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The synergistic role of ultrasound-guided interventions and radiotherapy in hepatocellular carcinoma: A meta-analysis of treatment outcomes

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► ***Original article***

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ABSTRACT

Background: To assess the effectiveness and safety of combining ultrasound-guided interventional therapy with radiotherapy (RT) in treating Hepatocellular Carcinoma (HCC). ***Materials and Methods:*** Literature was searched in PubMed, Coghlan's database and Web of Science (WOS) up to November 2024 without language restriction. Outcome indicators included complete response (CR), partial response (PR), stable disease (SD), disease progression (PD), 1-year survival rate, and adverse events (AEs). The Cochrane Collaboration tool was utilized to evaluate the risk of bias in the included studies. Statistical analysis was performed based on revman software, and P<0.05 was considered statistically significant. ***Results:*** Five studies were included in the analysis, and the overall quality of the studies was high. The combination therapy group demonstrated statistically significant differences compared to the control group in PR (OR=2.14, 95% CI: 1.32–3.48, P=0.002), PD (OR=0.45, 95% CI: 0.27–0.76, P=0.003), and AEs (OR=0.54, 95% CI: 0.35–0.82, P=0.004). No statistically significant differences were observed between the two groups in terms of CR (OR=1.31, 95% CI: 0.24–7.01, P=0.760), SD (OR=0.88, 95% CI: 0.50–1.55, P=0.670), and one-year survival rate (OR=1.62, 95% CI: 0.85–3.09, P=0.140). ***Conclusion:*** Ultrasound-guided interventional therapy combined with RT demonstrates certain clinical advantages in the treatment of HCC, particularly in improving PR, reducing PD, and managing AEs. Additional studies are required to confirm its long-term effectiveness and safety.

INTRODUCTION

Primary liver cancer (PLC) is the commonest type of liver cancer (LC), which is characterized by rapid onset and high malignancy [1]. PLC, as a common and severe malignant gastrointestinal tumor, holds a significant position both in China and worldwide. HCC accounts for approximately 90% of PLC cases [2]. Alcoholic cirrhosis, prolonged carcinogen exposure, and specific genetic factors are significant risk factors HCC [3, 4]. Advanced liver cancer symptoms, including abdominal pain, weight loss, jaundice, and ascites, frequently lead to delayed diagnosis and treatment of HCC [5, 6]. Lifestyle changes have elevated the incidence of metabolic syndrome and obesity, subsequently raising the prevalence of non-alcoholic fatty liver disease. This condition of lifestyle changing is considered as a significant risk indicator for HCC, contributing to the annual increase in HCC patients [7, 8]. The prevalence of HCC adversely impacts patients' physical health and imposes substantial psychological and financial strains on both patients and their families [9]. Finding effective treatment options is crucial to improving patient quality of life.

Treatment options for HCC include surgery, local therapies, transcatheter arterial chemoembolization (TACE), radiotherapy (RT), and targeted therapy [10, 11]. Clinicians determine the optimal treatment strategy based on tumor stage, and the overall health status. High-intensity focused ultrasound (HIFU) is employing focused ultrasound waves to generate high temperatures, inducing coagulative necrosis of tumor tissues. It is particularly suitable for patients with small, well-demarcated tumors and those who are ineligible for surgery or liver transplantation [13]. The key advantages of HIFU consist of noninvasiveness, short recovery period, and target tumors in anatomically challenging locations. However, its efficacy is limited for larger tumors or lesions near critical structures, and incomplete ablation may occur in tumors with irregular shapes [14]. RT Uses high-energy ionizing radiation to shrink tumors through radioisotopes. It is usually indicated as an intervention for patients with moderately advanced HCC or those who have been assessed as unsuitable for surgery or other local therapies [15].

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The primary advantage of RT lies in its ability to effectively treat large tumors or those adjacent to critical structures that may not be amenable to HIFU. However, radiation-induced liver injury remains a significant concern in treatment decision-making [16]. Overall, both HIFU and RT have demonstrated efficacy in controlling tumor progression and improving survival outcomes in HCC patients. This study was the first to systematically evaluate the evidence-based medical evidence of the synergistic effect of ultrasound-guided interventional therapy and RT, breaking through the limitations of previous efficacy analyses that have been singularly focused on radiotherapy or local ablation. Secondly, the multidimensional efficacy evaluation system reveals the unique advantages of this combination therapy in the dynamic change of tumor response, which provides a new basis for optimizing the sequential treatment regimen in terms of slowing down the progression of the disease and improving the safety of the treatment.

MATERIALS AND METHODS

The research followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, and is registered on the INPLASY platform with a specific registration number (INPLASY2024110094). Relevant records are available at Inplasy.com (https://inplasy.com/). This study was a secondary data analysis of previously published literature that did not involve any patient data use and therefore did not require patient consent.

Study population and inclusion and exclusion criteria

This study included publicly available randomized controlled trials (RCTs) and semi-randomized controlled trials (CCTs) without language restrictions. Additionally, clinical studies that did not publish complete methodological details but provided sufficient data for analysis were also considered. Data were included in the analysis if the data met the following criteria. (1) randomized controlled trials published in peer-reviewed journals; (2) patients with a confirmed diagnosis of hepatocellular carcinoma (HCC); (3) experimental groups receiving ultrasound-guided therapies; (4) control groups undergoing a single treatment modality; and (5) studies reporting complete remission (CR), partial remission (PR), stable disease (SD), progressive disease (PD), 1-year survival rate, or adverse events (AEs). Studies with the following scenarios were excluded from analysis. (1) duplicate studies; (2) studies with identical/incomplete data, with preference given to the most recent study from the same research center; (3) conference abstracts, case reports, or literature lacking relevant data; (4) studies investigating multiple combination therapies; and (5) literature unavailable in its original form.

Intervention measures

The experimental group in this study received a combination of ultrasound-guided treatment and RT as intervention measures. The control group was treated with only a single treatment modality, such as HIFU alone, RT, or surgical treatment. In all the included studies, the treatment protocols for both the experimental and control groups had clearly defined intervention criteria, and all treatments were administered by trained professional physicians.

Outcome indicators

CR: the complete disappearance of the tumor with no measurable lesions. PR: Refers to a reduction in tumor size by more than 50%, but the tumor has not completely disappeared. SD: Refers to no significant progression of the tumor after treatment, and it has not met the criteria for remission. PD: Refers to tumor growth or the appearance of new lesions after treatment. One-year Survival Rate: Refers to the proportion of patients who remain alive within one year after receiving treatment. AEs: Includes all negative reactions occurring during the treatment process, such as liver damage and skin reactions caused by radiotherapy. All the included studies reported at least one outcome indicator, with clear and comparable evaluation standards.

Search strategy

In November 2024, a comprehensive search was conducted in PubMed, Cochrane Library, and Web of Science databases (WoS) database. The search employed both indexed and free-text terms, with the strategy tailored to each database's characteristics. We also examined references from seminal review articles. The WHO International Clinical Trials Registry Platform (ICTRP) was also searched to identify any studies that might have been overlooked. EndNote software (EndNote X9, Australia) was utilized for literature management.

Screening of literature and extraction of data

Two independent researchers first reviewed titles and abstracts to exclude articles that did not meet the inclusion criteria. Full texts were then independently reviewed to identify potentially eligible studies. In instances of uncertainty, discussions were held, and a third researcher resolved any persisting ambiguities if needed. The extracted data included publication year, authorship, clinical characteristics, intervention protocols, outcome measures and adverse events. For multi-arm studies, only data from the eligible study arms were extracted. When there was disagreement about whether to include the study, a third researcher was invited to vote.

Assessment of study quality

Two researchers assessed the bias of the studies

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by using the Cochrane Collaboration's risk of bias tool. This tool evaluates key methodological domains, including blinding of participants and researchers, blinding of outcome assessment, random sequence generation, allocation concealment, completeness of outcome data, selective reporting, and other potential sources of bias. The studies were divided into low, unclear, or high risk of bias. When there was disagreement in the two researchers, a third researcher adjudicated the final decision.

Statistical analysis

RevMan software version 5.4 (RevMan software, United Kingdom) was used to do the analysis of data. The meta-analysis employed Odds Ratio (OR) as the primary effect size measure for binary outcome variables. The precision of the effect size was assessed using the 95% confidence interval (CI) of the OR. When the 95% CI of the OR includes 1, it indicates a lack of significant effect of the intervention on the outcome. Statistical analyses were conducted using two-sided tests with a significance threshold of $P < 0.05$.

RESULTS

Literature search results

In PubMed, search strategy #1 retrieved 14,931 articles, #2 retrieved 312,681 articles, and #3 retrieved 158,466 articles. The combined search (#1 AND #2 AND #3) yielded 30 relevant articles. In the Web of Science (WOS) database, #1 retrieved 842,919 articles, #2 retrieved 1,759,236 articles, and #3 retrieved 446,160 articles, with 2,706 articles identified through the combined search. Similarly, in the Scopus database, #1 retrieved 796,239 articles, #2 retrieved 802,675 articles, and #3 retrieved 352,529 articles, yielding 1,972 articles after applying the combined search strategy. Additionally, 34 relevant references were identified through a review of existing literature and Clinical Trials.gov. After merging and deduplicating all identified records, 4,271 articles remained. Following further screening, the data of five studies were analyzed (figure 1).

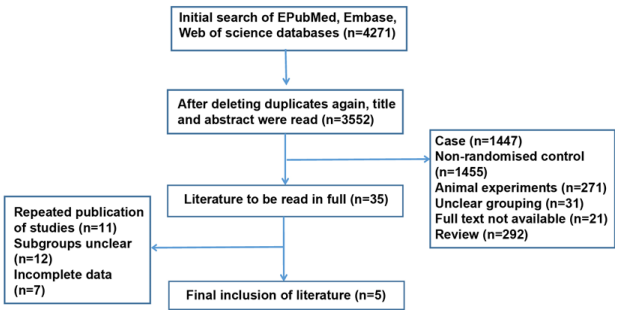

Figure 1. The process and fundamental details about the studies included.

Characteristics of the studies

The five studies were published as early as 2011 and as late as 2018. All studies clearly mentioned the diagnostic criteria, inclusion and exclusion criteria. All patients met the pathologic diagnostic criteria for hepatocellular carcinoma. Each study explicitly mentioned the treatment regimen (synergistic treatment group vs. control group) including, but not limited to, the radiation dose, radiation cycles, and specific sessions of ultrasound-guided interventions. The basic information for this analysis was presented in table 1.

Table 1. Basic information of the literature.

No.	Study	Publication year	Synergistic treatment group	Control group	Research type
1	Ke *et al.* (17)	2011	3DCRT & HIFU	surgical resection	RCT
2	Ding *et al.* (18)	2016	3DCRT & RFA	Radiotherapy	RCT
3	Li *et al.* (19)	2014	3DCRT & HIFU	Radiotherapy	RCT
4	Wang *et al.* (20)	2018	3DCRT & HIFU	SBRT	RCT
5	Zhou *et al.* (21)	2015	IMRT & HIFU	IMRT	RCT

Note: IMRT (Intensity-Modulated Radiation Therapy); RFA: HIFU (High-Intensity Focused Ultrasound); 3DCRT (Three-Dimensional Conformal Radiation Therapy); SBRT (Stereotactic Body Radiation Therapy); RCT (Randomized Controlled Trial).

Risk of bias assessment

An evaluation of bias was conducted, using green for low risk, white for unclear risk, and red for high risk. The majority of studies showed a low risk of bias in randomized sequence generation, allocation concealment, and outcome assessment blinding. However, there were instances of unclear or high risk in participant and researcher blinding, as well as in selective reporting (figure 2A). The included studies were generally of high quality, though some exhibited a potential risk of bias that warrants attention (figure 2B).

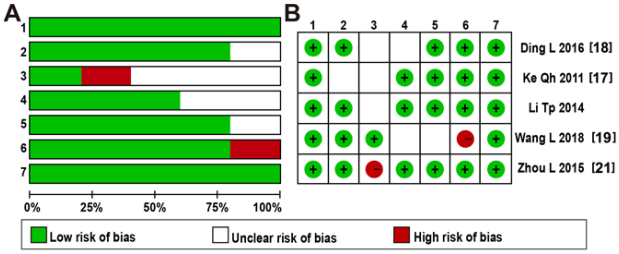

Figure 2. Article quality evaluation charts (**A.** Risk of bias graph; **B.** Risk of bias summary).

Note: 1.Random sequence generation to address selection bias. Allocation concealment (selection bias): 3.Blinding of participants and personnel (performance bias); 4.Blinding of participants and personnel, as well as outcome assessment (detection bias), 5.Incomplete outcome data (attrition bias); 6.Selective reporting (reporting bias); 7.Other bias.

Meta-analysis of outcome indicators

Efficacy indicators

The meta-analysis demonstrated no statistically significant difference in the CR rate between the synergistic treatment group and the control group (OR=1.31, 95% CI: 0.24–7.01, P=0.760) (figure 3A).

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Heterogeneity analysis indicated moderate heterogeneity across studies (I^2 = 67%, P=0.030). In contrast, the PR rate was significantly higher in the synergistic treatment group compared to the control group (OR=2.14, 95% CI: 1.32–3.48, P=0.002), with no heterogeneity observed (I^2 = 0, P = 0.460) (figure 3B). No significant difference in SD was found between the synergistic treatment group and the control group (OR = 0.88, 95% CI: 0.50–1.55, P = 0.670), and no heterogeneity was detected (I^2 = 0, P=0.430) (figure 3C). Finally, the PD rate was significantly lower in the synergistic treatment group (OR = 0.45, 95% CI: 0.27–0.76, P = 0.003), with no evidence of heterogeneity (I^2 = 0, P = 0.720) (figure 3D).

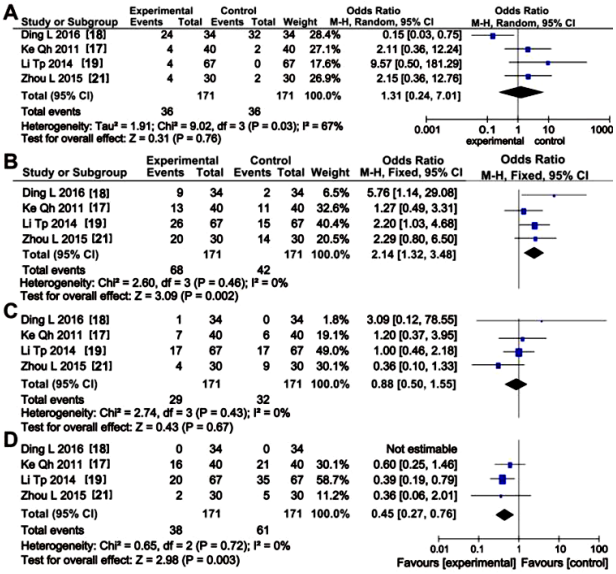

Figure 3. Meta-analysis of efficacy indicators between experimental and control groups. (**A.** CR; **B.** PR; **C.** SD; **D.** PD)

Note: Diamond symbols: combined total effect sizes and their confidence intervals, located at the bottom of the chart; M-H. Fixed: OR and its 95% CI calculated by Mantel-Haenszel fixed-effects model; Weight: the weight (%) of each study in the combined results, reflecting its contribution to the total effect size (the higher the weight, the higher the precision of the study).

Survival Indicators

The 1-year survival rate was a common endpoint in four of the included studies. The meta-analysis indicated no significant difference in 1-year survival rates between the synergistic treatment and control groups (OR=1.62, 95%CI: 0.85–3.09, P=0.140) (Figure 4A). The synergistic treatment and control groups showed no heterogeneity (I^2=11%, P=0.330).

Adverse Events (AEs)

The meta-analysis indicated a significant difference in AEs between the synergistic treatment and control groups (OR=0.54, 95%CI: 0.35–0.82, P=0.004) (Figure 4B). The synergistic treatment group exhibited fewer AEs than the control group, indicating that synergistic treatment may enhance both efficacy and safety. There was no significant heterogeneity between the two groups (I^2=39%, P=0.180).

Subgroup analysis

Subgroup analysis revealed that patient treatment benefits between the synergistic treatment group and the control group were not influenced by sex (OR = 1.11, 95% CI: 0.71–1.72, P = 0.650) or HCC stage (OR = 1.02, 95% CI: 0.69–1.49, P = 0.500). The event numbers of Stage- HCC in the synergistic treatment group and control group were 55/171 and 82/171, with OR of 0.38 (95% CI: 0.09–1.69; P = 0.200). Significant heterogeneity was observed (I^2 = 79%, P = 0.008). The event numbers of Stage-Ⅱ in the synergistic treatment group and control group were 79/171 and 71/171, with OR of 1.21 (95% CI: 0.79–1.86; P = 0.380), with no heterogeneity (I^2 = 0%, P = 0.750). The event numbers of Stage-III in the synergistic treatment group and control group were 36/171 and 17/171, resulting in a pooled OR of 7.09 (95% CI: 0.02–2128.96; P = 0.500). Extremely high heterogeneity was detected (I^2 = 93%, P 0.001). Tests for subgroup differences indicated no statistically significant variations in effect sizes across subgroups (Chi^2 = 2.55, df = 3, P = 0.470; I^2 = 0%).

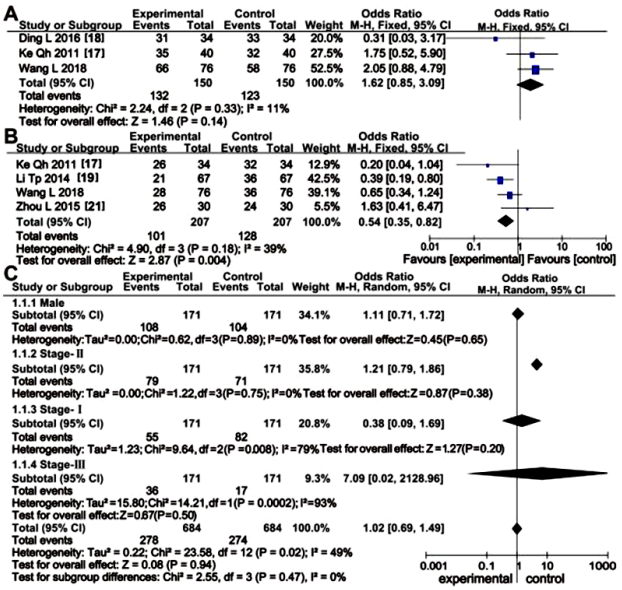

Figure 4. One-year survival rate, AEs and subgroup analysis (**A.** 1-year survival rate; **B.** AEs; **C.** subgroup analysis).

Note: Diamond symbols: combined total effect sizes and their confidence intervals, located at the bottom of the chart; M-H. Random: OR and its 95% CI calculated by Mantel-Haenszel random-effects model; Weight: the weight (%) of each study in the combined results, reflecting its contribution to the total effect size (the higher the weight, the higher the precision of the study); Z-value and P-value: testing whether the combined OR is significant or not.

Sensitivity analysis

A sensitivity analysis was conducted for outcome indicators showing statistically significant differences between the experimental and control groups by excluding studies one at a time. The sensitivity

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analysis demonstrated that the findings were consistent even after the sequential exclusion of studies.

Table 3. Sensitivity analysis parameters (One-by-One Exclusion Method).

Project-by-project exclusion	OR [95%CI]	Chi^2	Df (P)	I^2 (%)	z(P)
PR					
Zhou L 2015[21]	2.11 [1.22, 3.64]	2.57	2(0.28)	22	2.67(0.008)
Ke Qh 2011[17]	2.69 [1.37, 5.28]	1.12	1(0.29)	11	2.87(0.004)
PD					
Zhou L 2015[21]	0.46 [0.27, 0.80]	0.57	1(0.45)	0	2.74(0.006)
Ke Qh 2011[17]	0.39 [0.19, 0.79]	/	/	/	2.61(0.009)
AEs					
Zhou L 2015[21]	0.47 [0.30, 0.74]	2.20	2(0.33)	9	3.24(0.001)
Wang L 2018[20]	0.35 [0.18, 0.66]	0.53	1(0.47)	0	3.21(0.001)

Note: Chi^2: chi-square value of the heterogeneity test; Df(P): degrees of freedom (Df) and the corresponding P-value; I^2(%): heterogeneity statistic; z(P): z-test statistic and its P-value for testing the statistical significance of the combined effect size.

DISCUSSION

Due to the common presence of cirrhosis in most patients with HCC, achieving complete resection through surgery is often challenging. Our meta-analysis suggested that the combination of HIFU and RT can reduce the rate of PD and AEs, while increasing the PR rate, demonstrating superior therapeutic outcomes. The introduction of the HIFU combined with RT technique provides a new non-invasive approach for LC.

Currently, commonly used RT modalities include 3DCRT, carbon-ion radiotherapy (C-ion RT) [22], IMRT, and SBRT [23]. SBRT has proven to be an effective treatment option for both early- and advanced-stage HCC in Barcelona [24]. A study by Fujita *et al*. involving 560 early-stage HCC patients, it was found that early-stage patients without radiofrequency ablation (RFA) indications could benefit from C-ion RT [22]. 3DCRT, developed in the early 1990s, significantly improves the efficacy of radiotherapy. Although, 3DCRT's role in liver cancer treatment has increasingly been recognized, the presence of radio-resistant hypoxic cells and S-phase cells in HCC, especially the necrotic areas at the center of large tumors, often leads to local recurrence in the central region after treatment. Additionally, radiation-induced liver disease (RILD) and delayed radiation changes [25] further limit the applicability of radiotherapy. Kazuhiko *et al*. [26] involved 108 HCC patients found that the Child-Pugh score was a risk factor of RILD. Xu *et al*. [27] compared the efficacy of RFA and surgical resection in HCC patients. Their meta-analysis suggested that RFA had superior safety profiles, which aligns with our findings confirming the safety of RFA. However, Xu et al. also reported that the therapeutic efficacy of RFA alone was inferior to that of surgical resection. Li *et al*. [28] conducted a meta-analysis demonstrating that SBRT exhibited higher safety than surgical resection and achieved longer disease progression-free survival compared to RFA in HCC patients, thereby validating both the efficacy and safety of SBRT. We analyzed the ultrasound-guided interventions combined with RT (figure 3). Our findings provided evidence to support the clinical application of synergistic treatment combining RT and RFA in HCC management.

Numerous studies have investigated the integration of radiotherapy with alternative treatments for liver cancer. Yang *et al*. [29] performed a meta-analysis on 1265 HCC patients treated with surgery plus RT, and found that IMRT combined with surgery might be the optimal choice to prolong OS and disease-free survival (DFS). However, a study by Li *et al*. [30] claimed that the combination of surgery and chemotherapy for LC did not yield the expected outcomes, which might be due to local recurrence and distant metastasis. Transarterial chemoembolization (TACE) combined with RT has shown promising results in several studies, but considering the palliative nature of TACE, repeated TACE treatments can exacerbate liver damage [31]. In subsequent studies, we plan to incorporate subgroup analyses of TACE, a therapeutic approach for HCC, to enable a more comprehensive and objective comparison of the efficacy among TACE, RT, and RFA.

TNM stage is a critical factor influencing therapeutic efficacy in HCC. Wang *et al.* [32] reported in a cohort study that Stage III and IV HCC patients derived differing benefits from RT. Our findings further indicated that except for Stage IV patients (figure 4C). HIFU is an innovative non-invasive method proven effective in ablating solid tumors. HIFU and RT has shown good safety and tolerability in clinical applications. Studies have found that patients who received combined HIFU and RT treatments had a lower incidence of severe adverse events, with most patients being able to tolerate this treatment regimen [33]. This observation aligns with our study (figure 4B), suggesting that this synergistic treatment strategy provides a novel therapeutic option for HCC patients, particularly for those ineligibles for surgical intervention [34]. Some studies have delved into the mechanisms underlying the synergistic effects of HIFU and RT. The combination of HIFU and RT can enhance the activity of NK cells and T lymphocyte subgroups, thereby boosting the patient's immune function and inhibiting tumor cell growth. This approach can effectively help control pain during local treatment.

Although both HIFU and RT have shown certain therapeutic effects, there are relatively few clinical trials involving the combination of these two treatments for HCC. Several factors may contribute to this. First, HIFU is more suitable for patients with tumors that are localized and of moderate size, while RT is better suited for larger tumors or those that cannot be surgically resected [35]. As a result, the

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indications for combined HIFU and RT treatment are somewhat narrow. Second, balancing the dosage and treatment course of HIFU and RT when used in combination, to avoid overlapping effects or overtreatment, is a significant technical and management challenge. The absence of standardized treatment protocols and regimens for combining these two modalities complicates cross-study result comparisons, thereby impacting their clinical acceptability. Our meta-analysis results indicate that the combination of HIFU and RT may provide greater benefits to patients compared to single-modality treatments. The results suggested that synergistic treatment was more beneficial to patients than RT, and we look forward to large-scale randomized controlled trials to pan validate its benefits and long-term efficacy.

This study has some limitations. Although several studies were included, the cohort sizes of most studies were inadequate and there were few high-quality RCTs, which significantly limited the translational potential of the results of these studies. The short duration of follow-up in some reports further precludes the possibility of robust assessment of longitudinal outcomes after combined HIFU and RT. In addition, the enrollment population was largely limited to rigorously screened patients with primary hepatic malignancies who met the eligibility criteria for HIFU/RT. Therefore, extrapolation of these results to a broader clinical setting, particularly to patients with advanced hepatic insufficiency or suffering from complex multi-organ comorbidities, remains speculative and requires systematic validation.

CONCLUSION

This meta-analysis demonstrated that ultrasound-guided intervention combined with RT produced meaningful efficacy in HCC treatment. The combination therapy significantly increased the PR rate in some patient cohorts while reducing PD and AEs. In order to confirm the therapeutic benefits of this multimodal approach and to elucidate its differential efficacy in different HCC subgroups, large-scale clinical trials with extended follow-up will be necessary in the future.

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***Ethical consideration*:** Not applicable.

Author contribution: W.Z., and Y.L., contributed equally to the conception, design, and analysis of the study. W.Z., collected and analyzed the data, and Yu Liu contributed essential insights for interpreting the results. X.L., contributed to data analysis and manuscript drafting. G.C., oversaw the study, guided the methodology, and approved the final manuscript. All authors have reviewed and endorsed the final manuscript.

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