Efficacy and safety of the immune checkpoint inhibitor-radiotherapy combination in advanced/unresectable hepatocellular carcinoma: A systematic review and meta-analysis

RAN CUI[1*], XINLIN YU[1,2*], YAN JIANG[1,3] and XINGMING LI[1]

[1]Department of Oncology, The First People's Hospital of Neijiang, Neijiang, Sichuan 641000, P.R. China;
[2]Department of Oncology, Affiliated Hospital of Chengdu University, Chengdu, Sichuan 610000, P.R. China;
[3]Department of Gastroenterology, People's Hospital of Longchang, Neijiang, Sichuan 641000, P.R. China

Received February 6, 2025; Accepted July 10, 2025

DOI: 10.3892/ol.2025.15206

Abstract. Limited treatment options are available for patients with advanced stages of hepatocellular carcinoma (HCC), which is a major global health challenge. The present systematic review and meta-analysis examined the therapeutic potential of the combination of immune checkpoint inhibitors (ICIs) and radiotherapy (RT) for advanced (a)HCC or unresectable HCC. The PubMed, Embase, Cochrane Library and Web of Science databases were searched to identify studies examining the therapeutic efficacy of the ICI-RT combination for aHCC published until August 31, 2024. The following clinical outcomes were analyzed: Objective response rate (ORR), median progression-free survival (mPFS) and median overall survival (mOS). Additionally, targeted subgroup analyses were performed based on tumor thrombus presence and the use of transarterial chemoembolization (TACE) and stereotactic body RT. The present single-arm meta-analysis, encompassing 16 studies involving 633 patients with aHCC or unresectable HCC, revealed that the ICI-RT combination exhibits potent therapeutic efficacy. The pooled ORR of patients in the ICI-RT combination group was 54.4% [95% confidence interval (CI), 46.8-62.0%]. The mPFS and mOS of patients treated with the ICI-RT combination were 10.1 (95% CI, 7.2-12.9) and 18.3 months (95% CI, 14.6-21.9), respectively. The ORR of patients in the TACE combination subgroup was 53.8% (95% CI, 44.6-62.9%). Meanwhile, the ORR and mOS of patients with Barcelona Clinic Liver Cancer stage C tumors were 55.6% (95% CI, 44.3-66.9%) and 21.2 months (95% CI, 13.5-29.0), respectively. These findings suggest that ICI and RT exert synergistic effects. The ICI-RT combination, a promising therapeutic regime for aHCC, is associated with potent efficacy and favorable ORR and survival outcomes. Further studies are needed to optimize treatment strategies and identify patient subgroups who can benefit from this approach. The findings of the present study contribute to advances in aHCC treatment. The protocol for the present systematic review was registered at PROSPERO (registration no. CRD42024583148) and is available in full on the Health Technology Assessment website of the National Institutes of Health (http://www.hta.ac.uk/2283).

Correspondence to: Professor Xingming Li, Department of Oncology, The First People's Hospital of Neijiang, 1,866 West Section of Han'an Avenue, Shizhong, Neijiang, Sichuan 641000, P.R. China
E-mail: lixingming120120@163.com

*Contributed equally

Abbreviations: aHCC, advanced hepatocellular carcinoma; ICIs, immune checkpoint inhibitors; ORR, objective response rate; mPFS, median progression-free survival; mOS, median overall survival; TACE, transarterial chemoembolization; SBRT, stereotactic body radiation therapy; RCTs, randomized controlled trials; AEs, adverse events; NOS, Newcastle-Ottawa Scale; 3 D-CRT, three-dimensional conformal radiotherapy; EBRT, external beam radiation therapy; AST, aspartate transaminase; ALT, alanine transaminase; NGS, next-generation sequencing; TMB, tumor mutation rates

Key words: hepatocellular carcinoma, immune checkpoint inhibitors, radiotherapy, systematic review, meta-analysis

Introduction

Globally, hepatocellular carcinoma (HCC) is a leading cause of cancer-associated mortalities, accounting for ~760,000 mortalities each year (1). The high mortality rates of HCC can be attributed to its resistance to conventional therapies (2). The combination of immune checkpoint inhibitors (ICIs) and radiotherapy (RT) has emerged as a promising therapeutic strategy for patients with HCC, especially for those with advanced (a)HCC or unresectable HCC (3).

Advances in treatment modalities have not markedly improved the clinical outcomes of patients with aHCC. The emergence of immunotherapy has transformed cancer treatment. The objective response rates (ORRs) and median overall survival (mOS) duration of patients undergoing combination therapy with ICIs and targeted therapies are 23.9-29.8% and 16-21.2 months, respectively (4-7). The efficacy of ICI-targeted therapy combinations is higher compared with that of sorafenib. However, this combination does not address all clinical needs.

For example, the IMbrave 150 trial demonstrated that 50% of patients with aHCC exhibited disease progression within 7 months of initiating atezolizumab-bevacizumab therapy (4). Thus, there is an urgent need to develop effective combination therapies to improve patient outcomes.

The immunomodulatory effects of RT can be harnessed to potentiate the efficacy of immunotherapy in aHCC (8-10). Early-phase clinical trials have yielded promising results for the ICI-RT combination. For example, a phase II trial reported that the ORR and 1-year OS rate of patients with unresectable HCC undergoing stereotactic body RT (SBRT)-camrelizumab combination treatment were 60 and 52.4%, respectively (11). Another study reported that the ORR, complete response rate and 3-year OS rate of patients undergoing combination treatment with SBRT and immunotherapy were 88, 50 and 92%, respectively (12).

Several clinical trials have demonstrated the therapeutic potential of the ICI-RT combination in aHCC. A recent search of ClinicalTrials.gov identified 38 ongoing studies evaluating the efficacy and safety of the ICI-RT combination, including two phase III trials (NCT04709380 and NCT04167293). This research activity reflects the increasing interest in RT-immunotherapy combination as a novel treatment paradigm.

However, the efficacy and safety of the ICI-RT combination in aHCC have not been comprehensively reviewed. The present systematic review and meta-analysis aimed to evaluate the therapeutic potential and safety profile of the ICI-RT combination for aHCC or unresectable HCC. The available evidence was thoroughly examined to assess the clinical application of the ICI-RT combination. The findings of the present study can guide clinicians in optimizing treatment strategies and identifying patient subgroups who can benefit from this novel approach.

Subjects and methods

Search strategy. The relevant studies published until August 31, 2024, were searched for in the PubMed, Embase, Cochrane Library, and Web of Science databases. The following Medical Subject Headings terms and free-text words were used: ('radiotherapy' OR 'radiation therapy') AND ('immunotherapy' OR 'immune checkpoint inhibitors' OR 'Programmed Death-1 (PD-1) inhibitors' OR 'Programmed Death-Ligand 1 (PD-L1) inhibitors' OR 'Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) inhibitors' OR 'immune modulation' OR 'immunotherapy') AND ('Liver cancer' OR 'Hepatocellular Carcinoma' OR 'Hepatoma' OR 'HCC'). Only studies in the English language were searched. The references in the included studies were reviewed to identify further relevant studies.

Selection criteria. The inclusion criteria were as follows: i) Studies on patients diagnosed with aHCC; ii) studies on patients treated with the combination of ICIs and RT/chemo-RT; iii) prospective interventional research, retrospective analyses or randomized controlled trials (RCTs); iv) studies that reported the target clinical tumor outcomes, including ORR, 1-year progression-free survival (PFS), 1-year OS and adverse events (AEs); v) studies that evaluated tumor responses using the Response Evaluation Criteria in Solid Tumors (version 1.1) (13); and vi) studies that evaluated the incidence and severity of toxic effects using the Common Terminology Criteria for Adverse Events. The exclusion criteria were as follows: Animal studies, cell studies, reviews, meta-analyses, duplicates, case reports or letters.

The articles were screened by two investigators independently based on the inclusion and exclusion criteria. Any disagreements were resolved through discussion between the two investigators or with the involvement of a third investigator.

Data extraction and quality assessment. The data were extracted independently by two investigators from all included studies and their quality was evaluated. The following data were extracted from the included studies: Author's name, publication year, study type, sample size, intervention, tumor stage, median follow-up time, EGFR mutation status and reported endpoints. Clinical and safety outcomes were evaluated based on the ORR, OS, PFS, AEs and grade ≥3 AEs. The quality of the RCTs, retrospective studies and non-controlled trials were assessed using the Jadad scale, the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Patient Series and the Newcastle-Ottawa Scale (NOS), respectively.

Statistical analysis. The present meta-analysis was performed using STATA 14 software (StataCorp LP). Heterogeneity among studies was assessed using the χ^2 test and I^2 statistic. Differences were considered statistically significant at $P<0.05$. A random effects model was used in cases of significant variability ($P<0.1$ and $I^2>50\%$), whereas a fixed effects model was used in cases of decreased variability. Furthermore, the robustness and reliability of the findings were evaluated using sensitivity analyses. Publication bias was assessed using Begg's and Egger's tests.

Results

Study selection. A literature search in the PubMed, Embase, Cochrane Library and Web of Science databases revealed 5,595 relevant studies. After screening and full-text review, 16 high-quality studies, encompassing 633 patients, that satisfied the inclusion criteria were used for the present meta-analysis (11,12,14-27). The study selection process is shown in Fig. 1. The detailed study characteristics are listed in Table I. These studies used diverse RT techniques, including three-dimensional conformal RT (3D-CRT), external beam RT (EBRT), SBRT and proton therapy. The total radiation doses were in the range of 24-60 Gy. A broad spectrum of ICIs, including nivolumab, ipilimumab, sintilimab, avelumab, toripalimab, atezolizumab, pembrolizumab, camrelizumab and tislelizumab, were used in the included studies. Thus, a comprehensive landscape was available for evaluating the efficacy of combination therapy in aHCC.

Quality assessment. The methodological quality of retrospective studies (n=9) and prospective studies (n=5) was evaluated using the Joanna Briggs Institute's Case Series Critical Assessment Checklist in 10 areas, including case selection, description of illness or health issues and clarity in presenting case details. The quality of two single-arm studies was determined using the NOS, which analyzes studies across the following three domains with eight specific criteria:

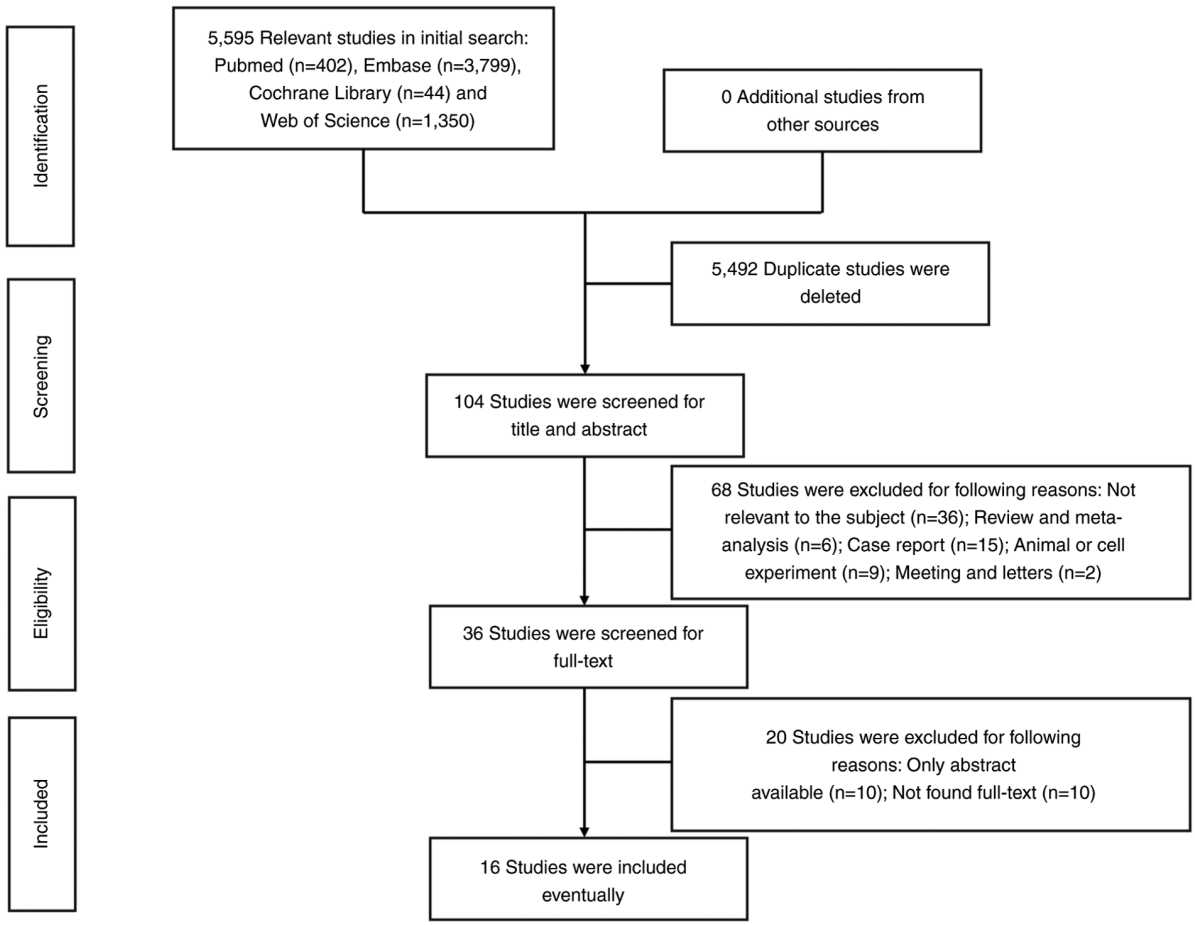

Figure 1. Flow diagram for the inclusion/exclusion of studies in the present meta-analysis.

Selection of the study groups, comparability of the groups and ascertainment of the outcome for cohort studies or the exposure for case-control studies. The details of these quality assessments are provided in Table II.

NOS for non-randomized studies. The improved NOS comprises the following eight items (Q1 to Q8): Q1, representative of the exposed cohort; Q2, representative of the non-exposed cohort; Q3, ascertainment of exposure; Q4, representative of the presence of the outcome of interest at the start of the study; Q5, representative of the cohorts based on the design or analysis; Q6, representative of the cohort assessment; Q7, duration for outcomes to occur; and Q8, adequacy of follow-up of cohorts.

JBI critical assessment checklist for patient series, including retrospective studies. JBI involves the following 10 queries: Q1, have the criteria for inclusion in the case series been clearly defined? Q2, have all participants in the case series been consistently and reliably evaluated? Q3, have reliable methods been used to identify the status of all participants in the case series? Q4, does the case series continuously include participants? Q5, have the participants been included in the case series? Q6, is the demographic report of the research participants clear? Q7, has the clinical information of the participants been reported? Q8, is the case result or subsequent discovery recorded? Q9, is the demographic information of the display location/clinic recorded? Q10, is statistical analysis performed properly?

Tumor response. The present meta-analysis evaluated the therapeutic efficacy of the ICI-RT combination in aHCC. The ORRs reported in the studies varied from 46.8 to 62.0%. A random effects model was applied as the inter-study heterogeneity was high (I^2=72.4%; P<0.001). The pooled ORR was 54.4% [95% confidence interval (CI), 46.8-62.0%; Fig. 2].

Survival. Some studies did not meet the predetermined endpoints. The present meta-analysis included 14 studies reporting mPFS and 9 studies reporting mOS of patients receiving concurrent ICIs and RT. The pooled mPFS and mOS were 10.1 (95% CI, 7.2-12.9; I^2=91.2%; P<0.001) and 18.3 months (95% CI, 14.6-21.9; I^2=80.0%; P<0.001), respectively (Fig. 3A and B).

Analysis of heterogeneity. The present study hypothesized that the observed heterogeneity in ORR is due to variations in research methodologies, including the combination of SBRT and transarterial chemoembolization (TACE), the incidence of portal vein tumor thrombosis (PVTT) and the proportion of patients with liver function classified as grade C. A meta-regression analysis was performed to evaluate these factors (Table SI). The regression coefficients for ORR suggest that these factors when considered individually do not directly account for the heterogeneity observed in ORR. Therefore, the source of this heterogeneity may involve multiple factors.

Table I. Characteristics of the studies included in the present meta-analysis.

First author, year	Study type	Sample size	PVTT	TACE	Liver function, n	Tumor staging	Treatment plan	Radiotherapy metrology	Intervention	Treatment sequence	Endpoints	(Refs.)
Juloori, 2022	Phase I	6	No	No	Child-Pugh classification A5, 6	NA	SBRT followed by nivolumab (PD-1) alone or nivolumab + ipilimumab treatment	40 Gy/5	SBRT + nivolumab + ipilimumab	Sequential therapy	ORR, OS, PFS, AEs	(16)
Ning, 2023	Retrospective	33	No	No	Child-Pugh classification A, 32 Child-Pugh classification B, 1	NA, 22 Recurrent, 11	8 weeks of ICIs (PD-1 or PD-L1) combination therapy followed by RT	40-60 Gy/8-10	RT + ICIs + TKIs therapy	Sequential therapy	ORR, PFS, AEs	(20)
Wang, 2024	Retrospective	146	No	No	Child-Pugh classification A, 135 Child-Pugh classification B, 11	BCLC stage B, 20 BCLC stage C, 126	SBRT followed by ICIs (PD-1) + lenvatinib treatment	40-52.5 Gy/5-10	SBRT + ICIs + lenvatinib	Sequential therapy	ORR, OS, PFS, AEs	(22)
Kim, 2023	Phase II	50	Yes	No	ALBI grade 1, 31 ALBI grade 2, 19	NA	EBRT + nivolumab (PD-1) simultaneously	30-50 Gy/10	EBRT + nivolumab	Synchronous treatment	ORR, OS, PFS, AEs	(17)
Chiang, 2024	Retrospective	30	No	No	ALBI grade 1, 16 ALBI grade 2, 13 ALBI grade 3, 1	BCLC stage A, 14 BCLC stage B, 4 BCLC stage C, 12	2 weeks of SBRT followed by nivolumab (PD-1)	25-45 Gy/5	SBRT + nivolumab	Sequential therapy	ORR, AEs	(12)
Chiang, 2021	Retrospective	16	No	No	ALBI grade 1, 8 ALBI grade 2, 7 ALBI grade 3, 1	BCLC stage A, 3 BCLC stage B, 5 BCLC stage C, 8	SBRT followed by nivolumab (PD-1)	25-50 Gy/10	SBRT + nivolumab	Sequential therapy	ORR, PFS, AEs	(14)
Ning, 2023	Retrospective	36	No	No	Child-Pugh classification A, 32 Child-Pugh classification B, 4	NA	ICIs (PD-1) followed by RT	24-50 Gy/3-10	RT + ICIs	Sequential therapy	ORR, OS, PFS, AEs	(19)
Yu, 2024	Single-arm	27	Yes	No	NA	BCLC stage C, 27	7-10 days of pembrolizumab (PD-1) followed by Y90	NA	Y90 + pembroli-zumab	Sequential therapy	ORR, OS, PFS, AEs	(24)
Tai, 2021	Phase II	36	Yes	No	Child-Pugh classification A, 27 Child-Pugh classification B, 9	BCLC stage A, 1 BCLC stage B, 11 BCLC stage C, 24	Y90 followed by nivolumab (PD-1)	NA	Y90 + nivolumab	Sequential therapy	ORR, OS, PFS, AEs	(21)
Chiang, 2023	Phase II	33	Yes	Yes	Child-Pugh classification A, 23 Child-Pugh classification B, 9 Child-Pugh classification C, 1	BCLC stage A, 4 BCLC stage B, 8 BCLC stage C, 21	RT was performed 28 days after TACE, and avelumab (PD-L1) treatment was performed 2 weeks after RT	27.5-40 Gy/5	RT + avelumab + TACE	Sequential therapy	ORR, PFS, AEs	(15)

Table I. Continued.

First author, year	Study type	Sample size	PVTT	TACE	Liver function, n	Tumor staging	Treatment plan	Radiotherapy metrology	Intervention	Treatment sequence	Endpoints	(Refs.)
Zhang, 2022	Retrospective	30	Yes	Yes	Child-Pugh classification A, 29 Child-Pugh classification B, 1	NA	Perform camrelizumab (PD-1) combination therapy or tislelizumab (PD-1) combination therapy 2 weeks after TACE, followed by RT therapy within 1 month	36-42 Gy/5	SBRT + ICIs + sorafenib + TACE	Sequential therapy	ORR, AEs	(26)
Li, 2022	Retrospective	37	No	No	ALBI grade ≤2, 36 ALBI grade 3, 1	BCLC stage B, 4 BCLC stage C, 33	RT and ICIs (PD-1) simultaneously	30-60 Gy/5	RT + ICIs	Synchronous treatment	ORR, OS, PFS, AEs	(18)
Xiang, 2022	Retrospective	31	No	No	ALBI grade 1, 13 ALBI grade 2, 18 ALBI grade 3, 0	NA	RT and toripalimab (PD-1) or sintilimab (PD-1) simultaneously	24-45 Gy/3-5	SBRT + ICIs	Synchronous treatment	ORR, PFS, AEs	(23)
Li, 2022	Single-arm	21	No	No	ALBI grade 1, 5 ALBI grade 2, 15 ALBI grade 3, 1	BCLC stage B, 2 BCLC stage C, 21	SBRT + camrelizumab (PD-1) simultaneously	30-50 Gy/5	SBRT + camrelizumab	Synchronous treatment	ORR, OS, PFS, AEs	(11)
Zhu, 2024	Phase II	46	Yes	No	NA	NA	Initially, sintilimab (PD-1) was used in combination therapy, which was suspended during radiotherapy and resumed after 2 weeks, when it was administered every 3 weeks until progression	30-50 Gy/10	RT + sintilimab + bevacizumab	Sequential therapy	ORR, PFS	(27)
Lin, 2022	Retrospective	55	Yes	Yes	Child-Pugh classification A, 33 Child-Pugh classification B, 22	NA	3-5 days after TACE, ICIs (PD-1) combination therapy was used synchronously, and 7-10 days later, I-125 particles were sequentially implanted	NA	I-125 + lenvatinib + TACE + ICIs	Sequential therapy	ORR, OS, PFS, AEs	(25)

PVTT, portal vein tumor thrombosis; RCT, randomized clinical trial; TACE, transarterial chemoembolization; SBRT, stereotactic body radiation therapy; ORR, objective response rate; TKI, tyrosine kinase inhibitor; OS, overall survival; PFS, progression-free survival; AEs, adverse events; RT, radiotherapy; ICIs, immune checkpoint inhibitors; EBRT, external beam radiation therapy; Y90, yttrium-90 radioembolization; PD-1, programmed cell death protein-1; PD-L1, programmed death-ligand 1.

Table II. Quality assessment of the studies included in the present meta-analysis.

A, Joanna Briggs Institute Critical Appraisal Checklist for Case Series for included retrospective studies and prospective studies

First author, year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Total	(Refs.)
Ning, 2023	2	0	2	2	2	0	2	2	2	2	16	(20)
Wang, 2024	2	0	2	2	2	0	2	2	2	2	16	(22)
Kim, 2023	2	0	2	2	2	0	2	2	2	2	16	(17)
Chiang, 2024	2	0	2	2	2	0	2	2	2	2	16	(12)
Chiang, 2021	2	0	2	2	2	0	2	2	2	2	16	(14)
Ning, 2023	2	0	2	2	2	0	2	2	2	2	16	(19)
Zhang, 2022	2	0	2	2	2	0	2	2	2	2	16	(26)
Li, 2022	2	0	2	2	2	0	2	2	2	2	16	(18)
Xiang, 2022	2	0	2	2	2	0	2	2	2	2	16	(23)
Juloori, 2022	2	0	2	2	2	0	2	2	2	2	16	(16)
Tai, 2021	2	0	2	2	2	0	2	2	2	2	16	(21)
Chiang, 2023	2	0	2	2	2	0	2	2	2	2	16	(15)
Zhu, 2024	2	0	2	2	2	0	2	2	2	2	16	(27)
Lin, 2022	2	0	2	2	2	0	2	2	2	2	16	(25)

B, Improved Newcastle-Ottawa Scale for non-randomized studies

First author, year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Total	(Refs.)
Yu, 2024	1	0	1	1	0	1	0	1	5	(24)
Li, 2022	1	0	1	1	0	1	0	1	5	(11)

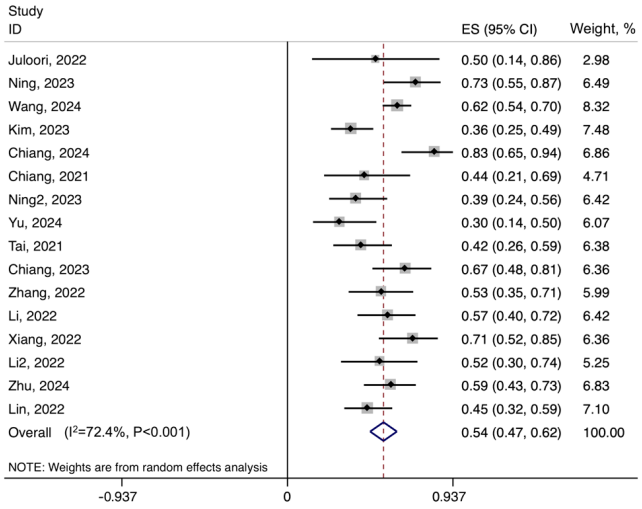

Figure 2. Forest plot of the pooled objective response rate. ES, effect size; CI, confidence interval.

Subgroup analysis comparing different RT modalities. Subgroup analysis examined the impact of PVTT, TACE, SBRT, the majority of patients with Barcelona Clinic Liver Cancer (BCLC) stage C tumors, RT metrology (groups exposed to >5 Gy/dose and groups exposed to <5 Gy/dose) and treatment sequence (synchronous treatment; RT followed by ICI therapy; ICI therapy followed by RT) and biomarkers (PD-1 or PD-L1) on the ORR, PFS and OS.

The ORRs of patients with emboli, cases receiving TACE, cases receiving SBRT and patients with BCLC stage C tumors were 47.1 (95% CI, 37.8-56.5%; I^2=61.4%; P=0.017; Fig. 4A), 53.8 (95% CI, 44.6-62.9%; I^2=46.6%; P=0.154; Fig. 4B), 58.4 (95% CI, 51.8-65.0%; I^2=0%; P=0.542; Fig. 5A) and 55.6% (95% CI, 44.3-66.9%; I^2=75.5%; P<0.001; Fig. 5B), respectively. Meanwhile, the ORRs of patients exposed to >5 Gy and <5 Gy were 62.5 (95% CI, 51.2-73.8%; I^2=52.8%; P=0.060) and 46.0% (95% CI, 30.5-61.6%; I^2=63.8%; P=0.063) (Fig. 6A), respectively. Furthermore, the ORR of patients receiving synchronous therapy was 53.4% (95% CI, 37.2-69.7%; I^2=75.1%; P=0.007). Meanwhile, the ORR of patients receiving RT followed by ICI therapy was 60.0% (95% CI, 47.5-72.5%; I^2=70.4%; P=0.005), while that of patients receiving ICI therapy followed by RT was 50.0% (95% CI, 38.2-61.8%; I^2=69.2%; P=0.006) (Fig. 6B). The ORRs of patients exhibiting PD-1 and PD-L1 expression were 52.1 (95% CI, 44.0-60.2%; I^2=72.7%; P=0.001) and 69.8% (95% CI, 58.2-81.4%; I^2=0.0%; P=0.610), respectively (Fig. 7).

The mPFS and mOS of patients with PVTT were 11.1 (95% CI, 7.0-15.3; I^2=85.3%; P<0.001) and 18.9 months (95% CI, 14.7-23.1; I^2=52.8%; P=0.096), respectively (Fig. 8A and B). The mPFS and mOS of patients in the SBRT subgroup were 9.0 (95% CI, 2.4-15.7; I^2=96.5%; P<0.001) and 16.8 months (95%

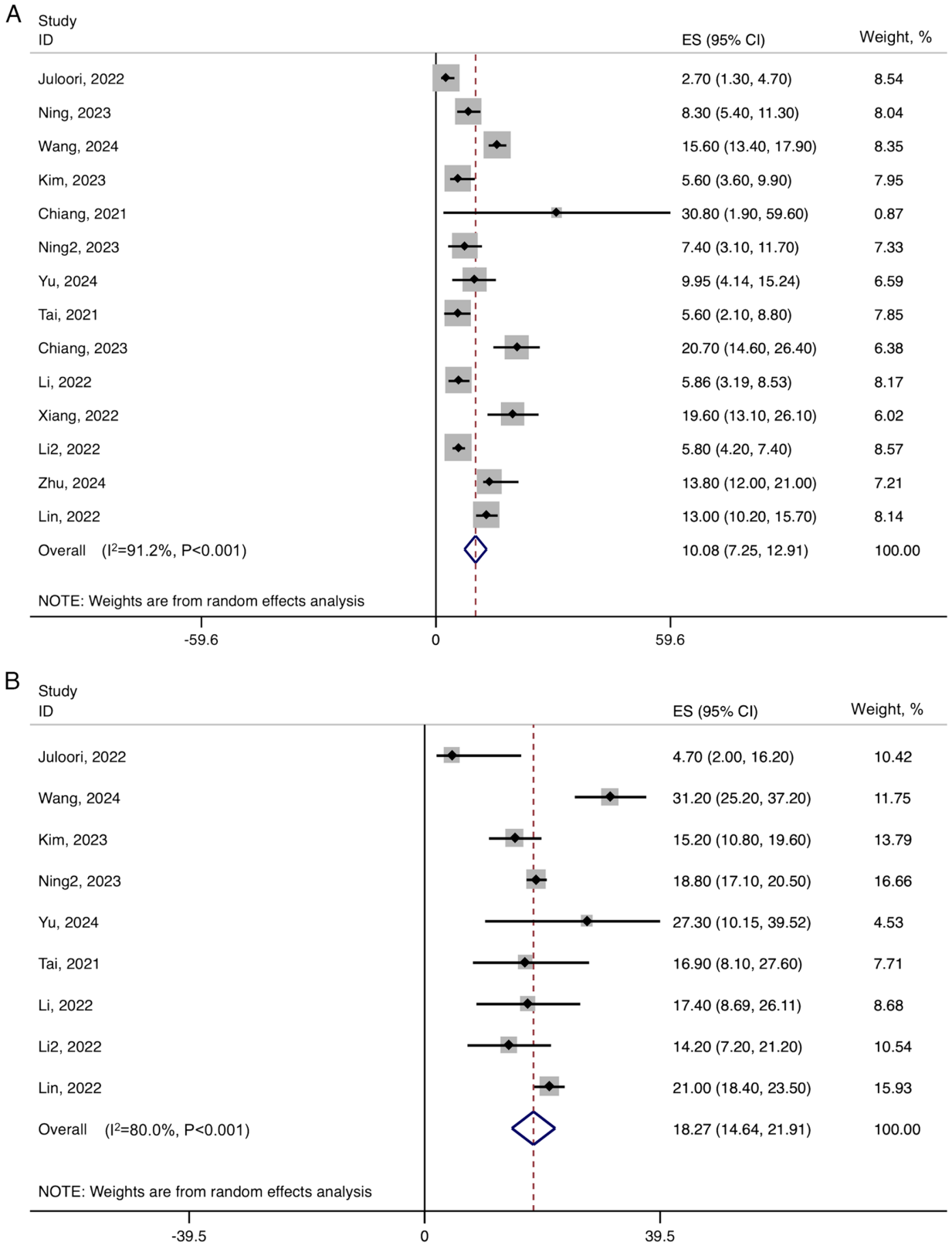

Figure 3. Forest plots of the pooled mPFS and mOS. (A) mPFS and (B) mOS of treatment regimen. ES, effect size; CI, confidence interval; mPFS, median progression-free survival; mOS, median overall survival.

CI, 1.1-32.5; I^2=94.0%; P<0.001), respectively (Fig. 9A and B). The mPFS and mOS of patients with BCLC stage C tumors were 10.7 months (95% CI, 6.23-15.20; I^2=92.0%; P<0.001) and 21.2 months (95% CI, 13.5-29.0; I^2=75.6%; P=0.003), respectively (Fig. 10A and B).

Toxicities. Subsequently, the present study analyzed the safety profile of the ICI-RT combination in aHCC (Table III). The side effects in most patients were mild to moderate. The incidence rate of grades 1-2 AEs was 79.9% (95% CI, 68.4-91.5%; I^2=88.8%; P<0.001), and these AEs were generally

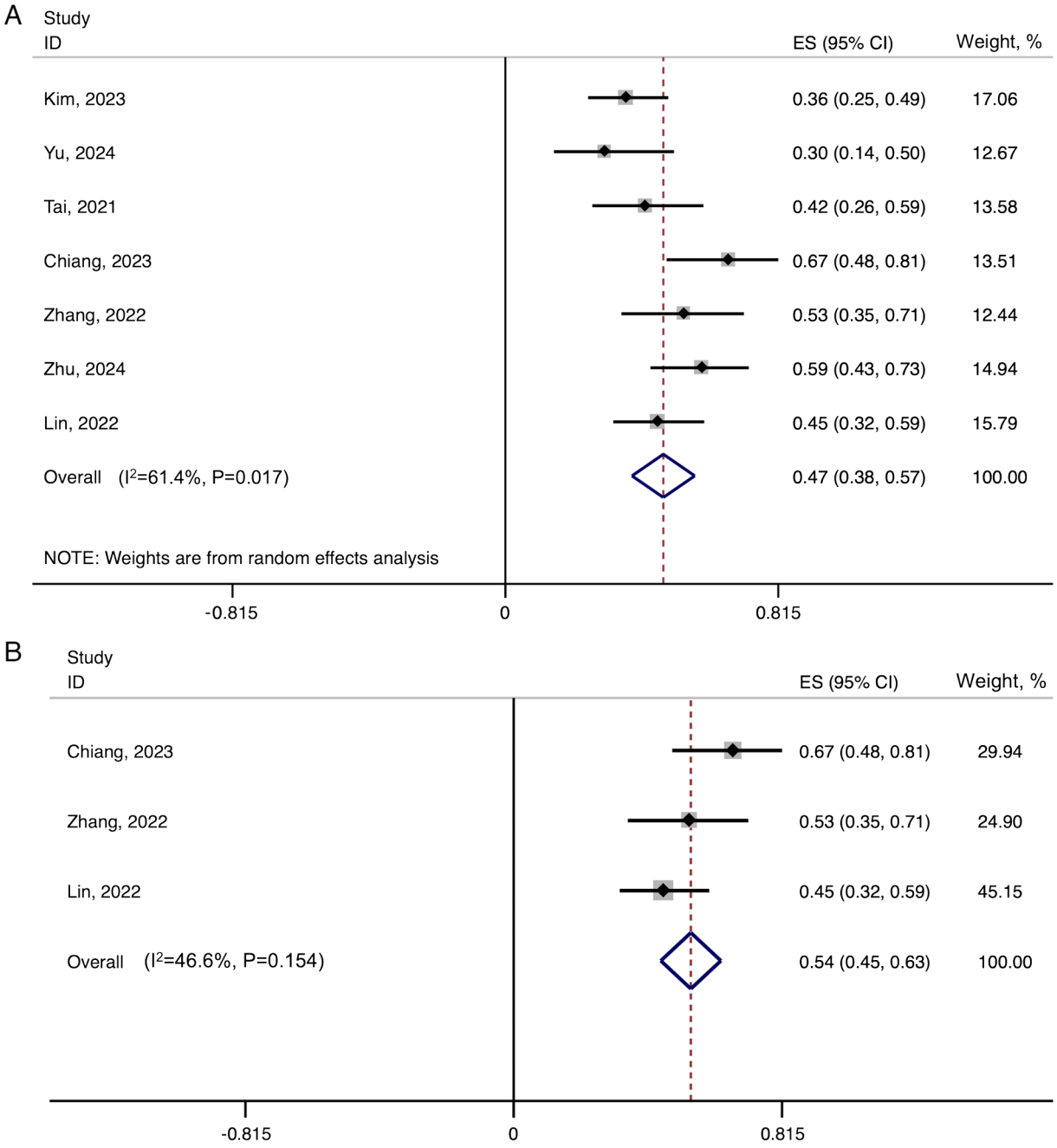

Figure 4. Forest plots of the pooled ORR. (A) ORR of the subgroup with tumor thrombus. (B) ORR of the subgroup treated with transarterial chemoembolization. ES, effect size; CI, confidence interval; ORR, objective response rate.

well-tolerated. Meanwhile, the incidence rate of severe AEs (grade ≥3) was 20.0% (95% CI, 13.8-26.2%; I^2=67.5%; P<0.001) (Fig. 11A and B).

The three most prevalent AEs across all grades were elevated aspartate transaminase (AST)/alanine transaminase (ALT) levels (39.5%; 95% CI, 19.8-59.2%; I^2=97.6%; P<0.001), decreased leukocyte counts (31.4%; 95% CI, 17.8-45.0%; I^2=89.3%; P<0.001) and increased bilirubin levels (27.1%; 95% CI, 13.2-41.0%; I^2=93.2%; P<0.001) (Table III). These findings indicate the importance of regular liver function monitoring and hematological assessments during treatment.

The incidence of grade ≥3 AEs was within an acceptable range, indicating a manageable safety profile of this combination therapy. The most frequently observed grade ≥3 AEs were elevated AST/ALT levels (6.2%; 95% CI, 2.1-10.4%; I^2=50.5%; P=0.04), thrombocytopenia (5.0%; 95% CI, 0.0-11.1%; I^2=0.0%; P=0.105) and increased bilirubin levels (4.4%; 95% CI, 0.6-8.3%; I^2=0.0%; P=0.023). Although serious AEs occurred, they were infrequent and were manageable with appropriate clinical oversight.

In the CheckMate 459 trial, the AE rates varied between the combination therapy (SBRT and PVTT) and nivolumab monotherapy groups (Table IV). The most common AEs were upregulated AST and ALT levels (51.9, 40.7 and 44.2% in the SBRT, PVTT and BCLC stage C tumor groups, respectively). The incidence rate of AST/ALT upregulation in the CheckMate 459 trial was 10.6%. Other AEs included nausea and fatigue.

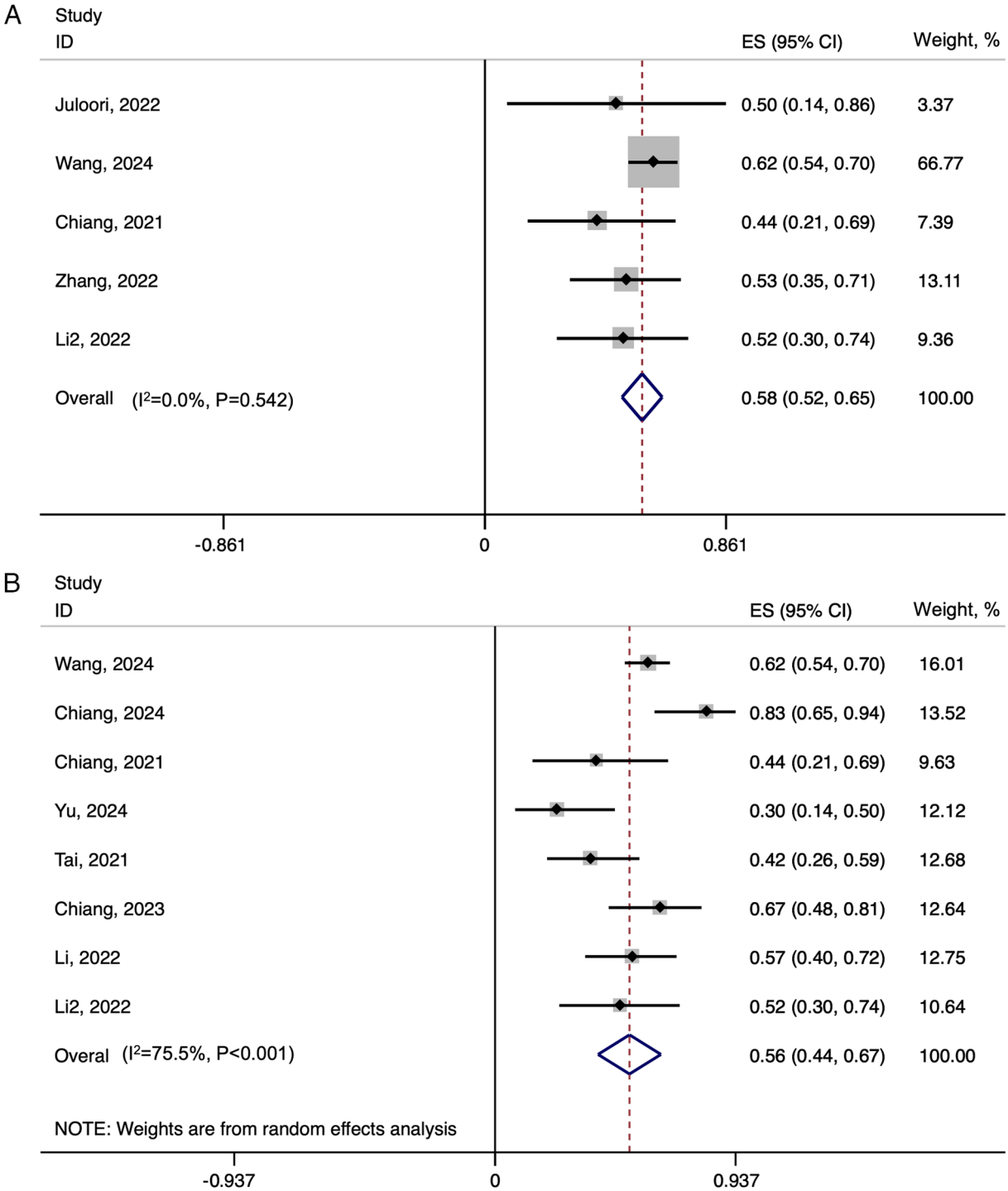

Figure 5. Forest plots of the pooled ORR. (A) ORR of the subgroup treated with stereotactic body radiotherapy. (B) ORR of the subgroup treated with Barcelona Clinic Liver Cancer stage C. ES, effect size; CI, confidence interval; ORR, objective response rate.

However, the AEs were not significantly different between the combination therapy and monotherapy groups (P>0.05).

Sensitivity analysis. To perform sensitivity analysis, one study was excluded at a time to assess its impact on the combined results. The pooled results and their 95% CI values remained unchanged regardless of which study was excluded (Fig. S1).

Publication bias. To ensure the robustness of the meta-analysis findings, potential publication bias was determined using the Egger's and Begg's tests. The P-values for Egger's and Begg's tests for different parameters were as follows: ORR, 0.46 and 0.75, respectively; mPFS, 0.07 and 0.23, respectively; mOS, 0.48 and 0.92, respectively; AEs, 0.22 and 0.06, respectively; AE grade ≥3, 0.01 and 0.01, respectively. The analysis of AE grade ≥3 suggested indications of publication bias. After correcting publication bias using the trim-and-fill method, three studies were imputed after five iterations, resulting in 17 bias-free studies. The pooled effect was 1.16 (95% CI, 1.11-1.24), reversing prior results. This indicates unstable

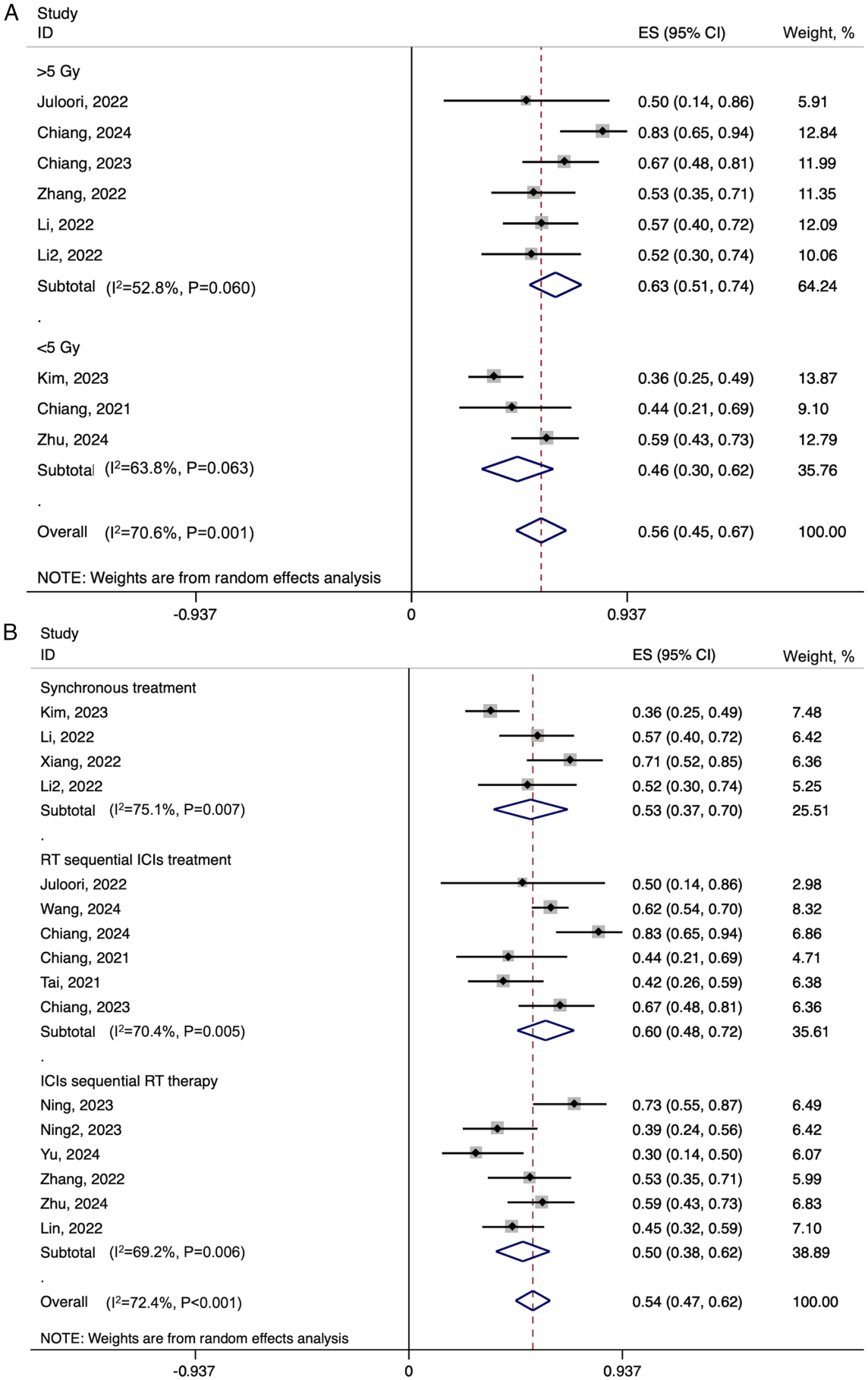

Figure 6. Forest plots of the pooled ORR. (A) ORR of the subgroup of RT metrology (groups >5 Gy and groups <5 Gy). (B) ORR of the subgroup of treatment sequence (synchronous treatment; RT sequential ICIs therapy; ICIs sequential RT therapy). ES, effect size; CI, confidence interval; ORR, objective response rate; RT, radiotherapy; ICIs, immune checkpoint inhibitors.

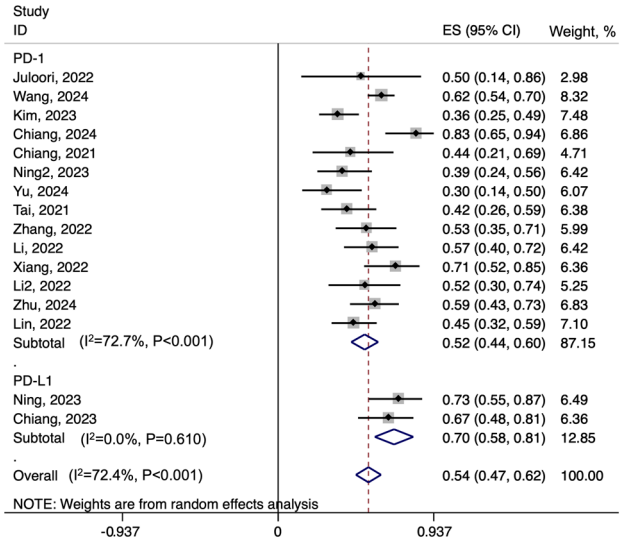

Figure 7. Forest plot of the objective response rate of the subgroup of biomarkers (PD-1 or PD-L1). ES, effect size; CI, confidence interval; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1.

Table III. AEs of the studies included in the present meta-analysis.

	All grades		Grade ≥3	
AEs	ES, %	I^2, %	ES, %	I^2, %
AST/ALT upregulation	39.5	97.6	6.2	50.5
Nausea and vomiting	15.9	65.7	0.0	0.0
Fever	15.4	80.5	0.0	0.0
Weight loss	9.6	18.7	0.0	0.0
Pain	17.9	48.1	0.0	0.0
Fatigue	22.0	82.4	3.7	0.0
Diarrhea	10.9	56.8	0.8	0.0
Hypertension	12.8	0.0	1.5	0.0
Pruritus	23.9	79.9	3.2	0.0
Rash	16.4	75.2	2.8	0.0
Bilirubin upregulation	27.1	93.2	4.4	0.0
Appetite loss	11.6	64.1	0.0	0.0
Thrombocytopenia	26.3	87.0	5.0	0.0
Decreased leukocyte count	31.4	89.3	2.6	0.0

AE, adverse event; AST, aspartate transaminase; ALT, alanine transaminase; ES, effect size.

outcomes for grade ≥3 AEs in some meta-analyses with the potential for new data to alter the conclusions. Contributing factors may include differences in definitions, evaluation criteria and treatment protocols for grade ≥3 AEs across studies, insufficient data comparability and small sample sizes or short follow-up periods in some studies that did not completely capture delayed or cumulative toxicity.

Discussion

HCC, especially aHCC or unresectable HCC, is a major global health challenge. The development of various monotherapies and combination strategies in the past decade has increased the treatment options for patients with HCC. The present meta-analysis of 16 studies (633 patients) evaluated the therapeutic potential of ICI-RT combination for aHCC. Subgroup analyses identified strategies for optimal patient selection. The present study directly addresses a clinical need in aHCC treatment, offering valuable guidance for future therapeutic strategies. The studies included were published until August 2024, capturing recent advancements in this rapidly evolving field and enhancing its relevance for ongoing clinical practice and research initiatives.

The SHARP trial established sorafenib as the standard first-line therapy (28). The mOS of patients in the sorafenib group (10.7 months) was higher compared with that of patients in the placebo group (7.9 months) (29). The efficacy of lenvatinib was similar to that of sorafenib in the REFLECT trial (mOS=13.6 months) (30). Several studies (4,5,6,31) have examined the efficacy of various combination approaches in improving the clinical outcomes of patients. The TACTICS trial investigated the efficacy of the TACE-sorafenib combination. The PFS of patients in the combination treatment group (25.2 months) was notably higher compared with that of patients in the TACE alone group (13.5 months) (32). Anti-angiogenic therapy is a promising therapeutic strategy for HCC. The CELESTIAL trial demonstrated that cabozantinib, a multi-kinase inhibitor, is effective as a second-line therapy. The mOS of patients in the cabozantinib group (10.2 months) was higher compared with that of patients in the placebo group (8.0 months) (33). Similarly, the REACH-2 trial revealed that ramucirumab, an anti-VEGFR2 antibody, improved the OS of patients exhibiting upregulated a-fetoprotein levels (34). These trials have expanded the therapeutic arsenal for aHCC. However, the overall prognosis of patients with aHCC continues to be suboptimal. Thus, there is a need to develop effective treatment strategies with long-term beneficial effects to a broad patient population.

Immunotherapy has revolutionized oncology treatment paradigms, including those for HCC. For example, the CheckMate 459 trial, which investigated nivolumab as a first-line monotherapy for aHCC, reported that the ORR and mOS of patients in the nivolumab group (15% and 16.4 months, respectively) were higher compared with those of patients in the sorafenib group (7% and 14.7 months, respectively) (35). The KEYNOTE-224 study reported that the ORR of patients treated with pembrolizumab who were previously treated with sorafenib was 17% (36). However, the efficacy of single-agent immunotherapy in aHCC is limited with only 30% of patients benefiting from the treatment (37).

To maximize the synergistic antitumor effects of immune checkpoint blockade, various combination strategies have been explored, including the combination of ICIs with locoregional therapies, tyrosine kinase inhibitors, other ICIs or anti-VEGF therapies. For example, the IMbrave 150 trial demonstrated that the mOS of patients in the atezolizumab-bevacizumab combination group (19.2 months) was higher compared with that of patients in the sorafenib group (13.4 months) (8). The COSMIC-312 study reported that the PFS of patients in the cabozantinib-atezolizumab combination group was higher compared with that of patients in the sorafenib group (4,38). The HIMALAYA trial explored the dual checkpoint inhibition

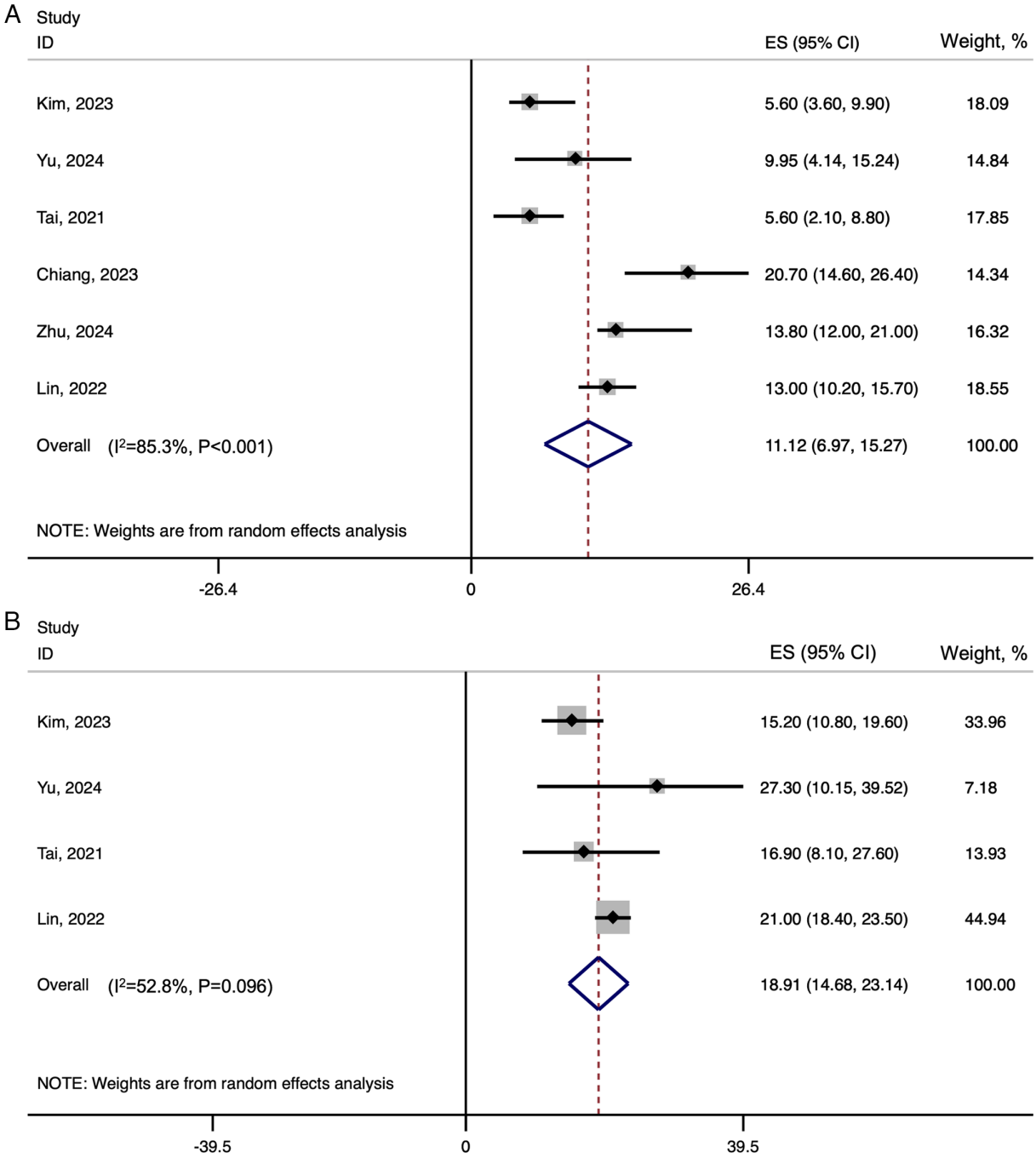

Figure 8. Forest plots of the pooled mPFS and mOS. (A) mPFS of the subgroup with tumor thrombus. (B) mOS of the subgroup with tumor thrombus. ES, effect size; CI, confidence interval; mPFS, median progression-free survival; mOS, median overall survival.

strategy with tremelimumab and durvalumab and reported an mOS of 16.4 months (6). However, these improvements are suboptimal for the management of aHCC.

Previously, the potential synergistic effects of RT on the immune system have piqued the interest of the scientific community. Previous studies (39,40) have examined the efficacy of the RT-immunotherapy combination in aHCC to further enhance treatment efficacy and outcomes. The enhanced efficacy of the ICI-RT combination approach can be attributed to the immunomodulatory effects of RT, which may augment the antitumor activity of ICIs. RT induces immunogenic cell death, promoting antigen presentation and T-cell activity in the tumor (41-43). Additionally, RT can upregulate the expression of PD-L1 on the tumor cell surface, increasing the tumor susceptibility to PD-1/PD-L1 blockade (44). The synergistic effects of RT and immunotherapy may overcome some ICI monotherapy-associated resistance mechanisms in HCC (45). The radiation-induced changes in the tumor microenvironment, including increased T-cell infiltration and enhanced antigen presentation, can aid in overcoming these barriers and increase the proportion of patients who benefit from immunotherapy (46-48). Ongoing and future clinical trials are expected to provide notable evidence for the effectiveness and safety of the RT-ICI combination in aHCC (Table V). These studies are critical for future clinical practice and reshaping the prospect of aHCC treatment.

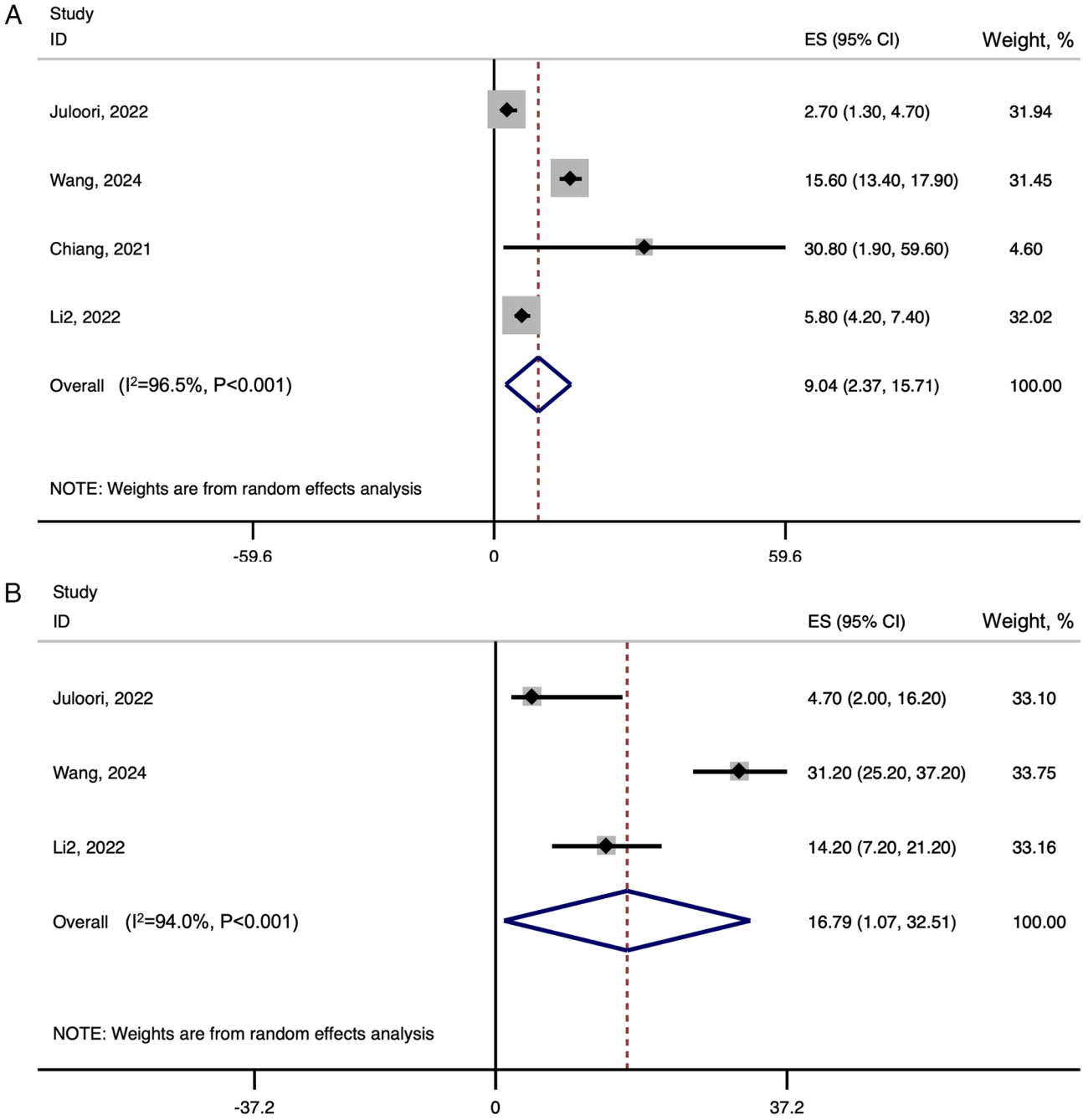

Figure 9. Forest plots of the pooled mPFS and mOS. (A) mPFS of the subgroup undergoing SBRT. (B) mOS of the subgroup undergoing SBRT. ES, effect size; CI, confidence interval; mPFS, median progression-free survival; mOS, median overall survival; SBRT, stereotactic body radiation therapy.

The present meta-analysis included 16 studies involving 633 patients to evaluate the efficacy and safety of the ICI-RT combination in aHCC. Compared with previous meta-analyses (49-52), the present meta-analysis focused on evaluating the efficacy of RT-immunotherapy combination for aHCC and unresectable HCC and has several strengths. Firstly, it is the first systematic review on the ICI-RT-immunotherapy combination for aHCC or unresectable HCC, addressing a critical knowledge gap not covered by broader ICI meta-analyses. Rigorous systematic review and meta-analysis methods were used to ensure the reliability and robustness of the research results. Additionally, the present study performed subgroup analyses based on PVTT status, TACE application, SBRT application (ORR=55.6%), tumor staging, RT metrology (>5 Gy/dose was associated with enhanced outcomes), treatment sequencing (OS for sequential approach=21.2 months) and ICI types. The subgroup analysis provided useful insights for identifying patients who are most likely to benefit from this combination therapy. Furthermore, the present study demonstrated that patients with aHCC, which is associated with poor prognosis and limited treatment options, can benefit from the RT-immunotherapy combination with a pooled ORR of 54.4%.

The mPFS and mOS of patients in the combination therapy group were 10.1 and 18.3 months, respectively, indicating that the efficacy of the combination therapy was higher

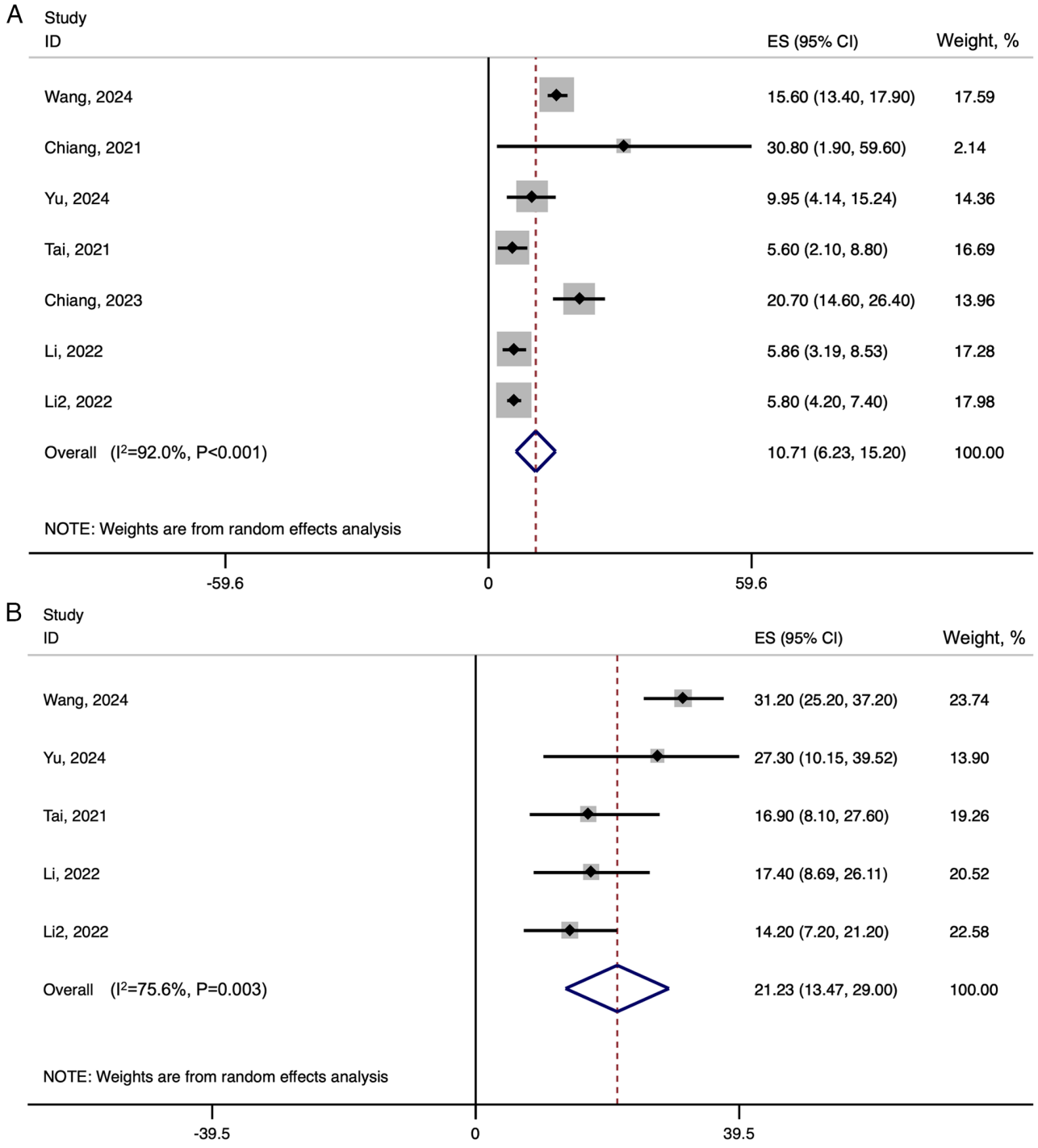

Figure 10. Forest plots of the pooled mPFS and mOS. (A) mPFS with Barcelona Clinic Liver Cancer stage C subgroup. (B) mOS with stage C subgroup. ES, effect size; CI, confidence interval; mPFS, median progression-free survival; mOS, median overall survival.

compared with that of known ICI monotherapy approaches. For example, the CheckMate 459 trial, which investigated nivolumab as a first-line monotherapy in aHCC, reported that the ORR and mOS of patients in the nivolumab group (15% and 16.4 months, respectively) were higher compared with those of patients in the sorafenib group (7% and 14.7 months, respectively). Similarly, the KEYNOTE-224 study revealed that the ORR and mOS of patients in the pembrolizumab group were 17% and 12.9 months, respectively. The higher ORR (54.4%) and improved mOS (18.3 months) reported in the present study indicate that RT and immunotherapy exert synergistic growth-inhibitory effects on aHCC compared with those treated with currently used monotherapies. The findings of the present study provide evidence supporting the clinical application of the RT-ICI combination for patients with aHCC.

The present study revealed differential efficacies of various combination treatment approaches. The ORR of patients in the TACE-immunotherapy-RT combination subgroup (53.8%) was notably higher compared with that of patients in the CheckMate 459 trial (15%). This suggests that incorporating TACE into radio-immunotherapy regimens may markedly

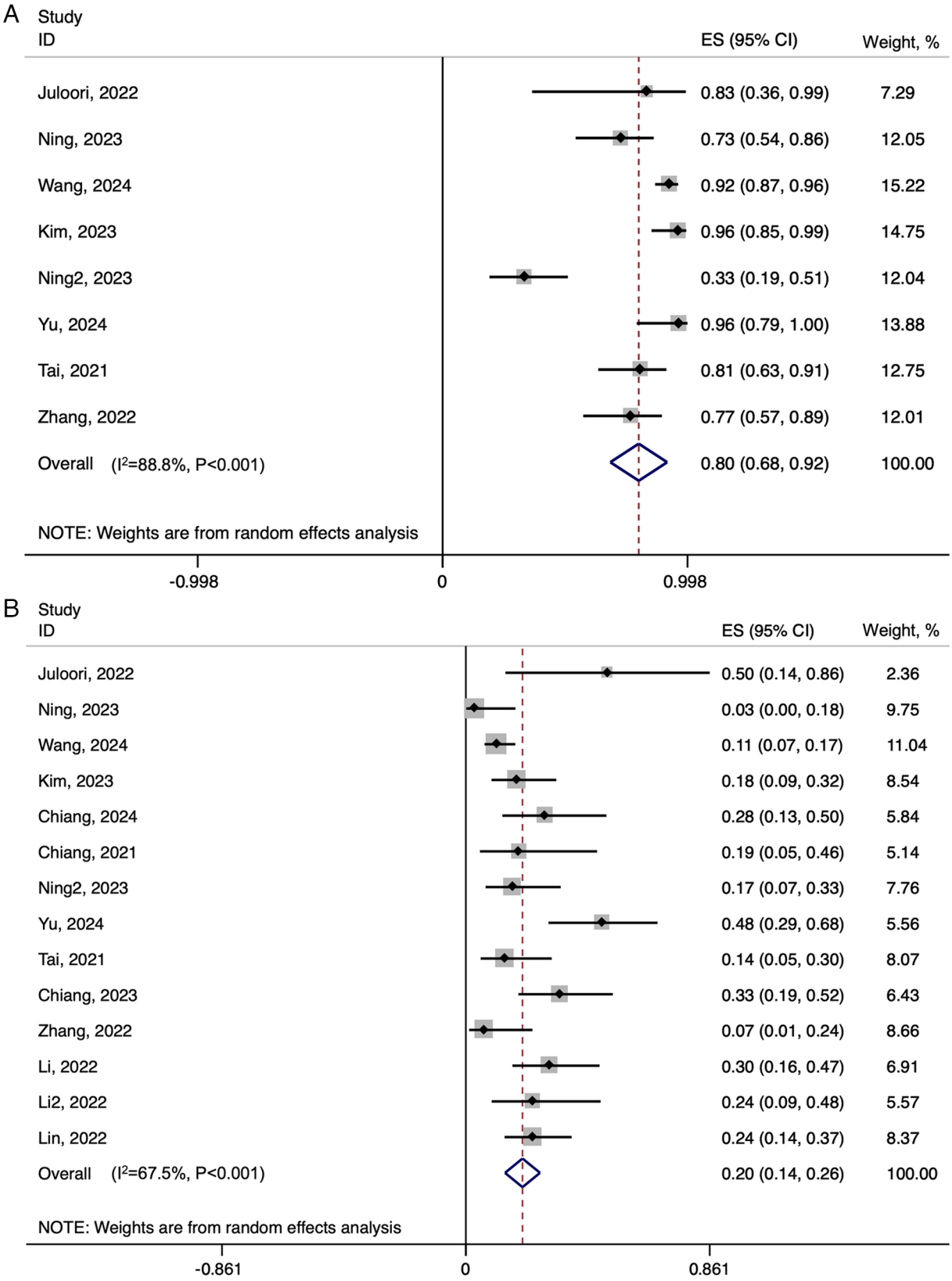

Figure 11. Forest plots of the pooled AEs. (A) All grades of AEs. (B) AEs of grade ≥3. ES, effect size; CI, confidence interval; AEs, adverse events.

enhance treatment efficacy. The observed benefit could be attributed to the synergistic effects of TACE-mediated localized tumor control and immunotherapy-induced systemic immune stimulation. However, the PFS and OS outcomes of patients in the TACE subgroup were not superior to those reported in the TACTICS trial. This may be because of several factors, including a small sample size and potential differences in patient selection criteria. The TACTICS trial, which examined a large cohort and used different patient characteristics, may have captured a comprehensive overview

Table IV. AEs for subgroups and CheckMate 459.

	All grade, ES %				
AEs	SBRT	PVTT	Stage C	CheckMate 459	P-value
AST/ALT increased	51.9	40.7	44.2	10.6	0.5
Nausea and vomiting	15.5	17.0	16.9	4.6	0.7
Fever	13.4	24.1	11.0	NA	NA
Weight loss	5.7	21.2	9.2	1.1	0.8
Pain	15.1	29.7	15.9	NA	NA
Fatigue	25.0	15.6	29.2	15.3	0.7
Diarrhea	5.7	7.4	5.9	8.4	0.7
Hypertension	15.4	13.2	13.4	0.8	0.7
Pruritus	19.6	37.1	24.7	10.6	0.8
Rash	14.0	17.8	15.3	12.5	0.9
Bilirubin increased	16.3	42.5	32.5	NA	NA
Appetite lost	8.4	27.3	9.7	6.0	0.7
Thrombocytopenia	61.1	43.7	44.8	NA	NA
Leukocytes reduction	23.4	39.0	33.1	NA	NA

AEs, adverse events; ES, effect size; SBRT, stereotactic body radiation therapy; PVTT, portal vein tumor thrombosis; AST, aspartate transaminase; ALT, alanine transaminase.

of long-term outcomes. Additionally, differential treatment protocols, follow-up durations and definitions of progression between studies can explain these different efficacies. Thus, there is a need to validate the findings of the present study and improve the understanding of the long-term benefits of combining TACE with radio-immunotherapy in HCC. Future studies should address these limitations by performing large RCTs with standardized protocols and long follow-up periods.

The prognosis of patients in the SBRT subgroup was superior to that of those in the non-SBRT subgroup (ORR=58.4%). This can be attributed to the ability of SBRT to precisely deliver high doses of radiation to the tumor with minimal damage to surrounding healthy tissues. The enhanced local control achieved through SBRT can amplify the immunomodulatory effects of radiation and provide improved outcomes when combined with immunotherapy.

In addition to being associated with poor prognosis, PVTT in patients with aHCC has limited treatment options, contributing to poor outcomes. In the present study, the RT-ICI combination improved the outcomes of patients with PVTT. In patients with PVTT, the ORR and mPFS of patients with PVTT after treatment with the RT-ICI combination (47.1% and 11.1 months, respectively) were higher compared with those after treatment with conventional therapies. Additionally, the mOS of patients with PVTT undergoing radio-immunotherapy combination treatment was 18.9 months. Thus, the mOS of patients in the PVTT group undergoing radio-immunotherapy combination treatment was >2-fold higher compared with that of patients with macrovascular invasion undergoing sorafenib treatment in the SHARP trial (8.1 months) (28). These results suggest that the synergistic effects of immunotherapy and RT may be beneficial for patients with aHCC exhibiting PVTT.

The combination therapy of RT-ICI improved the prognosis of BCLC C-stage aHCC patients compared with the subgroup without ICI combination (ORR=55.6%; mPFS=10.7 months; mOS=21.2). Although the combination therapy exhibited enhanced efficacy, this strategy must be further optimized to maximize its therapeutic benefits.

The optimization of the ideal synergy between immunotherapy and RT is a key challenge. The optimal RT dosing and fractionation schedules for this approach have not been conclusively established. The present analysis included studies employing a wide range of RT protocols. The studies employed total radiation doses ranging from 24 to 60 Gy and diverse delivery techniques, such as 3D-CRT, EBRT, SBRT and proton therapy. This heterogeneity in dosing and delivery methods may influence both treatment outcomes and AE profiles. Studies utilizing SBRT, such as those performed by Zhu *et al* (27) and Chiang *et al* (14) reported interesting outcomes with doses of 36-60 Gy delivered in 3-5 fractions. In the present study, dose stratification analysis of RT revealed that the ORR of patients receiving >5 Gy/dose (62.5%) was higher compared with that of patients receiving <5 Gy (46.0%). This suggests that high doses of RT may be associated with improved treatment responses. Thus, hypofractionated regimens in combination with immunotherapy can promote immunogenic cell death and tumor antigen presentation. However, these findings must be validated through extensive and rigorous clinical investigations to establish the most effective RT parameters in this combination approach for aHCC.

Furthermore, the optimal timing and sequencing of RT relative to immunotherapy administration are crucial factors. In the present study, the ORR of patients treated with RT followed by ICI was 60.0%, indicating excellent therapeutic efficacy. Previous studies have demonstrated that the efficacy of administering ICI after RT against other tumors is higher compared with that of administering ICI before RT (53). This can be attributed to the immunostimulatory effect of RT that can enhance the efficacy

Table V. Ongoing trials of RT + ICIs in HCC.

Trial, NCI ID	Phase	Type of RT	Type of ICI	Design	Target enrollment	Primary endpoint
NCT05625893	II	Proton RT	Atezo-bev (anti-PD-L1/ anti-VEGF)	Atezolizumab + bevacizumab q3w; Proton Beam Therapy initiated 1 week (±7 d) after cycle 2	63	PFS
NCT06040177	II	SBRT	Cadonilimab (anti-PD-1/CTLA-4)	Renvatinib SBRT → cadonilimab	30	ORR
NCT04913480	II	SBRT	Durvalumab (anti-PD-L1)	Durvalumab commences 1 week pre-SBRT	37	PFS at 1 year
NCT03942328	I/II	EBRT	Autologous dendritic cells + atezo-bev (anti-PD-L1/anti-VEGF)	EBRT (1-3 weeks) → autologous dendritic cells + atezo-bev	54	DLT PFS at 2 years
NCT05286320	I/II	SBRT	Pembrolizumab + lenvatinib (anti-PD-1/TKI)	Pembrolizumab + lenvatinib SBRT during C2 of pembrolizumab	27	Phase 1, DLT; Phase 2, ORR
NCT04988945	II	SBRT	Durva-treme (anti-PD-L1/CTLA-4)	TACE and SBRT → durva-treme	33	Downstaging for resection rate
NCT05488522	I	SBRT	Atezo-bev (anti-PD-L1/ anti-VEGF)	Atezo-bev SBRT on week 2	18	DLT
NCT06133062	II	Proton RT	Atezo-bev (anti-PD-L1/ anti-VEGF)	Proton RT with atezo-bev	45	PFS
NCT03316872	II	SBRT	Pembrolizumab (anti-PD-1)	Pembrolizumab SBRT on C1D2 of pembrolizumab	30	ORR
NCT04430452	II	RT	Durva-treme (anti-PD-L1/CTLA-4)	Hypofractionated RT → durvalumab or durva-treme	21	ORR
NCT05396937	II	SBRT	Atezo-bev (anti-PD-L1/ anti-VEGF)	Atezo-bev SBRT 1-2 weeks after C1 atezo-bev	42	ORR
NCT05809869	II	Yttrium-90	Durva-treme (anti-PD-L1/CTLA-4)	Durva-treme radioembolisation on week 2	25	ORR
NCT04547452	II	SBRT	Sintilimab (anti-PD-1)	SBRT + sintilimab or sintilimab	84	PFS
NCT05377034	II	SIRT	Atezolzumab (anti-PD-L1)	SIRT-Y90 + atezolizumab + bevacizumab	176	BORR
NCT02837029	I	SIRT	Nivolumab (anti-PD-1)	SIRT-Y90 + nivolumab	27	ORR
NCT04785287	I/II	SBRT	Nivolumab (anti-PD-1) and BMS986218 (anti-CTLA-4)	SBRT + BM5986218 ± nivolumab	13	IAE
NCT04709380	II	RT	Toripalimab (anti-PD-1)	(RT + toripalirab) vs. sorafenib	85	TTP
NCT05530785	II	RT	Sintilmab (anti-PD-1)	RT + sintilimab and bevacizumab biosimila	35	ORR
NCT05010434	II	RT	Sintilimab (anti-PD-1)	RT + sintilmab + bevaczumab	46	ORR

Table V. Continued.

Trial, NCI ID	Phase	Type of RT	Type of ICI	Design	Target enrollment	Primary endpoint
NCT04611165	II	EBRT	Nivolumab (anti-PD-1)	Nivolumab → EBRT	50	PFS
NCT04850157	II	lMRT	Tislelizumab (anti-PD-1)	Tislelizumab + IMRT	30	RFS

This information is available on clinicaltrials.gov/ (accessed on 7 October, 2024). BORR, best overall response rate; ORR, overall response rate; RFS, relapse-free survival; lMRT, intensity modulated radiation therapy; EBRT, external beam RT; TTP, time to progression; IAE, incidence of adverse events; PFS, progression-free survival; DLT, dose-limiting toxicity; PD-1, programmed cell death protein-1; PD-L1, programmed death-ligand 1 CTLA-4, cytotoxic t-lymphocyte associated protein 4; ICI, immune checkpoint inhibitor; atezo-bev, atezolizumab + bevacizumab; durva-treme, durvalumab + tremelimumab NCI ID, National Cancer Institute identifier.

of immunotherapy (54-56). Juloori *et al* (16) initiated ICI treatment 14 days after completing SBRT, utilizing the peak period of antigen release and immune cell infiltration 1-2 weeks after RT to amplify the immunogenicity of RT. However, further studies are needed to validate the efficacy of this regimen. The potential advantages of sequential approaches have not been determined in aHCC. Future studies must examine the comparative efficacy of concurrent and sequential strategies and determine the ideal therapeutic window for combining these modalities. Theoretically, a concurrent approach may leverage the immediate immune-stimulating effects of radiation, whereas a sequential approach can allow for effective priming of the immune system or enhanced tumor debulking before immunotherapy initiation. However, these hypotheses require rigorous testing through well-designed clinical trials to determine the most effective strategy for integrating RT and immunotherapy in aHCC.

The safety profile of the RT-immunotherapy combination in aHCC must also be considered. The present study compared AEs associated with the combination approach and conventional monotherapies. These results align with prior studies (17,21,24) suggesting that combining RT and immunotherapy does not markedly exacerbate toxicity compared with monotherapy, even in high-risk populations such as patients with PVTT patients. Notably, transient liver enzyme elevations observed here are consistent with the known safety profile of ICIs in aHCC (4,57). While these findings support the feasibility of combining ICIs with RT to enhance efficacy without compromising short-term safety, larger RCTs remain critical to confirm long-term tolerability and address potential rare or delayed toxicities in diverse aHCC cohorts.

To achieve long-term benefits of RT combined with immunotherapy for advanced HCC, it is necessary to clarify the synergistic mechanism and establish a precise patient stratification system. Next-generation sequencing (NGS), with its multidimensional omics analysis capabilities, can comprehensively analyze tumor genomic features [such as tumor mutational burden (TMB) and high-frequency mutations] and dynamic changes in the immune microenvironment, providing a establishing a robust foundation for precision therapeutic strategies for personalized treatment (58). Studies have shown that TMB is positively associated with the efficacy of PD-1/PD-L1 inhibitors (assessed in lung cancer, bladder cancer and head and neck cancer) (59), while TP53/catenin b1 mutations in HCC may drive immune microenvironment remodeling (60). In addition, NGS can also predict the response rate and radiation sensitivity of patients to immunotherapy by analyzing the expression characteristics of immune genes, T cell receptor pool, inflammation related gene expression and microbial community composition (61-64). Based on these multidimensional omics data, a predictive model can be constructed to optimize the combined strategy of RT dose/timing and immunotherapy and achieve dynamic adjustment of treatment plans (65). Prospective clinical studies are needed to evaluate the clinical application value of biomarkers and explore the potential of circulating tumor DNA in efficacy monitoring and drug resistance mechanism analysis.

Studies included in the present meta-analysis exhibited heterogeneity. In particular, the ORR analysis revealed marked variability (I^2=72.4%). Thus, a random effects model was used. To elucidate potential sources of heterogeneity, subgroup analyses were performed examining factors, such as PVTT, TACE, SBRT, BCLC stage C tumors, RT metrology, treatment sequence and biomarkers. The ORRs ranged from 47.1% in patients belonging to the PVTT group to 58.4% in patients belonging to the SBRT group. The heterogeneity can be attributed to differences in study designs, patient populations and treatment protocols across the included studies. For example, the total radiation doses varied from 24 to 60 Gy, while a diverse spectrum of ICIs was employed, potentially impacting treatment outcomes.

The present study demonstrated that the ORR of patients in the PD-L1 inhibitor group (69.8%) was significantly higher compared with that of patients in the PD-1 inhibitor group (52.1%). This indicates that biomarkers can predict therapeutic efficacy. However, the conclusions are limited due to the lack of systematic biomarker detection and stratification. Future studies must include key biomarkers for stratified analysis to identify subgroups that can benefit from combination therapy and assist in individualized precision treatment. Variations in follow-up duration and outcome definitions may also have contributed to the observed heterogeneity. The results of sensitivity analyses, which were performed by systematically excluding one study at a time, supported the robustness of the findings. However, the high heterogeneity suggests that caution must be exercised in generalizing the results. Future studies must use meta-regression techniques to investigate the sources of heterogeneity, although a limited number of available studies may constrain such analyses. The findings of the present study provide valuable insights into the therapeutic potential of ICI-RT combinations for aHCC, highlighting the need for standardized protocols and implementing homogeneous study designs in future clinical trials.

The present study has several limitations. The AE rates were not significantly different between the combination therapy and monotherapy approaches. Thus, the comparative safety profiles are not conclusive, especially for high-risk patients with PVTT. Heterogeneity in sample sizes, follow-up durations and study designs across included trials may affect the evidence quality and consistency, skewing the overall results. The strength of the evidence generated in the analysis is limited due to the absence of RCTs directly comparing RT-immunotherapy combinations with standard-of-care treatments. Although observational studies and single-arm trials are valuable for hypothesis generation, they are associated with selection bias and do not rigorously control confounding factors. Furthermore, potential publication bias may lead to an overestimation of treatment effects. The lack of validated biomarkers to predict the response of patients with aHCC to RT-immunotherapy combination therapies hinders the optimization of patient selection and the personalization of treatment strategies. The studies included in the meta-analysis are mainly retrospective and single-arm trials with small sample sizes and large differences. Thus, these studies can be potentially associated with selection bias and confounding factors and lack strict controls, limiting the generalizability and evidence strength of the results. These limitations indicate the need for performing well-designed RCTs and biomarker studies to further elucidate the role of RT-immunotherapy in aHCC management.

In conclusion, the present meta-analysis demonstrated the therapeutic potential of the ICI-RT combination for aHCC. The synergistic effects of the ICI-RT combination enhanced the response rates and survival outcomes, offering new hope for patients with aHCC. The ICI-RT combination exhibited enhanced efficacy in high-risk subgroups and a favorable safety profile. The findings of the present study challenge current treatment paradigms and may aid in the development of personalized, multimodal therapies for aHCC. The elucidation of the synergistic mechanisms of the immunotherapy-RT combination can aid in improving the outcomes of patients with aHCC who have limited treatment options.

Acknowledgements

Not applicable.

Funding

The present study was supported by a 2024 research project from the Sichuan Science and Technology Department Project (grant no. 2024ZYD0103).

Availability of data and materials

All data generated in the present study are included in the figures and/or tables of this article.

Authors' contributions

RC and XY designed the study and wrote the manuscript. XY, XL and YJ analyzed data. All authors have read and approved the final manuscript. RC and XY confirm the authenticity of all the raw data.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I and Jemal A: Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 74: 229-263, 2024.
2. Bertuccio P, Turati F, Carioli G, Rodriguez T, La Vecchia C, Malvezzi M and Negri E: Global trends and predictions in hepatocellular carcinoma mortality. J Hepatol 67: 302-309, 2017.
3. Valery PC, Laversanne M, Clark PJ, Petrick JL, McGlynn KA and Bray F: Projections of primary liver cancer to 2030 in 30 countries worldwide. Hepatology 67: 600-611, 2018.
4. Cheng AL, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, Lim HY, Kudo M, Breder V, Merle P, *et al*: Updated efficacy and safety data from IMbrave150: Atezolizumab plus bevacizumab vs. sorafenib for unresectable hepatocellular carcinoma. J Hepatol 76: 862-873, 2022.
5. Llovet JM, Kudo M, Merle P, Meyer T, Qin S, Ikeda M, Xu R, Edeline J, Ryoo BY, Ren Z, *et al*: Lenvatinib plus pembrolizumab versus lenvatinib plus placebo for advanced hepatocellular carcinoma (LEAP-002): A randomised, double-blind, phase 3 trial. Lancet Oncol 24: 1399-1410, 2023.
6. Sangro B, Chan SL, Kelley RK, Lau G, Kudo M, Sukeepaisarnjaroen W, Yarchoan M, De Toni EN, Furuse J, Kang YK, *et al*: Four-year overall survival update from the phase III HIMALAYA study of tremelimumab plus durvalumab in unresectable hepatocellular carcinoma. Ann Oncol 35: 448-457, 2024.
7. Zongyi Y and Xiaowu L: Immunotherapy for hepatocellular carcinoma. Cancer Lett 470: 8-17, 2020.
8. Finn RS, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, Kudo M, Breder V, Merle P, Kaseb AO, *et al*: Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. N Engl J Med 382: 1894-1905, 2020.
9. Huang Y, Zhang Y, Zhang M, Zhao K, Feng L, Guan J, Dong R, Liu J, Tian D, Liu M, *et al*: Combined immunotherapy for hepatocellular carcinoma: How to maximize immune checkpoint blockade synergic anti-tumor effect. Crit Rev Oncol Hematol 189: 104070, 2023.
10. Yang Y, Swierczak A, Ibahim M, Paiva P, Cann L, Stevenson AW, Crosbie JC, Anderson RL and Rogers PAW: Synchrotron microbeam radiotherapy evokes a different early tumor immunomodulatory response to conventional radiotherapy in EMT6.5 mammary tumors. Radiother Oncol 133: 93-99, 2019.
11. Li JX, Su TS, Gong WF, Zhong JH, Yan LY, Zhang J, Li LQ, He ML, Zhang RJ, Du YQ, *et al*: Combining stereotactic body radiotherapy with camrelizumab for unresectable hepatocellular carcinoma: A single-arm trial. Hepatol Int 16: 1179-1187, 2022.
12. Chiang CL, Lee FAS, Chan KSK, Lee VWY, Chiu KWH, Ho RLM, Fong JKS, Wong NSM, Yip WWL, Yeung CSY, *et al*: Survival outcome analysis of stereotactic body radiotherapy and immunotherapy (SBRT-IO) versus SBRT-alone in unresectable hepatocellular carcinoma. Liver Cancer 13: 265-276, 2024.
13. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, *et al*: New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 45: 228-247, 2009.
14. Chiang CL, Chiu KW, Lee FA, Kong FS and Chan AC: Combined stereotactic body radiotherapy and immunotherapy versus transarterial chemoembolization in locally advanced hepatocellular carcinoma: A propensity score matching analysis. Front Oncol 11: 798832, 2021.

15. Chiang CL, Chiu KWH, Chan KSK, Lee FAS, Li JCB, Wan CWS, Dai WC, Lam TC, Chen W, Wong NSM, *et al*: Sequential transarterial chemoembolisation and stereotactic body radiotherapy followed by immunotherapy as conversion therapy for patients with locally advanced, unresectable hepatocellular carcinoma (START-FIT): A single-arm, phase 2 trial. Lancet Gastroenterol Hepatol 8: 169-178, 2023.
16. Juloori A, Katipally RR, Lemons JM, Singh AK, Iyer R, Robbins JR, George B, Hall WA, Pitroda SP, Arif F, *et al*: Phase 1 randomized trial of stereotactic body radiation therapy followed by nivolumab plus Ipilimumab or nivolumab alone in advanced/unresectable hepatocellular carcinoma. Int J Radiat Oncol Biol Phys 115: 202-213, 2023.
17. Kim BH, Park HC, Kim TH, Koh YH, Hong JY, Cho Y, Sinn DH, Park B and Park JW: Concurrent nivolumab and external beam radiation therapy for hepatocellular carcinoma with macrovascular invasion: A phase II study. JHEP Rep 6: 100991, 2024.
18. Li JX, Deng WX, Huang ST, Lin XF, Long MY, Zhang J, Su TS, Li LQ, Pang YD, Liang CF, *et al*: Efficacy and safety of radiotherapy plus anti-PD1 versus transcatheter arterial chemoembolization plus sorafenib for advanced hepatocellular carcinoma: A real-world study. Radiat Oncol 17: 106, 2022.
19. Ning C, Jia J, Zhang X, Sun J, Wang Y, Xue J, Zhang L, Hou X, Yang X, Sang X, *et al*: Efficacy and safety of subsequent radiotherapy in patients with advanced-stage hepatocellular carcinoma treated with immune checkpoint inhibitors. Hepatobiliary Surg Nutr 12: 882-897, 2023.
20. Ning C, Zhang X, Wang Y, Yang X, Yang X, Chao J, Xun Z, Xue J, Wang Y, Sun H, *et al*: Radiation therapy with combination therapy of immune checkpoint inhibitors and antiangiogenic therapy for hepatocellular carcinoma. Int J Radiat Oncol Biol Phys 118: 1461-1471, 2024.
21. Tai D, Loke K, Gogna A, Kaya NA, Tan SH, Hennedige T, Ng D, Irani F, Lee J, Lim JQ, *et al*: Radioembolisation with Y90-resin microspheres followed by nivolumab for advanced hepatocellular carcinoma (CA 209-678): A single arm, single centre, phase 2 trial. Lancet Gastroenterol Hepatol 6: 1025-1035, 2021.
22. Wang Q, Ji X, Sun J, Zhang A, Jia J, Zhang T, Li W and Duan X: Stereotactic body radiotherapy combined with lenvatinib with or without PD-1 inhibitors as initial treatment for unresectable hepatocellular carcinoma. Int J Radiat Oncol Biol Phys 120: 1363-1376, 2024.
23. Xiang YJ, Wang K, Zheng YT, Feng S, Yu HM, Li XW, Cheng X, Cheng YQ, Feng JK, Zhou LP, *et al*: Effects of stereotactic body radiation therapy plus PD-1 inhibitors for patients with transarterial chemoembolization refractory. Front Oncol 12: 839605, 2022.
24. Yu S, Yu M, Keane B, Mauro DM, Helft PR, Harris WP, Sanoff HK, Johnson MS, O'Neil B, McRee AJ and Somasundaram A: A pilot study of pembrolizumab in combination with Y90 radioembolization in subjects with poor prognosis hepatocellular carcinoma. Oncologist 29: 270-e413, 2024.
25. Lin LW, Yan LY, Ke K, Yang WZ, Lin JQ and Huang N: Efficacy and safety of transarterial chemoembolization combined with lenvatinib, programmed death-1 inhibitor, and iodine-125 seed brachytherapy for hepatocellular carcinoma with portal vein tumor thrombosis. Brachytherapy 22: 858-871, 2023.
26. Zhang Z, Li C, Liao W, Huang Y and Wang Z: A combination of sorafenib, an immune checkpoint inhibitor, TACE and stereotactic body radiation therapy versus sorafenib and TACE in advanced hepatocellular carcinoma accompanied by portal vein tumor thrombus. Cancers (Basel) 14: 3619, 2022.
27. Zhu M, Liu Z, Chen S, Luo Z, Tu J, Qiao L, Wu J, Fan W and Peng Z: Sintilimab plus bevacizumab combined with radiotherapy as first-line treatment for hepatocellular carcinoma with portal vein tumor thrombus: A multicenter, single-arm, phase 2 study. Hepatology 80: 807-815, 2024.
28. Raoul JL, Bruix J, Greten TF, Sherman M, Mazzaferro V, Hilgard P, Scherubl H, Scheulen ME, Germanidis G, Dominguez S, *et al*: Relationship between baseline hepatic status and outcome, and effect of sorafenib on liver function: SHARP trial subanalyses. J Hepatol 56: 1080-1088, 2012.
29. Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, de Oliveira AC, Santoro A, Raoul JL, Forner A, *et al*: Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 359: 378-390, 2008.
30. Yamashita T, Kudo M, Ikeda K, Izumi N, Tateishi R, Ikeda M, Aikata H, Kawaguchi Y, Wada Y, Numata K, *et al*: REFLECT-a phase 3 trial comparing efficacy and safety of lenvatinib to sorafenib for the treatment of unresectable hepatocellular carcinoma: An analysis of Japanese subset. J Gastroenterol 55: 113-122, 2020.
31. Kudo M, Ueshima K, Ikeda M, Torimura T, Tanabe N, Aikata H, Izumi N, Yamasaki T, Nojiri S, Hino K, *et al*: Final results of TACTICS: A randomized, prospective trial comparing transarterial chemoembolization plus sorafenib to transarterial chemoembolization alone in patients with unresectable hepatocellular carcinoma. Liver Cancer 11: 354-367, 2022.
32. Kudo M, Ueshima K, Ikeda M, Torimura T, Tanabe N, Aikata H, Izumi N, Yamasaki T, Nojiri S, Hino K, *et al*: Randomised, multicentre prospective trial of transarterial chemoembolisation (TACE) plus sorafenib as compared with TACE alone in patients with hepatocellular carcinoma: TACTICS trial. Gut 69: 1492-1501, 2020.
33. Kelley RK, Ryoo BY, Merle P, Park JW, Bolondi L, Chan SL, Lim HY, Baron AD, Parnis F, Knox J, *et al*: Second-line cabozantinib after sorafenib treatment for advanced hepatocellular carcinoma: A subgroup analysis of the phase 3 CELESTIAL trial. ESMO Open 5: e000714, 2020.
34. Zhu AX, Kang YK, Yen CJ, Finn RS, Galle PR, Llovet JM, Assenat E, Brandi G, Pracht M, Lim HY, *et al*: Ramucirumab after sorafenib in patients with advanced hepatocellular carcinoma and increased alpha-fetoprotein concentrations (REACH-2): A randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 20: 282-296, 2019.
35. Yau T, Park JW, Finn RS, Cheng AL, Mathurin P, Edeline J, Kudo M, Harding JJ, Merle P, Rosmorduc O, *et al*: Nivolumab versus sorafenib in advanced hepatocellular carcinoma (CheckMate 459): A randomised, multicentre, open-label, phase 3 trial. Lancet Oncol 23: 77-90, 2022.
36. Kudo M, Finn RS, Edeline J, Cattan S, Ogasawara S, Palmer DH, Verslype C, Zagonel V, Fartoux L, Vogel A, *et al*: Updated efficacy and safety of KEYNOTE-224: A phase II study of pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib. Eur J Cancer 167: 1-12, 2022.
37. Li Q, Cao M, Lei L, Yang F, Li H, Yan X, He S, Zhang S, Teng Y, Xia C and Chen W: Burden of liver cancer: From epidemiology to prevention. Chin J Cancer Res 34: 554-566, 2022.
38. Kelley RK, Rimassa L, Cheng AL, Kaseb A, Qin S, Zhu AX, Chan SL, Melkadze T, Sukeepaisarnjaroen W, Breder V, *et al*: Cabozantinib plus atezolizumab versus sorafenib for advanced hepatocellular carcinoma (COSMIC-312): A multicentre, open-label, randomised, phase 3 trial. Lancet Oncol 23: 995-1008, 2022.
39. Kang SP, Gergich K, Lubiniecki GM, de Alwis DP, Chen C, Tice MAB and Rubin EH: Pembrolizumab KEYNOTE-001: An adaptive study leading to accelerated approval for two indications and a companion diagnostic. Ann Oncol 28: 1388-1398, 2017.
40. Yau T, Kang YK, Kim TY, El-Khoueiry AB, Santoro A, Sangro B, Melero I, Kudo M, Hou MM, Matilla A, *et al*: Efficacy and safety of nivolumab plus ipilimumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib: The CheckMate 040 randomized clinical trial. JAMA Oncol 6: e204564, 2020.
41. Yang Y, Xiong L, Li M, Jiang P, Wang J and Li C: Advances in radiotherapy and immunity in hepatocellular carcinoma. J Transl Med 21: 526, 2023.
42. Haikerwal SJ, Hagekyriakou J, MacManus M, Martin OA and Haynes NM: Building immunity to cancer with radiation therapy. Cancer Lett 368: 198-208, 2015.
43. Chen MF, Chen PT, Hsieh CC and Wang CC: Effect of proton therapy on tumor cell killing and immune microenvironment for hepatocellular carcinoma. Cells 12: 332, 2023.
44. Frey B, Rubner Y, Wunderlich R, Weiss EM, Pockley AG, Fietkau R and Gaipl US: Induction of abscopal anti-tumor immunity and immunogenic tumor cell death by ionizing irradiation-implications for cancer therapies. Curr Med Chem 19: 1751-1764, 2012.
45. Bernstein MB, Krishnan S, Hodge JW and Chang JY: Immunotherapy and stereotactic ablative radiotherapy (ISABR): A curative approach? Nat Rev Clin Oncol 13: 516-524, 2016.
46. Sharabi AB, Lim M, DeWeese TL and Drake CG: Radiation and checkpoint blockade immunotherapy: Radiosensitisation and potential mechanisms of synergy. Lancet Oncol 16: e498-e509, 2015.
47. Friedman D, Baird JR, Young KH, Cottam B, Crittenden MR, Friedman S, Gough MJ and Newell P: Programmed cell death-1 blockade enhances response to stereotactic radiation in an orthotopic murine model of hepatocellular carcinoma. Hepatol Res 47: 702-714, 2017.

48. Chiang CL, Chan ACY, ChiuKWH and Kong FS: Combined stereotactic body radiotherapy and checkpoint inhibition in unresectable hepatocellular carcinoma: A potential synergistic treatment strategy. Front Oncol 9: 1157, 2019.
49. Dawood ZS, Brown ZJ, Alaimo L, Lima HA, Shaikh C, Katayama ES, Munir MM, Moazzam Z, Endo Y, Woldesenbet S and Pawlik TM: Comparison of tumor response and outcomes of patients with hepatocellular carcinoma after multimodal treatment including immune checkpoint inhibitors-a systematic review and meta-analysis. HPB (Oxford) 26: 618-629, 2024.
50. Meyers BM, Knox JJ, Liu DM, McLeod D, Ramjeesingh R, Tam VC and Lim HJ: The evolution of immune checkpoint inhibitor combinations in advanced hepatocellular carcinoma-A systematic review. Cancer Treat Rev 118: 102584, 2023.
51. Tian C, Yu Y, Wang Y, Yang L, Tang Y, Yu C, Feng G, Zheng D and Wang X: Neoadjuvant immune checkpoint inhibitors in hepatocellular carcinoma: A meta-analysis and systematic review. Front Immunol 15: 1352873, 2024.
52. Xie E, Yeo YH, Scheiner B, Zhang Y, Hiraoka A, Tantai X, Fessas P, de Castro T, D'Alessio A, Fulgenzi CAM, *et al*: Immune checkpoint inhibitors for child-pugh class B advanced hepatocellular carcinoma: A systematic review and meta-analysis. JAMA Oncol 9: 1423-1431, 2023.
53. Higgins K, Hu C, Ross H, Jabbour S, Kozono D, Owonikoko T, Dib EG, Brownstein JM, Kuzma C, Kotecha R, *et al*: Concurrent chemoradiation±atezolizumab (atezo) in limited-stage small cell lung cancer (LS-SCLC): Results of NRG Oncology/Alliance LU005. Int J Radiat Oncol Biol Phys 120: S2, 2024.
54. Dovedi SJ, Adlard AL, Lipowska-Bhalla G, McKenna C, Jones S, Cheadle EJ, Stratford IJ, Poon E, Morrow M, Stewart R, *et al*: Acquired resistance to fractionated radiotherapy can be overcome by concurrent PD-L1 blockade. Cancer Res 74: 5458-5468, 2014.
55. Gunderson AJ and Young KH: Exploring optimal sequencing of radiation and immunotherapy combinations. Adv Radiat Oncol 3: 494-505, 2018.
56. Young KH, Baird JR, Savage T, Cottam B, Friedman D, Bambina S, Messenheimer DJ, Fox B, Newell P, Bahjat KS, *et al*: Optimizing timing of immunotherapy improves control of tumors by hypofractionated radiation therapy. PLoS One 11: e0157164, 2016.
57. Abou-Alfa GK, Lau G, Kudo M, Chan SL, Kelley RK, Furuse J, Sukeepaisarnjaroen W, Kang YK, Van Dao T, De Toni EN, *et al*: Tremelimumab plus durvalumab in unresectable hepatocellular carcinoma. NEJM Evid 1: EVIDoa2100070, 2022.
58. Mosele MF, Westphalen CB, Stenzinger A, Barlesi F, Bayle A, Bièche I, Bonastre J, Castro E, Dienstmann R, Krämer A, *et al*: Recommendations for the use of next-generation sequencing (NGS) for patients with advanced cancer in 2024: A report from the ESMO precision medicine working group. Ann Oncol 35: 588-606, 2024.
59. Chan TA, Yarchoan M, Jaffee E, Swanton C, Quezada SA, Stenzinger A and Peters S: Development of tumor mutation burden as an immunotherapy biomarker: Utility for the oncology clinic. Ann Oncol 30: 44-56, 2019.
60. Kumar S, Nadda N, Quadri A, Kumar R, Paul S, Tanwar P, Gamanagatti S, Dash NR, Saraya A, Shalimar and Nayak B: Assessments of TP53 and CTNNB1 gene hotspot mutations in circulating tumour DNA of hepatitis B virus-induced hepatocellular carcinoma. Front Genet 14: 1235260, 2023.
61. Bernicker E: Next-Generation sequencing and immunotherapy biomarkers: A medical oncology perspective. Arch Pathol Lab Med 140: 245-248, 2016.
62. Cui Y, Li B, Pollom EL, Horst KC and Li R: Integrating radiosensitivity and immune gene signatures for predicting benefit of radiotherapy in breast cancer. Clin Cancer Res 24: 4754-4762, 2018.
63. Jang BS and Kim IA: A radiosensitivity gene signature and PD-L1 predict the clinical outcomes of patients with lower grade glioma in TCGA. Radiother Oncol 128: 245-253, 2018.
64. Lee JH, Lee JH, Lim YS, Yeon JE, Song TJ, Yu SJ, Gwak GY, Kim KM, Kim YJ, Lee JW and Yoon J: Sustained efficacy of adjuvant immunotherapy with cytokine-induced killer cells for hepatocellular carcinoma: An extended 5-year follow-up. Cancer Immunol Immunother 68: 23-32, 2019.
65. Chen L, Zhang R, Lin Z, Tan Q, Huang Z and Liang B: Radiation therapy in the era of immune treatment for hepatocellular carcinoma. Front Immunol 14: 1100079, 2023.