Original Article

Efficacy and safety of subsequent radiotherapy in patients with advanced-stage hepatocellular carcinoma treated with immune checkpoint inhibitors

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Background: The development of immunotherapy resistance is associated with a poor prognosis in patients diagnosed with hepatocellular carcinoma (HCC) who are undergoing treatment with immune checkpoint inhibitors (ICI). This study aimed to evaluate the efficacy and safety of subsequent radiotherapy (RT) for patients with advanced-stage HCC who had lesion enlargement or new lesions (NLs) during ICI therapy.

Methods: This retrospective observational study enrolled 36 patients with advanced-stage HCC who underwent subsequent RT for lesion enlargement or NLs during ICI therapy from two centers. The primary endpoints were progression-free survival (PFS) and overall survival (OS). The secondary endpoints included objective response rate (ORR), disease control rate (DCR), 1- and 2-year local control (LC) rates, in-field PFS (IFPFS), out-field PFS (OFPFS), and safety.

Results: The median follow-up time was 15.3 months. The median PFS was 7.4 months [95% confidence interval (CI): 3.1–11.7 months], and the median OS was 18.8 months (95% CI: 17.1–20.5 months). ORR and DCR were 38.9% and 72.2%, respectively. In addition, the median IFPFS was 17.8 months (95% CI: 11.5–24.2 months), median OFPFS was 7.9 months (95% CI: 3.4–12.5 months), and estimated 1- and 2-year LC rates were 67.1% and 31.9%, respectively. The most common treatment-related adverse events (all grades) were diarrhea (33.3%), rash (30.6%), and malaise (27.8%); a total of 14 (38.9%) patients developed grade 3–4 AEs.

Conclusions: Subsequent RT showed reliable antitumor effects and an acceptable safety profile in patients with advanced-stage HCC who had unsatisfactory response to ICI therapy; therefore, it could serve as an optional salvage strategy.

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Keywords: Subsequent radiotherapy; immunotherapy; immune checkpoint inhibitors (ICIs); disease status; advanced-stage hepatocellular carcinoma

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Introduction

Background

Hepatocellular carcinoma (HCC) is a major cause of cancer-related mortality worldwide, ranking third in frequency (1). Unfortunately, most patients are diagnosed at an advanced stage, thereby lacking curative treatment options (2,3). Immunotherapy with immune checkpoint inhibitors (ICIs) has changed the landscape of HCC management (4). However, compared with sorafenib or placebo, monotherapy with nivolumab or pembrolizumab—anti-programmed death protein 1 (PD-1) humanized antibodies—has demonstrated unsatisfactory efficacy in patients with relapsed or refractory HCC (5,6). Therefore, combinations of ICI therapy and strategies capable of overcoming immunotherapy resistance are being widely applied to improve the response rate and survival of patients with HCC (7).

Highlight box

Key findings

- Subsequent radiotherapy (RT) showed reliable efficacy and acceptable safety as a salvage treatment strategy for patients with advanced-stage hepatocellular carcinoma (HCC) who have lesion enlargement or new lesions during immune checkpoint inhibitor (ICI) therapy.

What is known and what is new?

- There is no consensus on the subsequent treatment of patients with advanced-stage HCC who have lesion enlargement or new lesions during immunotherapy. RT + immunotherapy can reverse the immunosuppressive state of tumors and enhance immune response and antitumor effects.
- Subsequent RT can serve as a salvage strategy for advanced-stage HCC treated with ICI.

What is the implication, and what should change now?

- Despite numerous ICI-based systemic treatment regimens, salvage strategy for patients with lesion enlargement or new lesions during ICI therapy is lacking. We propose alternative salvage strategies for such patients, emphasizing the need to optimize fractionation, dose, and commencement date of subsequent RT.

Rationale and knowledge gap

Radiotherapy (RT) not only induces DNA damage and endoplasmic reticulum stress, which ultimately results in the death of tumor cells, but also leads to non-targeted and systemic effects (8). Accumulating evidence suggests that the immunogenic effects of RT, when combined with immunotherapy, can reverse the immunosuppressive state of tumors and enhance immune response and antitumor effects (9-11). In other words, subsequent RT may result in resensitization to immunotherapy. However, studies related to the use of RT as a salvage strategy for advanced-stage HCC are lacking.

Objective

This retrospective study aimed to evaluate the efficacy and safety of subsequent RT in patients with advanced-stage HCC who had lesion enlargement or new lesions (NLs) during ICI therapy. We present this article in accordance with the STROBE reporting checklist (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-23-134/rc).

Methods

Study design and patients

We conducted a retrospective analysis of 140 patients diagnosed with unresectable HCC and treated with a combination of ICI therapy and RT between June 2019 and June 2022 in Peking Union Medical College Hospital (PUMCH) and Fifth Medical Center of the People's Liberation Army General Hospital (PLAGH). This study adhered to the principles outlined in the Declaration of Helsinki (as revised in 2013) and was approved by the Institutional Review Board of PUMCH (No. S-K2097). Owing to the retrospective nature and lack of identifiable patient information, the requirement for informed consent was waived.

Patients with histologically or radiologically confirmed HCC with macrovascular invasion or extrahepatic metastasis [i.e., Barcelona Clinic Liver Cancer (BCLC)

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C stage]; age of ≥18 years; an Eastern Co-operative Group (ECOG) performance score of ≤2; a Child-Pugh classification of A–B; lesion enlargement or NLs confirmed by imaging examination [contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI)] after treatment with ≥2 cycles of ICIs; durative ICI therapy after initiation; and a history of treatment, except RT, were considered eligible. Patients who commenced RT within 6 weeks from the initiation of ICI treatment, which was defined as concurrent RT, who discontinued ICI therapy after RT, or with incomplete medical information were excluded (12).

Treatment

ICI therapy was initiated either simultaneously or sequentially with antiangiogenic agents. The ICIs atezolizumab, pembrolizumab, camrelizumab, sintilimab, toripalimab, or tislelizumab were allowed, and 200 mg (atezolizumab: 1,200 mg and toripalimab: 240 mg) was administered intravenously every 3 weeks. The antiangiogenic agents bevacizumab (15 mg/kg), lenvatinib (12 mg), sorafenib (400 mg), donafenib (400 mg), apatinib (750 mg), or regorafenib (160 mg) were administered intravenously every 3 weeks or orally once a day (dose was determined according to the patients' body weight). Systemic therapy was not interrupted during RT unless intolerable or grade 3–4 adverse events (AEs) were observed.

For intensity-modulated radiation therapy (IMRT; Truebeam, version 2.7, Varian Medical Systems, Palo Alto, USA), CT combined with silver indication, was performed to define the clinical target volume (CTV), which refers to the tumor bed plus a 1.0-cm margin. The planning target volume (PTV) was determined by expanding CTV by 0.6–0.8, 0.5–0.7, and 0.8–1.0 cm in the anterior–posterior, left–right, and cranial–caudal directions, respectively. The prescribed doses were 30–70 Gy/5–30 fractions, which covered 95% of PTV.

Before initiating stereotactic body radiation therapy (G4 CyberKnife, Accuracy, USA), 4–6 fiducial markers were implanted to determine treatment location based on CT simulation images. PTV expanded the gross tumor volume (GTV) by 0.3–0.5 cm. The prescribed doses were 24–50 Gy/3–10 fractions, and the isodose curve enclosed 100% of GTV.

A biologically effective dose (BED) calculated based on Eq. [1] was used to determine the correlation of various RT fractions with therapeutic efficacy:

$$BED_{10} = n \times d \times \left(1 + \frac{d}{\alpha / \beta}\right) \quad [1]$$

where n represents the number of fractions and d represents the fraction size. For liver tumors, an α/β ratio of 10 Gy was assumed.

Patients with intrahepatic progressive lesions (n≤3), which were confined to the same lobe, or extrahepatic oligometastases (n≤5) were deemed ineligible for curative resection or standard locoregional treatment, such as transarterial chemoembolization (TACE) and radiofrequency ablation (RFA), due to the BCLC C stage; they underwent multidisciplinary evaluation before RT initiation. Appropriate ICI therapy, antiangiogenic agent therapy, and RT regimen were determined jointly by physicians and patients based on real-world experience. The indications for RT in advanced-stage HCC included unresectable macroscopic vessel tumor thrombus; symptomatic metastatic lesions such as bone, soft tissue, and retroperitoneal lymph node; and lesions causing mass effect and/or located away from the gut among oligometastases such as hepatic portal lymph node, adrenal gland, and pelvic metastases. In addition, sequential delivery of RT was considered when target lesions located in more than two organs to enhance treatment tolerance.

Assessment

Contrast-enhanced CT and/or MRI were performed 1 month after RT, every 6–8 weeks for the first 2 years, and every 6 months thereafter. Along with the imaging data, physical examinations and laboratory tests were also performed. The primary endpoints were progression-free survival (PFS) and overall survival (OS), whereas the secondary endpoints included objective response rate (ORR), disease control rate (DCR), 1- and 2-year local control (LC) rates, in-field PFS (IFPFS), out-field PFS (OFPFS), and safety. The overall and in-field tumor responses were assessed according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST) guidelines (13). ORR and DCR were defined as the rates of complete response (CR) + partial response (PR) or CR + PR + stable disease (SD) in terms of whole-body response and in-field response, respectively. Best objective response was defined as the best whole-body response compared with baseline. PFS was defined as the duration from the date the first dose of ICI (PFS1) or RT (PFS2) initiation to

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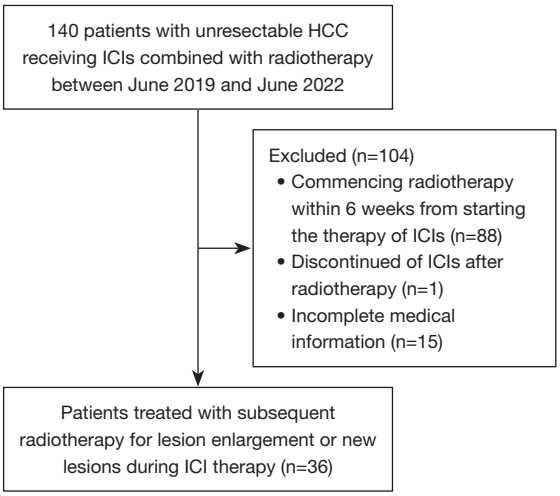

Figure 1 Patient flowchart. HCC, hepatocellular carcinoma; ICIs, immune checkpoint inhibitors.

that of progressive disease (PD), death from any cause in the absence of progression, or last follow-up. A PFS2/PFS1 ratio of ≥1.3 was used to indicate the therapeutic benefits of RT (14,15). The disease status before RT included residual lesions [RLs; defined as an increase of 10–19% in the sum of the diameters of viable (enhancing) RLs], progression of existing lesions [PELs; defined as an increase of at least 20% in the sum of the diameters of viable (enhancing) existing lesions], and NLs (defined as the appearance of one or more NLs). LC was defined as the absence of progression or recurrence within the irradiated volume and was evaluated based on IFPFS (16). OFPFS was defined as the duration between the initial date of RT and the date of disease progression outside the irradiated volume (17). OS was defined as the time from RT initiation to death from any cause. Treatment-related AEs (TRAEs) were graded using the US National Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0). Acute and late toxicities were defined as TRAEs occurring within and after 90 days of RT, respectively.

Statistical analyses

Continuous variables are expressed as median and range. The ordinal variable was analyzed using the Friedman test. PFS, OS, and IFPFS were estimated using the Kaplan-Meier method. Cox proportional hazards regression models were used to assess the potential predictors of PFS, OS, IFPFS, and OFPFS. All data were analyzed using R (version 4.0.3, Vienna, Austria), and a two-tailed P value of less than 0.05 was deemed statistically significant.

Results

Patient characteristics

Between June 2019 and June 2022, 36 patients with advanced-stage HCC who underwent subsequent RT during ICI treatment (PUMCH group =26 and PLAGH group =10) were included in this study (*Figure 1*). The baseline characteristics are summarized in *Table 1*. Their median age was 52 years, and 34 (94.4%) patients were men. The most common etiology of HCC was hepatitis B virus (HBV)/hepatitis C virus infection (97.2%), and most patients (80.6%) had an ECOG performance status score of 0–1. A total of 32 patients (88.9%) had Child-Pugh class A disease and 16 (44.4%) had an ALBI (albumin-bilirubin) score of 1. At baseline, 22 (61.1%) patients exhibited portal invasion, whereas 23 (63.9%) patients exhibited extrahepatic spread. In total, 38.9% and 86.1% of patients previously underwent hepatectomy and hepatic local treatment, respectively. Overall, 22 patients (61.1%) progressed after receiving first-line ICIs and 14 (38.9%) received ≥2 lines of systemic therapy before study enrollment. The median PFS1 was 4.1 months [95% confidence interval (CI), 1.2–7.0 months] and median interval between ICIs and RT was 5.0 months (range, 1.6–24.1 months). During this interval, patients received multiple lines of combination therapy, including RFA, TACE, and antiangiogenic treatments, due to disease progression. Except the 4 patients who temporarily interrupted and switched ICIs due to intolerance or disease progression, all other patients received continuous immunotherapy. Overall, 25.0% of patients had NL, 52.8% had PEL, and 22.2% had RL.

Treatment

A total of 34 patients completed RT on schedule combined with systemic therapy, whereas two patients discontinued therapy due to decreased platelet count and ascites, respectively. These 2 HBV-infected patients with cirrhosis eventually received 2,750- and 3,000-cGy radiation and resumed systemic therapy after 4 and 2 weeks, respectively. The RT details are summarized in *Table 2*. Four patients had incomplete RT-related data. RT was mainly delivered to portal or hepatic vein tumor thrombus in 17 (47.2%) patients and to liver lesions in 13 (36.1%) patients. Among

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Table 1 Baseline characteristics of the study cohort (n=36)

Characteristics	Values
Age (years), median [range]	52 [21–70]
Sex, n (%)	
Male	34 (94.4)
Female	2 (5.6)
Virus infection, n (%)	
Positive	35 (97.2)
Negative	1 (2.8)
ECOG performance, n (%)	
0–1	29 (80.6)
2	7 (19.4)
Serum AFP level (ng/mL), n (%)	
<400	21 (58.3)
≥400	15 (41.7)
Child-Pugh class, n (%)	
A	32 (88.9)
B	4 (11.1)
ALBI score, n (%)	
1	16 (44.4)
2	20 (55.6)
Portal invasion, n (%)	
Absent	14 (38.9)
Present	22 (61.1)
Extrahepatic spread, n (%)	
Absent	13 (36.1)
Present	23 (63.9)
Prior hepatectomy, n (%)	
Absent	22 (61.1)
Present	14 (38.9)
Prior hepatic local treatment, n (%)	
Absent	5 (13.9)
Present	31 (86.1)
Maximal tumor diameter (cm), n (%)	
<10	27 (75.0)
≥10	9 (25.0)
Tumor number, n (%)	
<3	11 (30.6)
≥3	25 (69.4)
Disease status, n (%)	
NL	9 (25.0)
PEL	19 (52.8)
RL	8 (22.2)
Lines of ICIs, n (%)	
1	22 (61.1)
≥2	14 (38.9)
PFS1[†] (months), median [95% CI]	4.1 [1.2–7.0]
Interval between ICIs and RT (months), median [range]	5.0 [1.6–24.1]

[†]PFS1, PFS during immunotherapy before radiotherapy. ECOG, Eastern Co-operative Oncology Group; AFP, α-fetoprotein; ALBI, albumin-bilirubin; NL, new lesion; PEL, progression of existing lesion; RL, residual lesion; ICIs, immune checkpoint inhibitors; PFS, progression-free survival; CI, confidence interval; RT, radiotherapy.

Table 2 Details of radiotherapy (n=36)

Radiotherapy parameters	Values
Radiotherapy site, n (%)	
PVTT or HVTT	17 (47.2)
Liver lesions	13 (36.1)
Extrahepatic metastasis	7 (19.4)
Bone or soft tissue metastasis	5 (13.9)
Lymph nodes	4 (11.1)
Total prescribed dose (gray)[†], median [range]	48 [24–70]
Radiotherapy fraction[‡], median [range]	10 [3–30]
BED_{10} (gray)[§], median [range]	60 [34.4–87.5]
Radiotherapy technique, n (%)	
IMRT	22 (61.1)
SBRT	14 (38.9)

[†,‡,§], details of radiotherapy were missing for 4 of the 36 patients. PVTT, portal vein tumor thrombus; HVTT, hepatic vein tumor thrombus; BED_{10}, biologically effective dose at an alpha/beta ratio of 10; IMRT, intensity modulated radiotherapy; SBRT, stereotactic body radiotherapy.

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the 13 patients, 9 only received RT for intrahepatic lesions and the other 4 had extrahepatic irradiated lesions. The median RT fraction and BED_{10} were 10 (range, 3–30) and 60 Gy (range, 34.4–87.5 Gy), respectively. RT was performed using the IMRT method in 61.1% of the patients.

Table 3 Therapeutic efficacy

Therapeutic response assessment (N=36)	Response 1 (before RT)[†]	Response 2 (after RT)[‡]
CR, n (%)	0	2 (5.6)
PR, n (%)	6 (16.7)	12 (33.3)
SD, n (%)	23 (63.9)	12 (33.3)
PD, n (%)	7 (19.4)	10 (27.8)
ORR, n (%)	6 (16.7)	14 (38.9)
DCR, n (%)	29 (80.6)	26 (72.2)

[†,‡], the best whole-body response per mRECIST compared with baseline before commencement of immunotherapy (Response 1) and radiotherapy (Response 2), respectively. CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate; RT, radiotherapy.

Efficacy

In the intention-to-treat analysis of 36 patients who received RT, 2 patients achieved CR, 12 achieved PR, and 12 had SD, as assessed in accordance with mRECIST per independent central review (ORR 38.9%, DCR 72.2%; *Table 3*). However, the best objective response achieved during ICI therapy before RT had an ORR of 16.7%. A summary of the therapeutic effects is shown in *Figure 2*. Sixteen (57.1%) of the patients (n=28) with PEL and NL achieved a PFS2/PFS1 ratio of ≥1.3. Three (30.0%) of the patients (n=10) with PD after RT achieved a PFS2/PFS1 ratio of ≥1.3. Overall, 23 (63.9%) patients achieved therapeutic benefits from RT. Five (13.9%) patients achieved disease-free survival (DFS) after undergoing sequential downstaging surgery.

At the time of data cutoff (November 20, 2022), the median follow-up duration was 15.3 months (95% CI: 10.8–19.8 months), and 29 patients (80.6%) died or

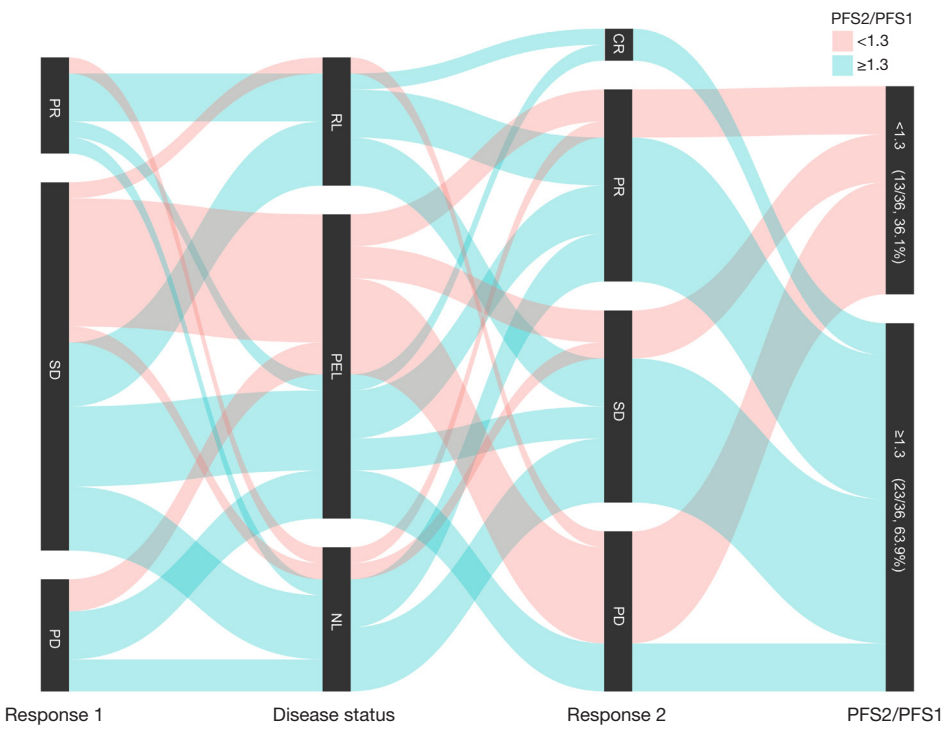

Figure 2 Flow diagram. The best whole-body response per mRECIST compared with baseline before commencement of immunotherapy (Response 1) and radiotherapy (Response 2), respectively. PR, partial response; SD, stable disease; PD, progressive disease; RL, residual lesion; PEL, progression of existing lesion; NL, new lesion; CR, complete response; PFS, progression-free survival.

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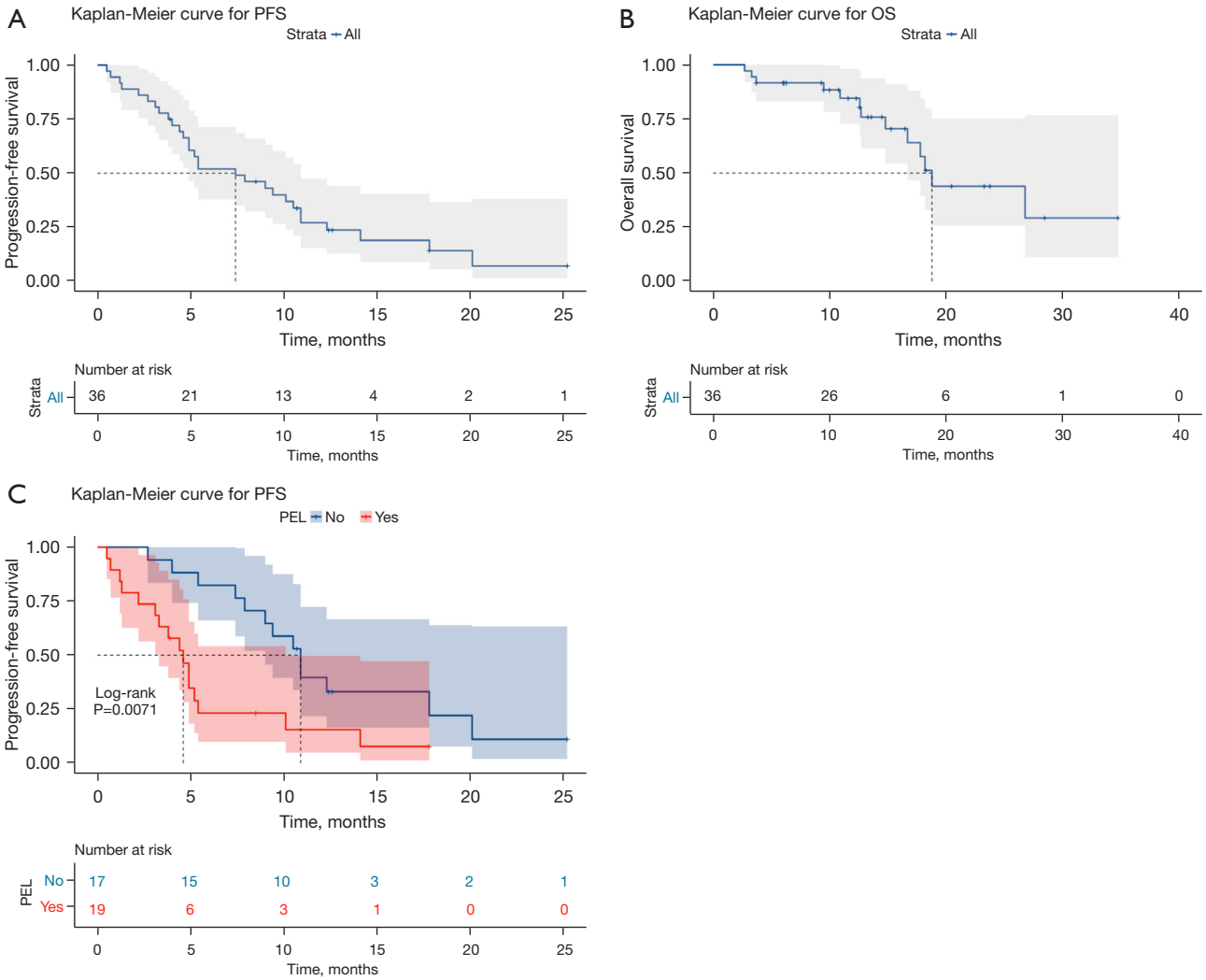

Figure 3 Survival analysis. Kaplan-Meier curves for progression-free survival (A) and overall survival (B). Kaplan-Meier curves stratified by absence or presence of PEL for progression-free survival (C). PFS, progression-free survival; OS, overall survival; PEL, progression of existing lesion.

experienced PD. The median PFS was 7.4 months (95% CI: 3.1–11.7 months; *Figure 3A*) and median OS was 18.8 months (95% CI: 17.1–20.5 months; *Figure 3B*). In addition, the median IFPFS was 17.8 months (95% CI: 11.5–24.2 months), median OFPFS was 7.9 months (95% CI: 3.4–12.5 months), and estimated 1- and 2-year LC rates were 67.1% and 31.9%, respectively.

Seven potential predictors of PFS were included in multivariable Cox analysis (*Table 4*). A baseline ECOG score of ≥2 [P=0.008, hazard ratio (HR): 3.76, 95% CI: 1.40–10.06] and PEL (P=0.001, HR: 4.76, 95% CI: 1.88–12.02) were prognostic factors for inferior PFS. Furthermore, a baseline ECOG score of ≥2 (P=0.005, HR: 9.15, 95% CI: 1.95–42.94) was an independent risk factor for OS (*Table 5*). Subgroup analysis showed longer median PFS with the absence of PEL [10.9 months (95% CI: 9.0–12.8 months) *vs.* 4.6 months (95% CI: 3.5–5.7 months), HR: 2.53, P=0.0071; *Figure 3C*]. However, no significant difference was found between the ECOG score of ≥2 subgroup or ECOG score of <2 subgroup in terms of median PFS (P=0.07; Figure S1A) and median OS (P=0.08; Figure S1B), respectively. Additionally, no independent risk factors for IFPFS were identified in multivariable Cox analysis (Table S1).

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Table 4 Univariate and multivariate analysis of progression-free survival

Variables	Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value
Age (<50 *vs.* ≥50 years)	0.99 (0.45–2.15)	0.979	–	–
Sex (male/female)	0.28 (0.04–2.06)	0.209	–	–
Virus infection (negative *vs.* positive)	0.75 (0.10–5.61)	0.776	–	–
ECOG (<2 *vs.* ≥2)	2.23 (0.92–5.38)	0.075	3.76 (1.40–10.06)	0.008
AFP (<400 *vs.* ≥400 ng/mL)	1.92 (0.90–4.07)	0.090	1.64 (0.74–3.60)	0.220
Child-Pugh class (A *vs.* B)	2.36 (0.67–8.36)	0.184	–	–
ALBI score (1 *vs.* 2)	2.14 (1.00–4.59)	0.050	1.55 (0.57–4.22)	0.391
Portal invasion (absent *vs.* present)	1.96 (0.88–4.38)	0.101	1.10 (0.36–3.34)	0.873
Extrahepatic spread (absent *vs.* present)	0.67 (0.31–1.42)	0.292	–	–
Prior hepatectomy (absent *vs.* present)	0.49 (0.22–1.12)	0.090	0.43 (0.15–1.25)	0.122
Prior hepatic local treatment (absent *vs.* present)	0.45 (0.16–1.21)	0.113	0.54 (0.19–1.52)	0.247
Maximal tumor diameter (<10 *vs.* ≥10 cm)	1.01 (0.43–2.38)	0.980	–	–
Tumor number (<3 *vs.* ≥3)	0.82 (0.35–1.91)	0.648	–	–
Disease control[†] (no *vs.* yes)	0.57 (0.23–1.42)	0.230	–	–
PFS1 (<4.1 *vs.* ≥4.1 months)	0.71 (0.33–1.53)	0.375	–	–
Interval between ICIs and RT (<5.0 *vs.* ≥5.0 months)	0.69 (0.33–1.46)	0.334	–	–
PEL (no *vs.* yes)	2.78 (1.28–6.01)	0.010	4.76 (1.88–12.02)	0.001
First-line of ICIs (no *vs.* yes)	1.30 (0.60–2.81)	0.512	–	–

Factors (P<0.15) in the univariate analysis were candidates for entry into a multivariable Cox analysis. [†], best objective response during immunotherapy before radiotherapy. ECOG, Eastern Co-operative Oncology Group; AFP, α-fetoprotein; ALBI, albumin-bilirubin; PFS, progression-free survival; ICIs, immune checkpoint inhibitors; RT, radiotherapy; PEL, progression of existing lesion; HR, hazard ratio; CI, confidence interval.

Safety

Twelve (33.3%) patients experienced ≥1 AEs that emerged within 90 days after RT initiation, and grade 3–4 events occurred in 6 (16.7%) patients (*Table 6*). The most common acute toxicities were decreased white blood cell count (25.0%), decreased lymphocyte count (19.4%), decreased platelet count (16.7%), and anorexia (16.7%). Late toxicities were reported in 27 (75%) patients. The most common TRAEs (any grade) were diarrhea in 10 (27.8%) patients, rash in 8 (22.2%) patients, and hypertension in 7 (19.4%) patients. Grade 3–4 late toxicities were reported in 10 (27.8%) patients; of these, decreased platelet count was observed in 3 patients. The ALBI score showed an upward trend compared with baseline within 3 months after RT (*Table 7*; P<0.001). Meanwhile, no radiation-induced liver disease [RILD; classic RILD: presence of nonmalignant ascites and an increase in alkaline phosphatase levels of at least two-fold compared with the pretreatment levels; non-classic RILD: elevated transaminase levels of at least five-fold compared to the upper limit of normal or the pretreatment level, in the absence of documented PD (18)] or treatment-related deaths were observed.

Discussion

Key findings

Subsequent RT showed reliable efficacy and acceptable safety as a salvage treatment strategy for patients with advanced-stage HCC who have lesion enlargement or NLs during ICI therapy.

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Table 5 Univariate and multivariate analysis of overall survival

Variables	Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value
Age (<50 *vs.* ≥50 years)	3.03 (0.66–13.88)	0.153	–	–
Sex (male/female)	1.38 (0.17–10.93)	0.762	–	–
Virus infection (negative *vs.* positive)	NE	–	–	–
ECOG (<2 *vs.* ≥2)	2.82 (0.84–9.43)	0.093	9.15 (1.95–42.94)	0.005
AFP (<400 *vs.* ≥400 ng/mL)	2.37 (0.74–7.52)	0.144	2.51 (0.61–10.33)	0.204
Child-Pugh class (A *vs.* B)	NE	–	–	–
ALBI score (1 *vs.* 2)	1.22 (0.41–3.68)	0.718	–	–
Portal invasion (absent *vs.* present)	1.36 (0.44–4.22)	0.590	–	–
Extrahepatic spread (absent *vs.* present)	0.55 (0.18–1.70)	0.296	–	–
Prior hepatectomy (absent *vs.* present)	0.30 (0.08–1.12)	0.073	0.25 (0.05–1.18)	0.080
Prior hepatic local treatment (absent *vs.* present)	0.34 (0.09–1.27)	0.108	0.45 (0.09–2.09)	0.306
Maximal tumor diameter (<10 *vs.* ≥10 cm)	0.82 (0.21–3.13)	0.769	–	–
Tumor number (<3 *vs.* ≥3)	1.54 (0.33–7.08)	0.580	–	–
Disease control[†] (no *vs.* yes)	0.50 (0.15–1.68)	0.260	–	–
PFS1 (<4.1 *vs.* ≥4.1 months)	1.02 (0.33–3.08)	0.979	–	–
Interval between ICIs and RT (<5.0 *vs.* ≥5.0 months)	1.58 (0.51–4.92)	0.428	–	–
PEL (no *vs.* yes)	3.11 (0.90–10.72)	0.073	3.57 (0.91–13.95)	0.067
First-line of ICIs (no *vs.* yes)	0.91 (0.30–2.76)	0.874	–	–

Factors (P<0.15) in the univariate analysis were candidates for entry into a multivariable Cox analysis. [†], best objective response during immunotherapy before radiotherapy. ECOG, Eastern Co-operative Oncology Group; AFP, α-fetoprotein; ALBI, albumin-bilirubin; PFS, progression-free survival; ICIs, immune checkpoint inhibitors; RT, radiotherapy; PEL, progression of existing lesion; HR, hazard ratio; CI, confidence interval; NE, not estimable.

Table 6 Safety summary

Treatment-related adverse events	Acute toxicity, n (%)		Late toxicity, n (%)	
	Any grade	Grade 3–4	Any grade	Grade 3–4
Diarrhea	1 (2.8)	0	10 (27.8)	1 (2.8)
Rash	2 (5.6)	0	8 (22.2)	1 (2.8)
Malaise	4 (11.1)	0	6 (16.7)	0
Anorexia	6 (16.7)	0	3 (8.3)	0
Platelet count decreased	5 (13.9)	1 (2.8)	0	3 (8.3)
White blood cell decreased	8 (22.2)	1 (2.8)	0	0
Hypertension	0	0	7 (19.4)	0
Lymphocyte count decreased	3 (8.3)	4 (11.1)	0	0
Nausea	5 (13.9)	0	2 (5.6)	0
Vomiting	5 (13.9)	0	2 (5.6)	0

Table 6 *(continued)*

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Table 6 *(continued)*

Treatment-related adverse events	Acute toxicity, n (%)		Late toxicity, n (%)	
	Any grade	Grade 3–4	Any grade	Grade 3–4
Hand-foot skin reaction	0	0	6 (16.7)	0
Abdominal pain	1 (2.8)	0	4 (11.1)	0
Bloating	4 (11.1)	0	1 (2.8)	0
Fever	2 (5.6)	0	3 (8.3)	0
Dry mouth	2 (5.6)	0	2 (5.6)	0
Epistaxis	1 (2.8)	0	3 (8.3)	0
ALT/AST increased	2 (5.6)	0	1 (2.8)	0
Blood bilirubin increased	1 (2.8)	0	1 (2.8)	1 (2.8)
Gastrointestinal ulcer	1 (2.8)	0	1 (2.8)	1 (2.8)
Gastroesophageal reflux disease	3 (8.3)	0	0	0
Hypothyroidism	1 (2.8)	0	2 (5.6)	0
Pruritus	0	0	3 (8.3)	0
Non-cardiac chest pain	1 (2.8)	0	1 (2.8)	0
Oral hemorrhage	1 (2.8)	0	1 (2.8)	0
Oropharyngeal pain	1 (2.8)	0	1 (2.8)	0
Proteinuria	0	0	1 (2.8)	1 (2.8)
RCCEP	0	0	1 (2.8)	1 (2.8)
TSH increased	0	0	2 (5.6)	0
Adrenal insufficiency	1 (2.8)	0	0	0
Alopecia	0	0	1 (2.8)	0
Anemia	1 (2.8)	0	0	0
Bone marrow hypocellular	0	1 (2.8)	0	0
Cardiac troponin T increased	0	0	1 (2.8)	0
Constipation	0	0	1 (2.8)	0
Dermatitis radiation	0	1 (2.8)	0	0
Gastrointestinal hemorrhage	0	0	0	1 (2.8)
Generalized edema	1 (2.8)	0	0	0
Hoarseness	0	0	1 (2.8)	0
Myalgia	0	0	1 (2.8)	0
Myocarditis	0	0	1 (2.8)	0
Myositis	0	0	0	1 (2.8)
Neutrophil count decreased	0	1 (2.8)	0	0
Radiation pneumonitis	1 (2.8)	0	0	0
Tinnitus	0	0	1 (2.8)	0

ALT, alanine aminotransferase; AST, aspartate aminotransferase; RCCEP, reactive cutaneous capillary endothelial proliferation; TSH, thyroid stimulating hormone.

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Table 7 Changes in albumin-bilirubin score

ALBI score, n (%)	Baseline	1 month after RT	3 months after RT	P value
1	16 (44.4)	13 (36.1)	9 (25.0)	<0.001
2	20 (55.6)	23 (63.9)	24 (66.7)	
3	0	0	3 (8.3)	

ALBI, albumin-bilirubin; RT, radiotherapy.

Strengths and limitations

To the best of our knowledge, this is the first retrospective study to investigate the efficacy and safety of subsequent RT in advanced-stage HCC patients treated with ICIs.

This study has some limitations. First, the sample size of this multicenter, single-arm study was small, and there was a potential selection bias related to differences in RT and systemic therapy regimens, which could be influenced by factors such as patient finances, preferences, and medical insurance coverage. Second, this study was mainly conducted on a patient population with HBV-related HCC and preserved liver function (Child-Pugh class A). Hence, further studies with a larger population are required to determine the feasibility and safety of subsequent RT. Lastly, no association was found between BED and clinical outcomes.

Explanations of findings and comparison with similar research

In this cohort of 36 patients, RT showed antitumor activity in those with all disease status, resulting in an ORR of 38.9%. Six (75.0%) patients with RL achieved DFS after receiving RT; 5 of these underwent downstaging surgery. Ten (52.6%) patients with PEL achieved disease control after RT, whereas 7 previously received locoregional therapy. In this study, the median IFPFS of 17.8 months and 1-year LC rate of 67.1% indicated effective tumor control of subsequent RT and provided opportunities for OS benefits. Previous studies have demonstrated that locally recurrent/residual HCC exhibits more biologically and morphologically malignant behavior than primary HCC after administering locoregional therapies, such as TACE and RFA (19,20). Notably, in a previous study, 367 patients with unresectable HCC who had earlier-stage disease were involved, of whom 81.5% had BCLC B stage and 98.6% received no previous treatment. However, the 1-year LC rate of TACE was only 74.4% (21). Additionally, the ORR before RT in this study was 16.7%, and the median PFS1 was 4.1 months. Although most patients enrolled in our study received ICIs combined with antiangiogenic agents before RT, the aggressive malignant behavior of recurrent/residual HCC induced by prior local treatment may compromise the effect of systemic therapy (22). Indeed, the median PFS in the PEL subgroup in this study was shorter than that in the no PEL subgroup (4.6 *vs.* 10.9 months, P=0.0071). Even so, the application of subsequent RT provided therapeutic benefit in 23 (63.9%) patients (ratio of PFS2/PFS1 ≥1.3). Furthermore, the multivariable Cox analysis demonstrated patients with a baseline ECOG score of <2 or the absence of PEL could obtain improved survival benefits from subsequent RT.

In the subgroup analysis conducted in the phase 3 CELESTIAL trial, the median PFS and OS with cabozantinib in patients who previously received sorafenib plus ICIs were 3.7 months (95% CI: 3.3–4.1 months) and 8.5 months (95% CI: 7.4–9.7 months), respectively (23,24). Additionally, a previous retrospective study investigating the effectiveness of lenvatinib plus pembrolizumab for unresectable HCC suggested that PFS and OS were compromised in patients who previously received systemic therapy, particularly after nivolumab failure (25). However, subsequent RT seemed to provide satisfactory survival benefits for patients who previously received immunotherapy (median PFS: 7.4 months and median OS: 18.8 months) in this study. Locoregional treatment destroys the primary tumor while releasing tumor neoantigens to activate the antitumor immunity (26,27). RT can transform the tumor microenvironment (TME) with low immunogenicity ("cold") and poor immune cell infiltration into an environment with high immunogenicity ("hot") that favors immune cell infiltration (28). Yu *et al.* found that liver metastases restrain the immunotherapy efficacy and that liver-directed RT combined with anti-PD-1 immunotherapy could enhance systemic antitumor immunity (29). Importantly, liver-directed RT reshapes the TME, improves the acquired immunotherapy resistance, and restores the immunotherapeutic efficacy in preclinical

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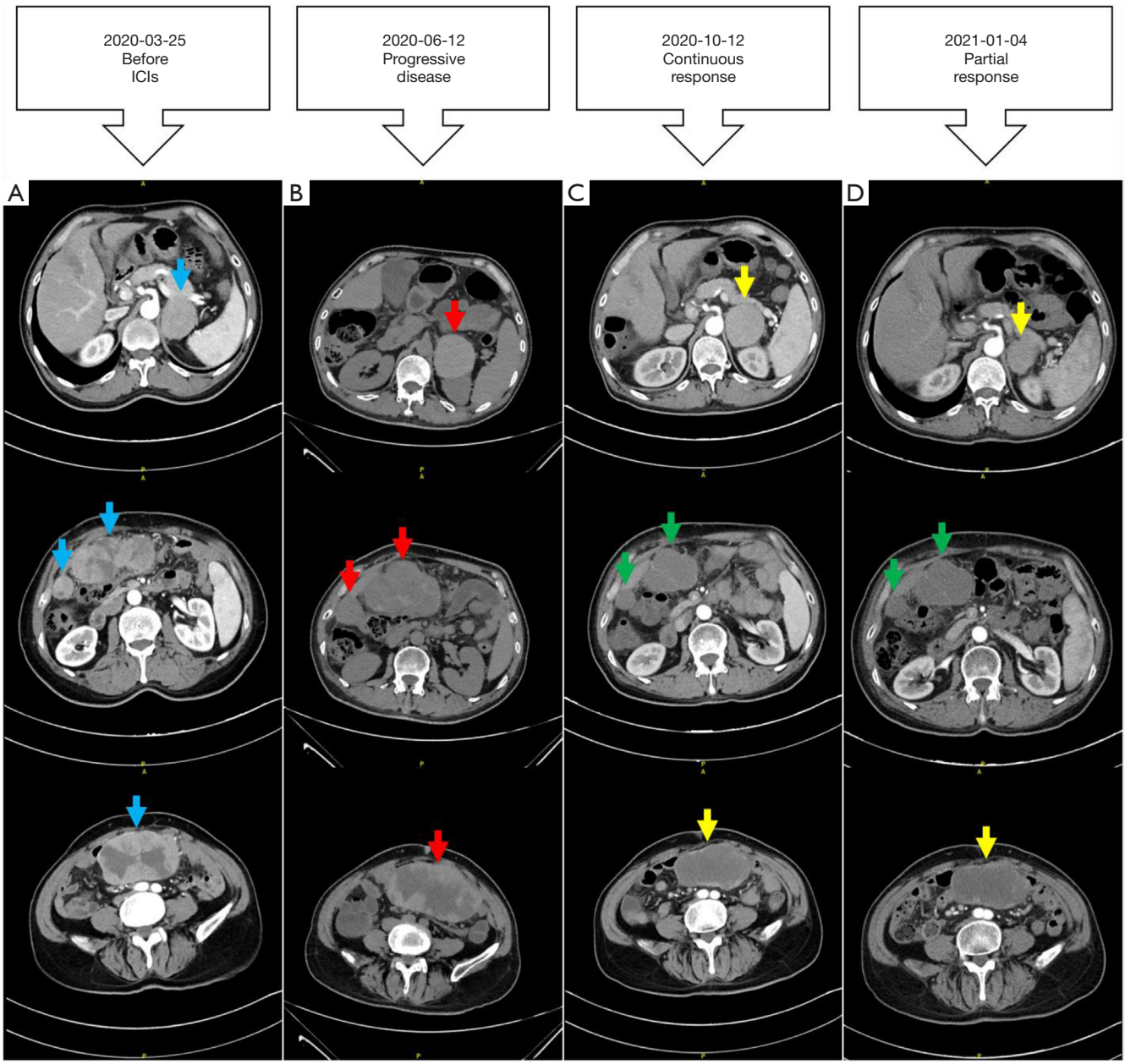

Figure 4 The course of treatment and CT scans. Enhanced CT before the first cycle of ICIs, and blue arrows depicted the metastatic lesions (A). CT after the third cycle of ICIs, and red arrows depicted the progressive lesions (B). Enhanced CT after RT (C). Enhanced CT before downstaging surgery (D). Yellow arrows depicted the irradiated lesions, and green arrows depicted the unirradiated lesions. ICIs, immune checkpoint inhibitors; CT, computed tomography; RT, radiotherapy.

models. One patient in our study, a man aged 54 years who experienced multiple abdominal and pelvic metastases (two abdominal, one pelvic, and one adrenal gland lesion; *Figure 4A*) after undergoing hepatectomy for HCC, experienced PD after receiving 3 cycles of ICIs (*Figure 4B*). Interestingly, two of the four lesions were treated with RT, while the other two lesions exhibited a response (*Figure 4C*). PR was achieved after 12 cycles of the previous regimen (*Figure 4D*). Pathology revealed extensive necrosis in the abdominal and pelvic metastases (*Figure 5A-5C*), except

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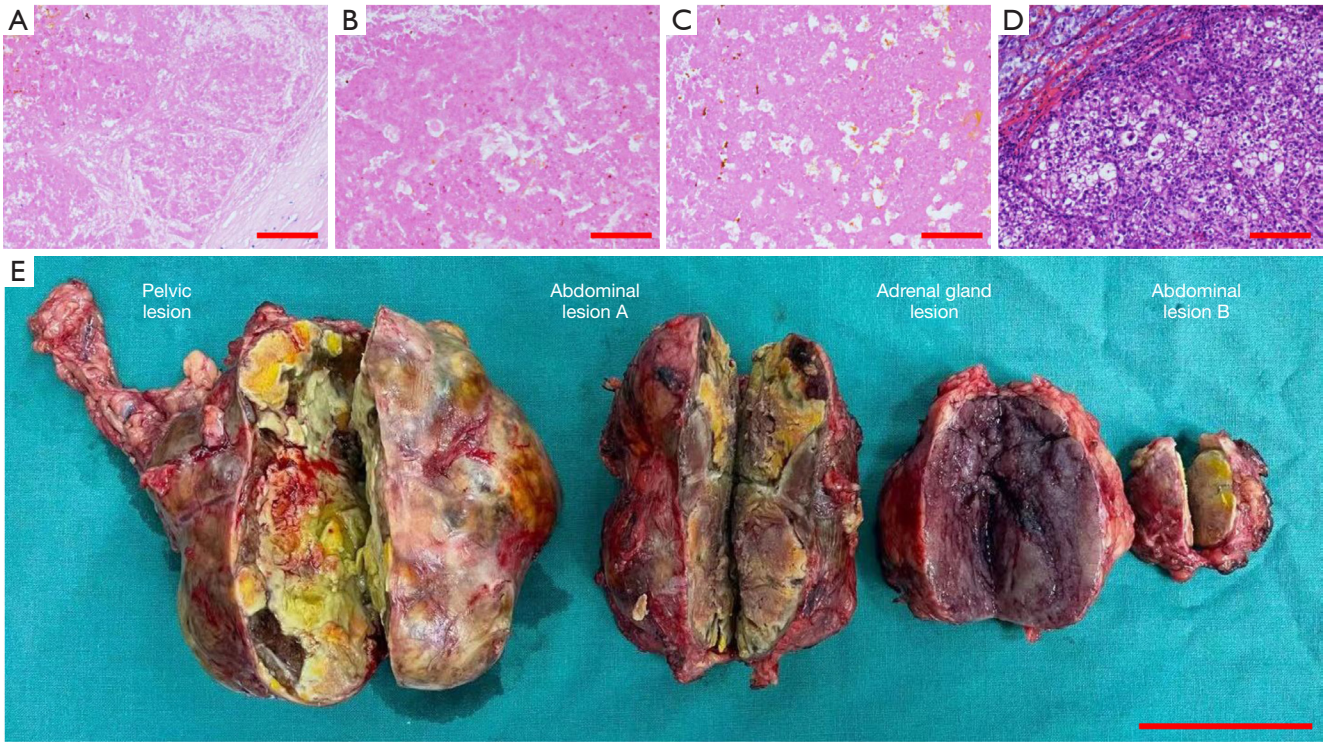

Figure 5 H&E staining and photographs of metastatic lesions. H&E of the pelvic lesion (A). H&E of the abdominal lesion A (B). H&E of the abdominal lesion B (C). H&E of the adrenal gland lesion (D). Photographs of four metastatic lesions (E). Scale bar =100 μm in (A-D), and 5 cm in (E). H&E, hematoxylin-eosin.

for the adrenal gland lesion (*Figure 5D*), after downstaging surgery (*Figure 5E*). The patient achieved a DFS of 20.5 months at the last follow-up. The effect of reversing the "immune desert" tumor provides additional insights into the application of subsequent RT for re-response in advanced-stage HCC patients with unsatisfactory therapeutic effect of ICIs (10).

However, RT does not always induce an antitumor response; for example, hypoxia plays a crucial role in radioresistance and the initial inflammatory response, facilitating tumor recurrence (30). Combining antiangiogenic treatment with the normalization of tumor vessels is beneficial in reducing tumor hypoxia and enhancing the response to RT (31). Lee *et al.* investigated the safety and effectiveness of RT in patients with advanced-stage HCC unsuitable for TACE. Although 29 (91%) patients had no extrahepatic metastasis at baseline and 53% of patients received sequential sorafenib treatment, out-field relapse remained the major cause of RT failure, with median OFPFS of approximately 10 months (17). Notably, a total of 23 (63.9%) patients experienced extrahepatic spread at baseline in this study, and the median OFPFS was 7.9 months. Therefore, dual-systemic therapy may provide better out-field control for patients with advanced-stage HCC after RT, which requires further exploration and validation.

The TRAEs observed in this study were tolerable and consistent with those reported in previous studies (32,33). The most common TRAEs (all grades) were diarrhea (33.3%), rash (30.6%), and malaise (27.8%); a total of 14 (38.9%) patients experienced grade 3–4 events. Notably, two patients discontinued RT owing to the decrease in platelet count and ascites, and it was difficult to identify whether these complications were related to the primary disease or treatment. For patients with HBV-related HCC, the degree of cirrhosis and its complications, including hypersplenism and ascites, should be evaluated before RT. Additionally, the increase in ALBI score suggested that changes in laboratory examination results, particularly liver function tests, during subsequent RT should be closely monitored. Furthermore, considering the irregular visits of patients and the impact of the coronavirus disease pandemic on real-world practice,

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clinicians should carefully monitor the patients, particularly during the late stages of systemic therapy (34).

Implications and actions needed

Despite numerous ICI-based systemic treatment regimens, salvage strategy for patients with lesion enlargement or NLs during ICI therapy is lacking. We propose alternative salvage strategies for such patients, emphasizing the need to optimize fractionation, dose, and commencement date of subsequent RT.

Conclusions

For patients with advanced-stage HCC treated with ICI, subsequent RT can serve as a salvage therapy and achieve a survival benefit with acceptable safety.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-23-134/rc

Data Sharing Statement: Available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-23-134/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-23-134/coif). H.Z. serves as an unpaid Deputy Editor-in-Chief of *Hepatobiliary Surgery and Nutrition* and X.S. serves as an unpaid editorial board member of *Hepatobiliary Surgery and Nutrition*. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of PUMCH (No. S-K2097) and individual consent for this retrospective analysis was waived.

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Supplementary

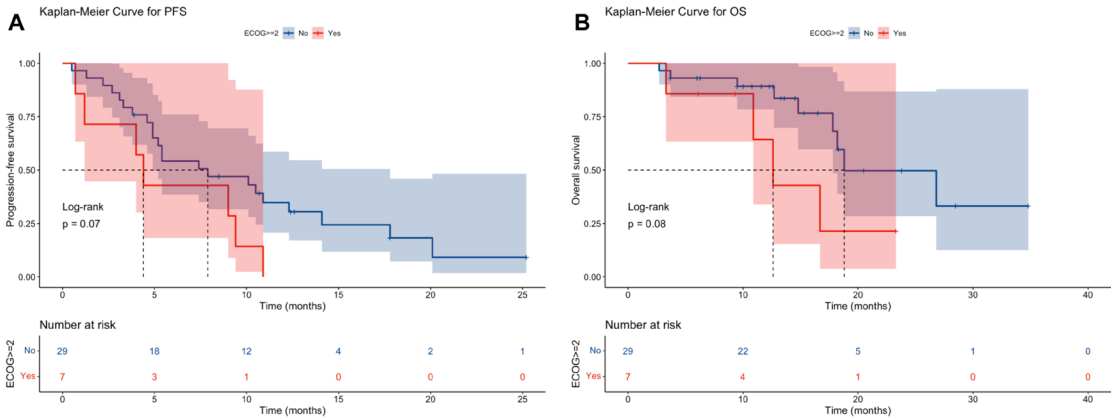

Figure S1 Survival analysis. Kaplan-Meier curves stratified by baseline ECOG score of <2 or ≥2 for progression-free survival (A). Kaplan-Meier curves stratified by baseline ECOG score of <2 or ≥2 for overall survival (B). PFS, progression-free survival; ECOG, Eastern Co-operative Group; OS, overall survival.

Table S1 Univariate and multivariate analysis of in-field progression-free survival

Variables[†]	Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value
Age (<50 vs. ≥50 years)	1.55 (0.34-7.04)	0.572		
Sex (male/female)	0.78 (0.10-6.11)	0.814		
Virus infection (negative vs. positive)	NE			
ECOG (<2 vs. ≥2)	1.67 (0.55-5.08)	0.367		
AFP (<400 vs. ≥400 ng/mL)	2.12 (0.70-6.42)	0.182		
Child-Pugh class (A vs. B)	4.35 (0.78-24.37)	0.095	1.99 (0.34-11.71)	0.445
ALBI score (1 vs. 2)	0.84 (0.27-2.65)	0.765		
Portal invasion (absent vs. present)	3.19 (0.98-10.40)	0.054	0.75 (0.09-6.02)	0.783
Extrahepatic spread (absent vs. present)	0.51 (0.18-1.50)	0.223		
Prior hepatectomy (absent vs. present)	0.24 (0.07-0.88)	0.032	0.20 (0.02-1.88)	0.159
Prior hepatic local treatment (absent vs. present)	0.93 (0.20-4.19)	0.920		
Maximal tumor diameter (<10 vs. ≥10 cm)	1.88 (0.58-6.13)	0.295		
Tumor number (<3 vs. ≥3)	1.09 (0.30-4.00)	0.893		
Disease control[‡] (no vs. yes)	0.93 (0.26-3.36)	0.917		
PFS1, months (<4.1 vs. ≥4.1)	0.97 (0.32-2.92)	0.958		
Interval between ICIs and RT (<5.0 vs. ≥5.0 months)	1.13 (0.38-3.41)	0.827		
PEL (no vs. yes)	1.65 (0.57-4.79)	0.355		
First-line of ICIs (no vs. yes)	2.93 (0.90-9.52)	0.074	2.93 (0.74-11.51)	0.124
BED_{10}, Gray (<60 vs. ≥60)	1.19 (0.41-3.52)	0.747		

Factors (P<0.15) in the univariate analysis were candidates for entry into a multivariable Cox analysis. [†], analysis for the 32 patients with complete radiotherapy data; [‡], best objective response during immunotherapy before radiotherapy. ECOG, Eastern Co-operative Oncology Group; AFP, α-fetoprotein; ALBI, albumin-bilirubin; PFS, progression-free survival; ICIs, immune checkpoint inhibitors; RT, radiotherapy; PEL, progression of existing lesion; BED10, biologically effective dose at an alpha/beta ratio of 10; HR, hazard ratio; CI, confidence interval; NE, not estimable.

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