Combination of radiotherapy and ICIs in advanced hepatocellular carcinoma: A systematic review of current evidence and future prospects (Review)

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Abstract. Hepatocellular carcinoma (HCC) is a global health concern because of its rising prevalence and high fatality rates. Conventional treatments for advanced HCC (aHCC) have limited success, emphasizing the need for novel treatment options. Radiotherapy (RT) treatments, such as stereotactic body radiation and proton therapy, improve local tumor management via precision targeting. Moreover, immune checkpoint inhibitors (ICIs) that target the programmed cell death protein 1(PD-1)/PD ligand 1 (PD-L1) and cytotoxic T lymphocyte associated protein 4 (CTLA-4) pathways have promise for systemic antitumor effectiveness. The combination of RT and ICIs takes advantage of their complementary mechanisms: RT kills immunogenic cells and controls the tumor microenvironment to increase antigen presentation, whereas ICIs enhance and maintain antitumor immune responses. This combination enhances tumor regression and immune response in aHCC, improving response rate and progression-free survival with manageable safety. The present review aimed to summarize the rationale for combining RT + ICIs in patients with aHCC and clinical outcomes, as well as ways to enhance this combination technique. The combination of these models is a promising technique for improving outcomes for patients with aHCC and warrants further investigation.

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Abbreviations: aHCC, advanced hepatocellular carcinoma; SBRT, stereotactic body radiation therapy; ICI, immune checkpoint inhibitor; PD-1, targeted programmed death-1; PD-L1, programmed death-ligand 1; CTLA-4, T lymphocyte-associated protein 4; OS, overall survival; DAMP, damage-associated molecular pattern; MHC, major histocompatibility complex; EBRT, external beam radiation therapy; RILD, radiation-induced liver disease; ICD, immunogenic cell death; HMGB1, high mobility group protein 1; Treg, regulatory T cell; TCR, T cell receptor; CI, confidence interval; LDRT, low-dose radiation treatment; CT, computed tomography; MRI, magnetic resonance imaging; irAE, immune-related adverse event

Key words: radiotherapy, immunotherapy, advanced hepatocellular cancer, combination therapy, prognosis

Contents

1. Introduction

Hepatocellular carcinoma (HCC) is the sixth most common malignant tumor in the world and the third greatest cause of cancer-associated mortality (1). The global incidence rate of HCC is expected to exceed 1 million cases by 2025, mainly driven by chronic viral hepatitis and metabolic related liver disease, of which metabolic related liver disease cases account for 15-20% in western countries (2). HCC often remains asymptomatic in the early stages, therefore, diagnosis typically occurs in the late stages, and the 5-year survival rate of patients with advanced HCC (aHCC) is <15%, underscoring the limitations of current aHCC treatment options (3).

Since its confirmation in the SHARP trial, sorafenib, a multi-kinase inhibitor, has been routinely used as the first-line treatment for aHCC (4). However, the effectiveness of sorafenib is limited. Compared with the placebo, it increased the median overall survival (mOS) by 2.8 months. However, it typically

has side effects (hand-foot skin reaction in 30-60% of patients, diarrhea in 40-55%) that adversely affect the quality of life (4). Due to these constraints, new treatments for patients with aHCC have been researched to increase survival rates and quality of life (5).

Immune checkpoint inhibitors (ICIs) have potential in treating aHCC because of their immune system modulatory activity (5,6). The CheckMate 040 and KEYNOTE-224 trials (7,8) revealed that nivolumab and pembrolizumab are both safe and effective in treating aHCC.

Despite advances in immunotherapy and targeted therapy for aHCC, a considerable proportion of patients are unable to obtain effective treatment because of variables such as the complicated tumor microenvironment (TME) of HCC (9). As a result, novel therapeutic strategies integrate multiple existing therapeutic approaches to use the complementary advantages of each strategy while addressing their limitations. Radiotherapy (RT) + ICI combinations have shown promise in non-small cell lung cancer and melanoma, improving survival by modulating the TME (10). Therefore, RT + ICI combinations in HCC may enhance tumor response to immunotherapy. Clinicians have hypothesized combining RT and ICIs as a potential synergistic method to improve the treatment of aHCC (11-13).

The justification for combining RT and ICIs in treating aHCC stems from their complementary mechanisms and antitumor efficacy. This combination therapy may be a more effective and comprehensive method of combating aHCC (14). RT has traditionally been considered a local treatment, but has been discovered to promote systemic immune responses via the 'abscopal effect', in which the tumor in the irradiated area degenerates due to immune activation (15,16). Radiation-induced cell death causes the production of tumor-associated antigens and damage-associated molecular patterns (DAMPs), which initiate an antitumor immune response (17,18). Furthermore, radiation can promote tumor immunogenicity by increasing expression of major histocompatibility complex class I and T cell infiltration and altering the TME (11,19). These radiation-induced changes convert immunologically 'cold' tumors (lacking immune cell infiltration and antigen presentation) into 'hot' tumors (with immune recognition and attack capacity), thereby increasing their susceptibility to ICIs (20,21). Moreover, ICIs boost the systemic immune response, overcoming the limitations of radiation, which may not totally eradicate malignancy.

RT can modulate the TME, leading to increased infiltration of $CD8^+$ T cells and production of effector cytokines such as IFN-γ and decreased levels of regulatory T cells (Tregs) (22,23). These changes enhance the efficacy of ICIs by improving immune system recognition of tumor cells (24). Furthermore, preclinical investigations have shown synergistic effects of RT and ICIs in aHCC models, with increased antitumor effects observed when these treatments are combined (22,25).

However, there are challenges associated with optimizing the combination of RT and ICIs for aHCC (26,27). Determining the appropriate sequencing, dosage and timing of RT in comparison with those of ICIs is key (28,29). Additionally, discovering predictive biomarkers for response to combination therapy is essential for tailored treatment approaches (30).

The present review aimed to summarize processes through which RT and ICIs may interact to improve clinical outcomes and methods to enhance this combination technique, as well as the potential of low-dose radiation treatment (LDRT) as a complementary or alternative strategy to high-dose regimens, particularly when paired with ICIs (31-33). Furthermore, the present review aimed to highlight the role of advanced imaging techniques and specialized equipment in accurately targeting tumor tissue and minimizing damage to surrounding healthy tissue, which is key for the successful implementation of LDRT (34,35).

Additionally, the present review aimed to summarize clinical trials assessing the safety and efficacy of combining RT and ICIs in aHCC, including those that have assessed the impact of different sequencing and timing strategies on treatment outcomes (36-39). Identification and validation of reliable biomarkers for predicting response to combined RT and ICIs may improve patient selection and therapy optimization (40-47).

2. RT in HCC

Historically, the use of external beam radiation therapy (EBRT) for HCC has been limited because of the radiosensitivity of the liver and the risk of radiation-induced liver disease (RILD) (48). Attempts to cure HCC with conventional radiation have shown limited efficacy and severe toxicity because it is challenging to provide an adequate radiation dose to tumors without destroying the surrounding healthy liver tissue (49,50). Developments in imaging and radiation transmission technology improved the accuracy of tumor targeting (51-53). Steroetactic body radiation therapy (SBRT) and three-dimensional conformal radiation have promise in the treatment of HCC (54,55). According to reports, local control rates have improved, and hazardous reactions are now acceptable (56,57). Blomgren *et al* (58), for example, reported that high-dose fractionated radiation achieves local tumor suppression in different types of liver cancer, including HCC, with manageable side effects.

Despite these advancements, irradiation for HCC has limitations, including radiation-induced hepatotoxicity, variability in tumor radiation sensitivity and technical complexity (59,60). Technical complexity refers to the challenges involved in accurately targeting tumors in the liver while sparing surrounding healthy tissue. This is difficult due to the anatomical variations of the liver, its proximity to key structures and the need to optimize radiation planning to minimize damage to healthy liver tissue while ensuring sufficient tumor dose delivery. These challenges require advanced imaging technology and highly precise radiation delivery systems, which can vary depending on tumor size, location and liver function (61).

Liver toxicity has switched from 'classical' to 'non-classical' RILD, with the former primarily characterized by widespread damage due to whole-liver irradiation, while the latter manifests as localized damage and elevated liver enzymes. This is often associated with an increased production of pro-inflammatory cytokines, such as TNF-α and interleukins, which contribute to hepatocyte injury and the activation of fibrogenic pathways. By contrast, non-classical RILD involves more localized liver damage and is associated

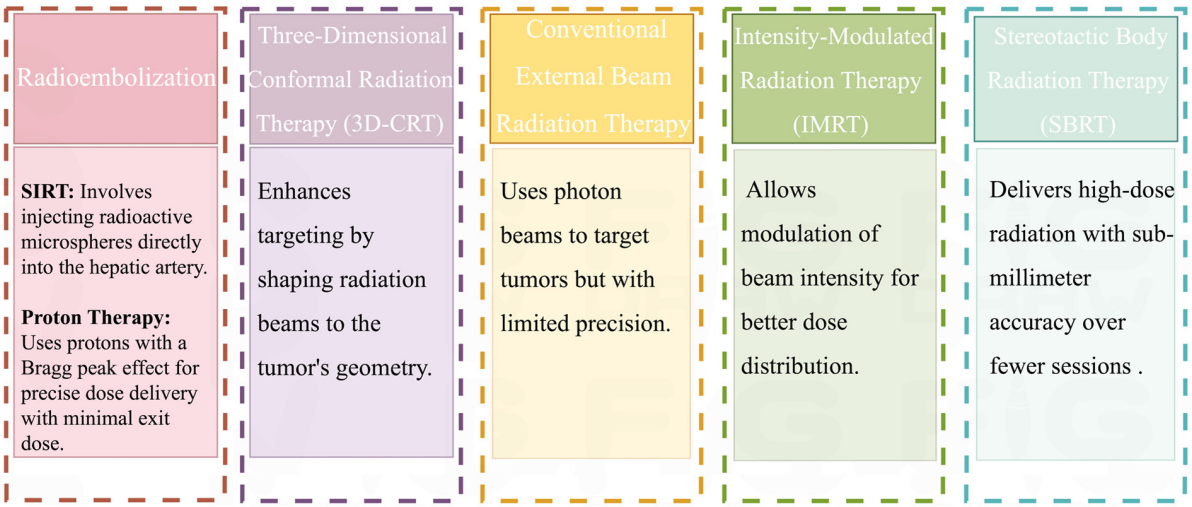

Figure 1. Radiation therapy is a key treatment modality for HCC. Radioembolism encompasses SIRT and Proton therapy. SIRT involves delivering radioactive microspheres via the hepatic artery to supply blood to tumors. IMRT and 3D-CRT can precisely match the radiation dose to the tumor three-dimensional shape. External beam radiation therapy emits high-energy radiation beams from outside the body to target and destroy cancer cells. Proton therapy utilizes charged particle beams to ensure dose consistency. Moreover, SBRT has achieved progress in offering accurate and high-dose radiotherapy for HCC tumors. HCC, hepatocellular carcinoma; SBRT, stereotactic body radiotherapy; SIRT, selective internal radiotherapy; 3D-CRT, three-dimensional conformal radiation therapy; IMRT, intensity-modulated radiation therapy.

with elevated levels of transaminases and jaundice (62). This form of toxicity is hypothesized to result from endothelial cell damage, increased vascular permeability and a dysregulated immune response in the irradiated liver region (62). Baseline liver function is the primary predictor of liver toxicity after SBRT, and patients with Child-Pugh grade ≥B8 have a greater risk (63,64). Cárdenes *et al* (63) revealed that a Child-Pugh score of ≥8 is associated with severe liver toxicity or mortality in ≤6 months. The American Society for Radiation Oncology guidelines establish dosage limits on the basis of various Child-Pugh scores: 15-18, 13-15 and 8-10 Gy for non-cirrhotic, Child-Pugh A and B7 grades, respectively (65,66). Technical advancements have markedly decreased these constraints. Modern EBRT employs three-dimensional computed tomography (CT) and intensity-modulated RT, as well as improved imaging technology, to portray tumors while preserving normal liver tissue (67,68). These approaches accommodate differing dosage distributions, allowing the dose of the tumor-specific treatment to be gradually increased while minimizing exposure to healthy liver parenchyma (69) (Fig. 1).

Chemotherapy and targeted molecular therapies are less popular in the treatment of aHCC due to key limitations. Chemotherapy exhibits poor efficacy, with high rates of chemo-resistance and considerable toxicity, particularly in patients with underlying liver dysfunction, resulting in minimal survival benefits (70). Targeted therapies, such as sorafenib and other tyrosine kinase inhibitors, offer modest improvements in OS while being associated with substantial side effects and a narrow therapeutic window (71). Additionally, resistance to targeted therapies often develops, driven by tumor heterogeneity and the immunosuppressive TME. These factors, combined with their lack of impact on modulating the TME, render chemotherapy and targeted molecular therapies less favorable compared with emerging strategies such as the combination of RT and ICIs. By contrast, RT combined with ICIs is preferred for aHCC (27). RT techniques such as SBRT and proton therapy provide precise dose delivery, ideal for targeting small- and medium-sized tumors in complex locations, making it more effective for tumors that are large or irregularly shaped (72). Second, RT enhances immune activation by altering the TME, promoting immune cell infiltration and improving tumor recognition, which synergizes with ICIs to boost immune responses, particularly in advanced stages where immune activity is often suppressed (73). Additionally, combining RT with ICIs helps overcome resistance to immunotherapy by enhancing T cell activation and preventing immune exhaustion (27). Moreover, RT + ICIs offers comprehensive treatment by targeting both primary tumors and metastases and providing broader control over both systemic and local disease, unlike therapies such as radioembolization, which are more suited for localized disease or portal vein invasion. Additionally, compared with tyrosine kinase inhibitors (such as sorafenib), which primarily target angiogenesis, RT + ICI combinations address both local tumor control and systemic immune activation, offering a dual therapeutic advantage (74). Finally, ongoing clinical trials show promising results, indicating that RT + ICIs provides enhanced antitumor activity and safety for patients with aHCC (36,75). Furthermore, careful patient selection, precise treatment planning and interdisciplinary collaboration are needed to improve outcomes and minimize adverse effects.

The combination of radiotherapy and systemic treatments, particularly ICIs, represents a promising frontier in the treatment of aHCC. Radiation can affect the TME, improve immune system identification of tumor cells and interact with ICIs (24). Clinical trials are being performed to determine the efficacy and safety of RT in combination with ICIs and other systemic treatments (36,75). This holistic strategy aims to improve the local and systemic control of aHCC while also addressing primary tumors and potential metastatic illness (Fig. 2).

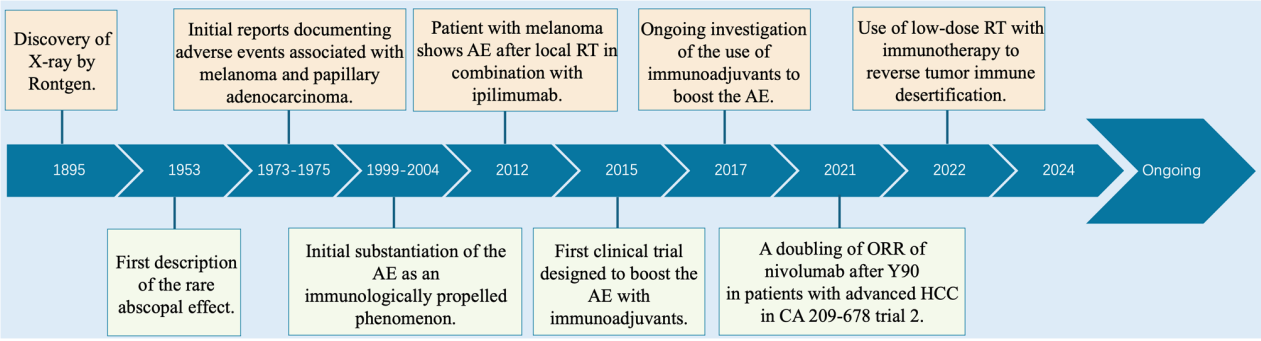

Figure 2. Timeline of RT use in liver cancer. RT, radiotherapy; ORR, overall response rate; HCC, hepatocellular carcinoma; AE, adverse event.

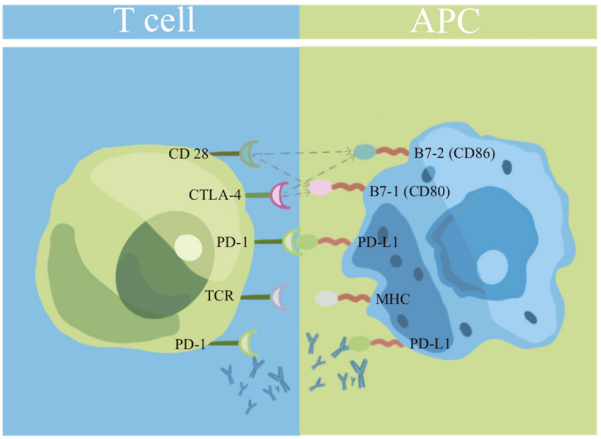

Figure 3. Mechanisms of immune checkpoint inhibition in hepatocellular carcinoma. PD-1 on T cells binds to PD-L1 on APCs, while CTLA-4 competes with CD28 for B7-1/B7-2 binding. These interactions maintain immune homeostasis but are exploited by tumors to evade detection. ICIs block PD-1/PD-L1 and CTLA-4/B7 interactions, reversing T cell exhaustion and restoring antitumor immunity. APC, antigen presenting cell; CTLA-4, cytotoxic T lymphocyte-associated protein; PD-1, programmed cell death protein 1; PD-L1, programmed cell death protein ligand-1; TCR, T cell receptor; MHC, major histocompatibility complex.

3. ICIs in HCC

The introduction of ICIs has transformed the therapeutic landscape for HCC, particularly for patients with advanced-stage illness. Traditional systemic medicines provide some survival advantage for these patients, emphasizing the need for innovative therapeutic options. ICIs have emerged as promising medications that induce an efficient antitumor response via the human immune system (4,25).

The ICI revolution in HCC is based on immune checkpoint regulation, specifically PD-1/PD-L1 and CTLA-4 (76,77). Tumors frequently exploit these molecular pathways, which are necessary for maintaining immunological homeostasis, to avoid immune surveillance. Checkpoint inhibitors revive depleted T cells by eliminating inhibitory signals, boosting antitumor immunity (78). (Fig. 3).

PD-1 drugs, including nivolumab and pembrolizumab, have demonstrated clinical success in treating aHCC. The CheckMate 040 and KEYNOTE-224 studies (8,79) reported objective response rates of 14-20 and 17%, respectively, indicating the possibility of disrupting the PD-1 axis. However, these response rates underscore the limited efficacy in treating HCC relative to other types of cancer (80). This variability in patient reactions highlights the complicated immunological landscape of aHCC and presence of immune subgroups within the patient population. The relatively low curative effect may be attributed to several factors, including the inherent immunosuppressive environment, the high heterogeneity of HCC tumors, the possibility of chronic liver diseases that impair immune function and the presence of immunosuppressive cells in the TME (81). Furthermore, HCC tumors may lack sufficient novel antigens or tumor mutation burdens to elicit robust immune responses (82). This requires further research into the mechanisms of response and resistance, as well as the creation of more tailored ICIs, to overcome these limits and enhance the treatment outcomes for patients with HCC.

Given the poor efficacy of ICIs as monotherapies, researchers have investigated combination methods with other treatment modalities, such as RT and anti-antigenic drugs, to improve therapeutic outcomes (83-86). A notable example is the IMbrave 150 study (87), which assessed the combination of atezolizumab (an anti-PD-L1 antibody) and bevacizumab [an anti-vascular endothelial growth factor (VEGF) drug]. After a median follow-up of 61.9 months, the mOS was 21.0 months [95% confidence interval (CI): 10.4-31.6 months]. The OS rates for 3, 4 and 5 years were 36.4, 25.7 and 25.7%, respectively (88). This combination is superior to sorafenib in the first-line treatment of aHCC, and exhibits synergistic potential. This technique improves the killing effect of T cells on tumor cells and modulates the tumor vascular system, potentially enhancing drug delivery and T cell infiltration, allowing the simultaneous treatment of multiple aspects of tumor biology (89).

The most recent advancements in ICIs emphasize the prospect of PD-1/PD-L1 inhibition, and the concurrent investigation of CTLA-4 blockade has potential, particularly in combination therapy (23,90,91). The HIMALAYA study (92), which used durvalumab (an anti-PD-L1 antibody) and tremelimumab (an anti-CTLA-4 antibody), highlights the concept of dual checkpoint blocking in aHCC. This method targets independent but complementary immune regulatory pathways, potentially overcoming resistance mechanisms and increasing the breadth and depth of antitumor immune responses.

The synergy of these pathways can be attributed to their distinct effects on T cell priming and effector activity. CTLA-4 suppression impacts the priming phase in lymphoid

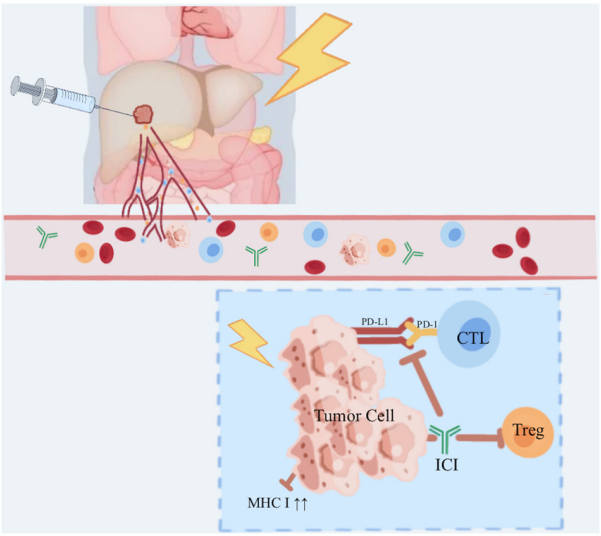

Figure 4. Combining radiation therapy and ICIs. RT induces immunogenic tumor cell death, increasing MHC I expression and tumor antigen release to activate CTLs. While RT upregulates PD-L1 on tumor cells, ICIs block PD-1/PD-L1 interaction to prevent CTL exhaustion and enhance tumor killing. CTL, cytotoxic T lymphocyte; Treg, regulatory T cell; MHC I, major histocompatibility complex I; RT, radiotherapy; PD-1, programmed cell death protein 1; PD-L1, programmed cell death protein ligand-1; ICI, immune checkpoint inhibitor.

organs, whereas PD-1/PD-L1 blocking improves effector T cell activity (93,94). This complementary process provides a theoretical foundation for development of future combined therapy options.

4. Rationale for combining RT + ICIs

For patients with aHCC, who frequently have few therapeutic options and a poor prognosis, combining RT + ICIs may provide clinical advantages. In addition to enhancing local tumor management, the synergistic effect can trigger systemic antitumor responses, leading to the resolution of primary tumors and metastatic lesions (95,96) (Fig. 4). This strategy is based on radiation-induced immunogenic cell death (ICD), a unique form of cell death that can effectively promote the immune system to target tumor cells.

Following RT, DAMPs are produced as a result of radiation-induced cell death. DAMPs, such as calreticulin, high mobility group box 1 protein (HMGB1) and ATP, are released from tumor cells undergoing necrosis or apoptosis. These molecules serve a key role in modulating immune responses in HCC by acting as endogenous ligands for pattern-recognition receptors (PRRs), including toll-like receptors, on immune cells (97-99). Following receptor activation, DAMPs initiate innate immune responses, which are key for the subsequent activation of adaptive immunity (97). This innate-to-adaptive immune transition is key in the context of ICI therapy, as it helps bridge the gap between the two immune systems.

DAMPs are key for the maturation of dendritic cells (DCs) and the enhancement of antigen presentation (98,100). They promote the activation of DCs and other antigen-presenting cells, improving T cell priming and activation (101,102). Garg *et al* (97) have revealed that DAMPs, such as surface-exposed calreticulin, secreted ATP and passively released HMGB1, interact with phagocytosis receptors, purinergic receptors and PRRs, respectively. These interactions are key for inducing ICD, leading to the activation of potent anticancer immunity (97,103-106). This helps overcome the immune suppression in the advanced stages of HCC. Immune activation is an important strategy to overcome immune suppression in aHCC (107). Chen *et al* (108) demonstrated that heat shock protein 70 (HSP70) levels (a DAMP) are markedly higher in the serum of patients with HCC compared with healthy individuals, while antibody levels remain unchanged, suggesting that HSP70 may counter immune suppression via non-antibody mechanisms. Ren *et al* (109) revealed that during HCC development, damaged or dying cells release DAMPs, which serve as ligands for cyclic GMP-AMP synthase (cGAS). This activates the cGAS-stimulator of interferon genes signaling pathway, potentially enhancing the anti-tumor immune response of the body (109). Furthermore, when synergized with ICIs such as PD-1/PD-L1 inhibitors, DAMPs enhance immune responses by restoring T cell function and counteracting immune exhaustion (97).

RT further illustrates the importance of DAMPs in immune activation. Radiation-induced ICD results in the release of DAMPs, such as calreticulin, HMGB1 and ATP, which enhance the ability of the immune system to target tumor cells. These DAMPs activate both innate and adaptive immune responses, effectively transforming irradiated tumors into *in situ* vaccines (99,110). Calreticulin, which translocates to the cell surface following radiation, serves as an 'eat-me' signal for DCs, prompting them to recognize and engulf dying tumor cells. HMGB1 and ATP stimulate immune activation by binding receptors on DCs, leading to the initiation of robust anti-tumor immunity (98).

The complementary effects of radiation-induced DAMPs (such as calreticulin, HMGB1, ATP) on the TME further elucidate the synergistic interaction between RT and ICIs. Singh *et al* (111) reported that intercellular adhesion molecule 1 (ICAM-1) serves a key role in breast carcinoma metastasis, promoting adhesion between breast cancer and endothelial cells, enhancing circulating tumor cell cluster formation and tumor cell survival. RT can modify the TME by altering cytokine secretion patterns, increasing the expression of adhesion molecules such as ICAM-1 and vascular CAM-1, and altering chemokine gradients (111). These modifications increase the recruitment and activation of effector immune cells, such as cytotoxic T lymphocytes and natural killer cells. Moreover, ICIs avoid T cell failure by inhibiting inhibitory signals (PD-1/PD-L1 and CTLA-4), increasing long-term antitumor activity and enhancing these effects. Exosomes regulate tumor growth, invasion, metastasis, angiogenesis and immune therapy resistance, serving a key role in intercellular communication in the TME (112,113). They carry proteins, DNA, microRNA and long non-coding RNA, altering recipient cell functions and phenotypes. RT factors enhance or inhibit these effects, influencing tumor progression and increasing their vulnerability to ICIs (114).

Preclinical investigations have established the existence of synergistic effects of RT + ICIs in models of aHCC (22,23,115). Pedros *et al* (115) revealed that in mouse models of melanoma and prostate cancer, the CTLA4 signaling pathway within

Treg cells is key for suppressing tumor immunity. Tregs lacking relevant key proteins weaken their inhibitory function, leading to inhibited tumor growth, increased levels of effector T cells and enhanced function (115). Studies have indicated increased infiltration of $CD8^+$ T cells and production of effector cytokines, including IFN-γ and decreased Tregs within the TME (22,23). Furthermore, radiation stimulates the diversification of the T cell receptor (TCR) pool, identifying a broader range of tumor antigens (116,117). Binder *et al* (117) revealed that RT stimulates the diversification of TCR pool and expands the recognition range of tumor antigens. When combined with ICIs (such as anti-CTLA-4), RT can increase the diversity of TCR clones within tumors and enhance the anti-tumor effect of the immune system (116,117). This diversification decreases the chance of immune escape and increases the persistent response.

Clinically, the abscopal effect, a phenomenon in which local RT causes regression of distant unirradiated tumors, demonstrates the efficacy of this combination method in systemic treatment (118). Although uncommon, the abscopal effect demonstrates that combining RT + ICIs induces broad antitumor immunity. ICIs have the ability to elicit broad antitumor immune responses. For patients with aHCC with numerous foci and metastases, this combined therapy may provide a solution for both local and distant tumor burden (119).

The continuous updating of technology and developments in treatment procedures provide a foundation for further improving the overall effectiveness of RT and ICIs. Advanced radiation procedures, such as SBRT, accurately administer high radiation doses while causing minimum injury to adjacent tissue (120). When combined with novel ICIs, these strategies provide therapeutic advantages, including tailored cancer vaccines, off-the-shelf T cell therapies, and oncolytic viruses, which operate through complementary but non-overlapping mechanisms (113). Furthermore, treatment planning and prediction can be improved by computational technologies such as radiomics and artificial intelligence.

For patients with aHCC, RT in conjunction with ICIs may improve survival rates and quality of life by balancing local tumor focus resolution with systemic metastasis management. Future research should refine treatment regimens, identify resistance mechanisms and develop biomarkers that can predict treatment efficacy.

5. RT + ICIs in aHCC

The combined strategy of RT + ICIs in treating aHCC is increasingly supported by preclinical and clinical evidence due to the synergistic effect of radiation-induced immunomodulation and IC suppression (84,121). Preclinical studies have clarified how RT increases tumor immunogenicity (10,22,122). Radiation, for example, causes ICD, as evidenced by the release of DAMPs, including calreticulin, HMGB1 and ATP. These DAMPs stimulate DC maturation and antigen presentation, effectively bridging innate and acquired immunity (100,123). Furthermore, RT increases tumor-associated antigen expression and upregulates key MHC-like molecules, making cytotoxic T cells more visible in the tumor (124).

In aHCC-specific models, the combination of RT + ICIs has demonstrated substantial antitumor activity (22,125). Combining radiation with anti-PD-1 or anti-CTLA-4 antibodies has increased $CD8^+$ T cell infiltration and decreased Tregs within the TME (116,126,127). Twyman-Saint *et al* (116) reported the tumor regression effect of anti-CTLA4 antibody and radiation therapy on patients with metastatic melanoma, and reproduced this effect in a mouse model. Drug resistance is associated with the upregulation of PD-L1 and T cell depletion in melanoma cells (115). The optimal therapeutic response requires the combination of RT, anti-CTLA4 and anti-PD-L1/PD-1 (116,126,127). Also, RT changes the immune-suppressing TME by decreasing immune-suppressing cytokines and myeloid-derived suppressor cells (10,128).

Early-phase trials have investigated the safety of RT + ICIs and preliminary efficacy in patients with aHCC, translating these preclinical findings into clinical settings (36,129). Juloori *et al* (36) conducted a phase I trial in patients with aHCC, comparing SBRT followed by nivolumab alone or nivolumab with ipilimumab (36). This study revealed adequate safety. Within 6 months of starting SBRT, 15.4% of patients experienced dose-limiting effects. The combination of SBRT with nivolumab and ipilimumab had ORR of 57%, a median progression-free survival time of 11.6 months and a mOS time of 41.6 months. Tai *et al* (129) conducted a phase I trial in patients with aHCC, evaluating the combination of SBRT and nivolumab (129). This combination was well tolerated, and the toxicity was moderate, consisting primarily of fatigue and skin events. Preliminary efficacy results suggested an encouraging ORR.

Other phase II trials have evaluated the efficacy of RT + ICI combinations in larger populations (38,130,131). Li *et al* (38) evaluated a combined therapy of SBRT, camrelizumab (an immune checkpoint inhibitor) and apatinib (a targeted anti-angiogenic drug) in HCC patients with portal vein tumor thrombus. The study reported a median overall survival of 12.7 months (95% CI: 10.2-not reached) and a median progression-free survival of 4.6 months (95% CI: 3.3-7.0). While the treatment was generally tolerable, over 22% of patients experienced grade 3 or higher adverse effects, such as hypertension or liver enzyme elevations.

Owing to the lack of extensive phase III data, retrospective analyses provide key insight into the true efficacy of RT-ICIs (37,132,133). Ning *et al* (134) conducted a retrospective analysis on the outcomes of 36 patients with aHCC treated with RT and anti-PD-1 drugs and reported markedly higher ORR and OS rates when compared with ICIs alone.

Optimizing the combination of RT and ICIs for aHCC remains an issue. Determining the appropriate sequencing, dosage and timing of RT in comparison with those of ICIs is key (28,29). Furthermore, discovering predictive biomarkers for response to combination medication is key for tailored treatment (80).

Clinical trials will likely offer high-level data to demonstrate the efficacy and safety of combined RT + ICIs in aHCC (Table I). These studies are key for future clinical practice and to redefine the landscape of aHCC treatment.

6. Optimizing RT + ICIs in aHCC treatment

The synergistic combination of RT and ICIs is a feasible technique for improving treatment for patients with aHCC. Numerous variables must be addressed to obtain the best

Table I. Trials of RT + ICIs in aHCC.

NCI no.	Phase	RT	ICI	Design	Target enrollment	Primary endpoint
NCT05625893	II	Proton	Atezo-Bev (anti-PDL1/anti VEGF)	Atezo-Bev + PBT 1 week after C2 Atezo-Bev	63	PFS
NCT06040177	II	SBRT	Cadonilimab (anti-PD1/CTLA-4)	Renvatinib + SBRT + cadonilimab	30	ORR
NCT04913480	II	SBRT	Durvalumab (anti-PDL1)	Durvalumab + SBRT 1 week after first durvalumab	37	PFS at 1 year
NCT03942328	I/II	EBRT	Autologous dendritic cells + Atezo-Bev (anti-PDL1/antiVEGF)	EBRT (1-3 weeks) + autologous dendritic cells + Atezo-Bev	54	DLT PFS at 2 years
NCT05286320	I/II	SBRT	Pembrolizumab + lenvatinib (anti-PD1/TKI)	Pembrolizumab + lenvatinib SBRT during C2 of pembrolizumab	27	Phase 1, DLT; phase 2, ORR
NCT04988945	II	SBRT	Durva-Treme (anti-PDL1/CTLA4)	TACE and SBRT + Durva-Treme	33	Downstaging for resection rate
NCT05488522	I	SBRT	Atezo-Bev (anti-PDL1/anti-VEGF)	Atezo-Bev SBRT on week 2	18	DLT
NCT06133062	II	Proton	Atezo-Bev (anti-PDL1/anti-VEGF)	Proton RT with Atezo-Bev	45	PFS
NCT03316872	II	SBRT	Pembrolizumab (anti-PD1)	Pembrolizumab SBRT on C1D2 of Pembrolizumab	30	ORR
NCT04430452	II	RT	Durva-Treme (anti-PDL1/CTLA4)	Hypofractionated RT + durvalumab or Durva-Treme	21	ORR
NCT05396937	II	SBRT	Atezo-Bev (anti-PDL1/anti-VEGF)	Atezo-Bev SBRT 1-2 weeks after C1 Atezo-Bev	42	ORR
NCT05809869	II	Yttrium-90	Durva-Treme (anti-PDL1/CTLA4)	Durva-Treme Radioembolisation on week 2	25	ORR
NCT04547452	II	SBRT	Sintilimab (antiPD-1)	SBRT + sintilimab OR sintilimab	84	PFS
NCT05377034	II	SIRT	Atezolzumab (antiPD-L1)	SIRT + atezolzumab + bevacizumab	176	BORR
NCT02837029	I	SIRT	Nivolumab (antiPD-1)	SRT + niolumab	27	ORR
NCT04785287	I/II	SBRT	Nivolumab (anti-PD-1) and BMS986218 (anti-CTLA-4)	5BRT + BM5986218 ± nivolumab	13	IAE
NCT04709380	II	RT	Toripalimab (anti-PD-1)	(RT + toripalirab) vs. sorafenib	85	TTP
NCT05530785	II	RT	Sintilmab (ant+PD-1)	RT + sintilimab and bevacizumab biosimila	35	ORR
NCT05010434	II	RT	Sintilimab (antiPD-1)	RT + sintilmab + bevaczumab	46	ORR
NCT04611165	II	EBRT	Nivolumab (anti-PD-1)	NVolumab + EBRT	50	PFS
NCT04850157	II	lMRT	Tislelizumab (anti-PD-1)	Tislelizumab + IMRT	30	RFS

This information is available at clinicaltrials.gov/ (accessed on 7 Oct, 2024). BORR, best overall response rate; PBT, proton beam therapy; RFS, relapse-free survival; IMRT, intensity-modulated radiotherapy; EBRT, external beam radiotherapy; TTP, time to progression; IAE, incidence of adverse events; PFS, progression-free survival; DLT, dose-limiting toxicity; ICI, immune checkpoint inhibitor; aHCC, advanced hepatocellular carcinoma, VEGF, vascular endothelial growth factor; PD-1, programmed cell death protein-1; SBRT, stereotactic body radiotherapy; CTLA-1, cytotoxic T lymphocyte-associated protein 4; TACE, trans arterial chemoembolisation; SIRT, selective internal radiotherapy.

therapeutic benefit while minimizing toxicity, including dosage, timing, staging and patient-specific characteristics.

The dosage and manner of RT must be optimized to maximize synergy with ICIs in patients with aHCC. Historically,

higher doses/fraction, such as those utilized in hypofractionated SBRT, have been employed to produce strong ICD and increase antitumor immune responses (135,136). Robbins *et al* (137) used a 40 Gy regimen delivered in five parts, demonstrating a move toward providing greater doses over shorter treatment duration to enhance immune activation and improve patient compliance (137).

There is interest in the immunostimulant properties of LDRT (31). LDRT at a dose of <2 Gy increases T cell infiltration, improves antigen presentation, regulates the tumor vasculature and induces phenotypical changes in tumor cells, increasing their susceptibility to immune-mediated death (32,33). LDRT may enhance the immune response while causing less damage to healthy tissue compared to conventional high-dose radiation therapy. The appropriate dosage range for balancing immune activation and tumor management is an important area for further study, as LDRT may provide a complementary or alternative strategy to high-dose regimens, particularly when paired with ICIs.

The choice of RT mode is important in maximizing treatment outcomes. Advanced technologies, such as proton treatment and SBRT, provide precision targeting, maximizing the tumor dose while minimizing damage to adjacent healthy tissue. Several factors influence the choice between these techniques, including the size and location of the tumor, the liver function of the patient and the specific immunological goals (34,35). Integrating LDRT as a supplement to these RT techniques may affect immune activation. Given the ability of LDRT to regulate the TME to promote immune-mediated tumor elimination (138), its combination may improve the overall therapeutic efficacy of these targeted RT technologies. Although LDRT holds promise, its precise delivery and monitoring presents challenges that limit its wider clinical application (139). The technical complexity of LDRT requires highly accurate targeting of tumor tissue while minimizing damage to surrounding healthy tissue, demanding advanced imaging techniques and specialized equipment, which may not be available in all clinical settings. Additionally, the variability in tumor shape, locations and movement, such as respiratory motion, complicates consistent treatment delivery, necessitating real-time adjustments (140). Achieving the required dosimetric precision is a challenge, as high doses of radiation delivered to small, localized areas can cause toxicity to nearby structures (141). Furthermore, real-time monitoring of treatment effects on both tumor and normal tissue remains difficult, as current imaging technology may not provide sufficient resolution or immediate feedback, leading to potential inaccuracies.

The sequence and timing of RT and ICIs are key factors in enhancing the synergy of combination therapy in patients with aHCC. ICI after radiotherapy is more effective than taking ICI before radiotherapy in other tumors (142). This technique exploits immunostimulatory effects, increasing immunotherapeutic drug efficacy (126,143-145). Juloori *et al* (36) initiated ICIs 14 days after SBRT completion to capitalize on the peak period of radiation-induced antigen release and immune cell infiltration, which normally occurs 1-2 weeks after RT. By delivering ICIs during this window, treatment takes advantage of the increased immunogenicity caused by RT.

By contrast, RT following ICI therapy has resulted in less notable effects. ICIs alone may not fully activate the immune system to exploit subsequent RT-induced ICD and antigen presentation (116). As a result, ICIs after RT remains the most commonly used approach in clinical practice. Theelen *et al* (146), which examined the efficacy of pembrolizumab with or without RT in patients with metastatic non-small cell lung cancer, lends support to this viewpoint; 564 individuals receiving pembrolizumab were evaluated, with 89 (15.8%) receiving RT either before or during therapy. There was no notable difference in the OS rate between patients who underwent RT (mOS;10.6 months) and patients who did not receive RT (mOS;10.9 months), with an adjusted hazard ratio of 1.13 (95% CI: 0.82-1.54; P=0.46). Similarly, the two groups had no notable difference in progression-free survival or ORR (147). These findings indicate that RT after or during ICI therapy may not provide considerable benefits in terms of survival or tumor response.

Determining the best sequence and timing of RT and ICIs is important in aHCC management (143). The timing of these procedures influences immediate treatment outcomes and may have an impact on the long-term prognoses of patients. To achieve the best clinical results, the treatment plan must be tailored to each patient and the immune dynamics of the TME, while also identifying and validating reliable biomarkers for predicting response to RT + ICIs (30).

Identifying biomarkers that predict response to RT + ICIs is important for patient selection and therapy optimization. Circulating tumor DNA is a potential biomarker that allows non-invasive monitoring of tumor load and molecular alterations throughout treatment (40-42). Analysis of cytokine profiles and circulating immune cell subsets offer information regarding systemic immunological activation and overall immune status, potentially indicating ICI timing and dose. In a study of 11 individuals receiving radioembolization or systemic therapy, assessments at 16 time points revealed that changes in tumor methylation score (TMS) more accurately predict tumor progression than α-fetoprotein (AFP), with Area Under the Receiver Operating Characteristic curve (AUROC) values of 0.800 and 0.783, respectively. Moreover, combining AFP and TMS into a composite score improved the accuracy of distinguishing tumor evolution, with an AUROC of 0.892 (43).

Tumor tissue biomarkers, such as immune cell infiltration patterns, molecular expression of ICs and tumor mutation and novel antigen loads, directly indicate TME features and susceptibility to combined RT + ICI methods (44,45). Imaging modalities such as CT, magnetic resonance imaging (MRI) and positron emission tomography (PET) serve a key role in improving RT planning by providing detailed, high-resolution images of the tumor and surrounding structures. CT imaging is essential for precise localization and accurate dose delivery as it allows 3D visualization of the size and position of the tumor. MRI is useful in delineating liver tumors due to its high soft tissue contrast, helping to distinguish tumors from adjacent liver tissue, which is key in liver-directed therapy. PET imaging, combined with CT, offers insight into tumor metabolism and activity, allowing more accurate identification of active tumor regions that may require higher radiation doses. These imaging techniques, when integrated into RT planning, enable more accurate tumor targeting, improved

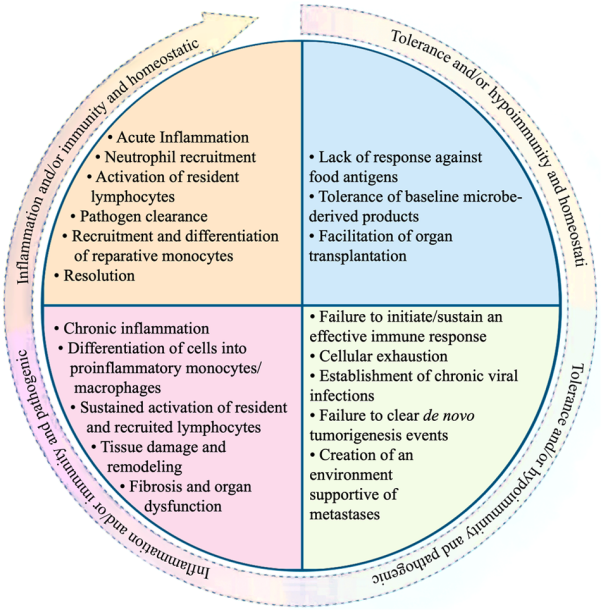

Figure 5. Immune-related adverse events of radiation therapy combined with immune checkpoint inhibitors.

dose distribution and decreased toxicity to surrounding healthy tissue (46,47).

Biomarker discovery and application may improve the understanding of the synergistic mechanism of RT and ICIs in aHCC, optimize treatment timing and sequence and improve patient selection accuracy and clinical efficacy. This holistic strategy demonstrates potential for enhancing customized medicine and providing more effective treatment options for patients with aHCC.

7. Toxicity and safety

With the widespread use of immune checkpoint inhibitors (ICIs), the incidence of immune-related adverse events (irAEs) has risen, affecting 60-80% of patients, with severe cases in 10-15%. Active management strategies, such as corticosteroids, are effective in addressing these events (148,149). Fatigue, dermatological responses, colitis, hepatitis, pneumonitis and endocrinopathy are among the most common AEs (150,151). Although the incidence of AEs may increase, these can be effectively managed with close monitoring and appropriate interventions, hence optimizing safety (152,153) (Fig. 5).

Clinical trials have assessed the safety of combining RT and ICIs in the treatment of aHCC and support the viability of this strategy (36-39). There was no notable difference between the rates of irAEs in patients who received a combination treatment plan and those who received only ICIs. These findings suggest that RT does not worsen immune-associated toxicity. Hepatotoxicity has garnered attention among irAEs since both can impair liver function (154,155). However, combination therapy does not always result in a disproportionate increase in hepatotoxicity (132,134,156). Trials of the treatment of aHCC with RT and ICI therapy have revealed that the incidence of severe hepatotoxicity is often tolerable (132,134,156). The aforementioned studies have also stressed the importance of regular hepatic function monitoring and aggressive risk-reduction methods. Additionally, Li *et al* (156) conducted a multicenter trial to evaluate the safety of a combination of RT + ICIs for patients with portal vein tumor thrombus: The findings revealed that the combined treatment was practical and had manageable safety. Compared with the historical control group that received either method alone, the number of AEs did not increase appreciably. The aforementioned study revealed that attentive monitoring and prompt treatment are key for improving patient outcomes.

The aforementioned clinical investigations indicate that while RT + ICIs may pose additional risks, these side effects are typically controllable and preclude the practicality of a combined strategy. Numerous studies have shown that the safety of this combination therapy can be improved through proactive techniques such as dose modification, vigilant monitoring and patient education (157,158). This enables practitioners to increase treatment outcomes while still ensuring patient safety. The combination of RT + ICIs is a promising therapeutic option for patients with aHCC.

8. Future directions and limitations

Combination strategies of RT + ICIs have improved the efficacy of aHCC treatment and novel combinations and strategies may maximize the benefits of currently available treatment options.

Combination of trans arterial chemoembolisation (TACE), RT and ICIs for the treatment of aHCC uses synergistic effects to improve therapeutic efficacy. TACE decreases the tumor load and releases tumor antigens, whereas SBRT increases the anticancer immune response by inducing ICD and influencing the TME. Subsequent ICI therapy increases T cell-mediated antitumor immunity, potentially extending the therapeutic window. The START-FIT trial investigated sequential TACE, SBRT and avelumab; 55% of patients exhibited tumors that decreased to a level that would allow surgical intervention and 42% achieved complete remission (75). This novel method improves local tumor control while also combating off-site disease development via systemic immune activation. This synergy occurs through increased tumor antigen presentation, PD-L1 expression levels following radiation and recruitment of tumor-infiltrating lymphocytes. Larger randomized controlled studies are needed to confirm the efficacy and safety of triple therapy as a strategy to downstage initially unresectable aHCC, making it eligible for curative treatments such as surgery or ablation.

Researchers have explored other triple therapies, including RT, ICIs and other drugs, such as anti-VEGF therapy or new immunomodulators designed to target aspects of tumor biology and the immune microenvironment at the same time, potentially leading to more potent and durable antitumor responses (37,84,159).

As understanding of the biology of aHCC and patient-specific variables increases, there is a greater emphasis on establishing tailored treatments (160,161). Tailoring therapy seeks to maximize the efficacy of combining RT + ICIs while limiting toxicity. The development and validation of biomarkers predictive of response to combination therapy is a key focus (162,163). Several possible biomarkers are being investigated, including the tumor mutational load, PD-L1

expression and genetic changes (164,165). The goal is to create a comprehensive biomarker panel that will guide treatment selection and sequencing, ensuring patients receive the most suitable and effective treatment.

There is emphasis on assessing therapies beyond clinical efficacy, including patient-centered outcomes such as quality of life, accessibility and cost-effectiveness (166,167). Understanding the real-world applicability of these medicines is key to turning clinical trial results into meaningful benefits for the patient population. Involving patients in research and clinical decision-making ensures their opinions and priorities are considered when developing and implementing treatment. Shared decision-making models encourage collaborative discussion between clinicians and patients to consider individual preferences, quality of life implications and life circumstances, resulting in increased patient satisfaction, treatment adherence and overall outcomes (168,169).

Constraints have hampered the widespread use and optimization of combined RT + ICIs in aHCC treatment. Determining adequate markers for the prognosis of combination therapy is difficult because of the large number of parameters to examine, including tumor features, liver function, general performance status, biomarker profiles and prior treatment history. HCC tumor heterogeneity may result in varying responses to RT and ICIs, making precise treatment outcome prediction difficult.

Another challenge in implementing RT + ICIs in clinical settings is the lack of established treatment procedures. Key topics requiring additional investigation include radiation dose and segmentation schemes, treatment timing and sequencing, ICIs and target volume specification. It is key to have standardized protocols for clinical trials and consistent methods across institutions.

Methodological limitations impede research on the combination of RT + ICIs, affecting the universality and robustness of findings. Several studies (37,133) have limited sample sizes, which decreases their statistical power and ability to establish confident findings. The paucity of large-scale randomized controlled trials comparing combination therapy with standard medication raises questions regarding its true efficacy and safety. The heterogeneity of patient populations and differences in measurement results and toxicity reports hinder the interpretation and comparison. Short-term follow-up may not demonstrate long-term outcomes, late toxicity or delayed responses to ICIs.

Addressing these problems is key for promoting the combination of RT and ICIs in the treatment of aHCC. Future research should prioritize large-scale, multicenter randomized controlled trials and use defined patient groups and standardized programs. Developing and validating predictive biomarkers will improve patient selection, allow individualized treatment options, maximize therapeutic effects and reduce unnecessary toxicity. Studying the optimal radiation dose, segmentation method and treatment sequence may aid in maximizing the synergistic effect of RT and ICIs.

9. Conclusion

RT + ICIs represents a substantial advancement in treating aHCC. RT increases tumor antigenicity and eliminates immunosuppressive barriers, which improves the efficacy of ICIs (170). Clinical evidence from early-phase trials reveals that combination treatment improves antitumor responses while maintaining tolerable safety (126,142-144). However, issues such as optimum patient selection, dosage technique, therapy sequencing and toxicity control persist. Large-scale randomized controlled studies should be prioritized to confirm therapeutic advantages and enhance treatment strategies. The incorporation of biomarker-driven approaches is key for personalizing medicines to patient and tumor features, potentially increasing response rates while minimizing side effects. Furthermore, prioritizing patient-centered outcomes, such as quality of life, and real-world applicability (e.g., effectiveness in diverse patient populations, treatment accessibility, and long-term safety), is critical for evaluating the practical impact of these therapies. Continuous research efforts to improve this combination, identify resistance mechanisms and develop predictive biomarkers are needed. By addressing the present constraints and supporting tailored treatment options, longer-lasting responses, enhanced OS rate and improved quality of life may be obtained.

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Authors' contributions

RC, OJ and LS conceived the study. RC and XY performed the literature review. XZ and RC wrote the manuscript. RC and CM edited the manuscript. Data authentication is not applicable. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

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Competing interests

The authors declare they have no competing interests.

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