Fund for Medical Sciences (CIFMS) (grant number 2021-I2M-1-066), Beijing Hope Run Special Fund of the Cancer Foundation of China (grant number LC2022A03), and National High Level Hospital Clinical Research Funding (2022-CICAMS-80102022203).

Conflicts of interest

The authors declare that they have no competing interests.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Designed the study: YZ, LW, HZhao, YXL, JWu, BC. Collected the data: YZ, FW, LX. Enrolled patients, collected the data, and made treatment decisions: YZ, LW, HZhao, FW, WS, YS, HZeng, JWang, JWu, SW, YT, HF, YL, NL, SQ, HJ, WZ, YS. Evaluated the responses and adverse events: YZ, FY, LN, BC. Finished follow ups: YZ, LX. Finished the analysis and interpretation of data: YZ, LW, HZhao, YXL, JWu, BC. Finished statistical analysis: YZ, FW, LX. Supervised the study: HZhao, YXL, JWu, BC. Wrote and reviewed the manuscript: YZ, LW, HZhao, YXL, JWu, BC. Contributed to the article and approved the submitted version: all authors.

Data availability statement

The data generated in the current study are available from the corresponding author on reasonable request.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhepr.2024.101287.

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Keywords: Sorafenib; Radiotherapy; Hepatocellular carcinoma; Tumor thrombosis.
Received 2 September 2024; received in revised form 1 November 2024; accepted 20 November 2024; Available online 28 November 2024