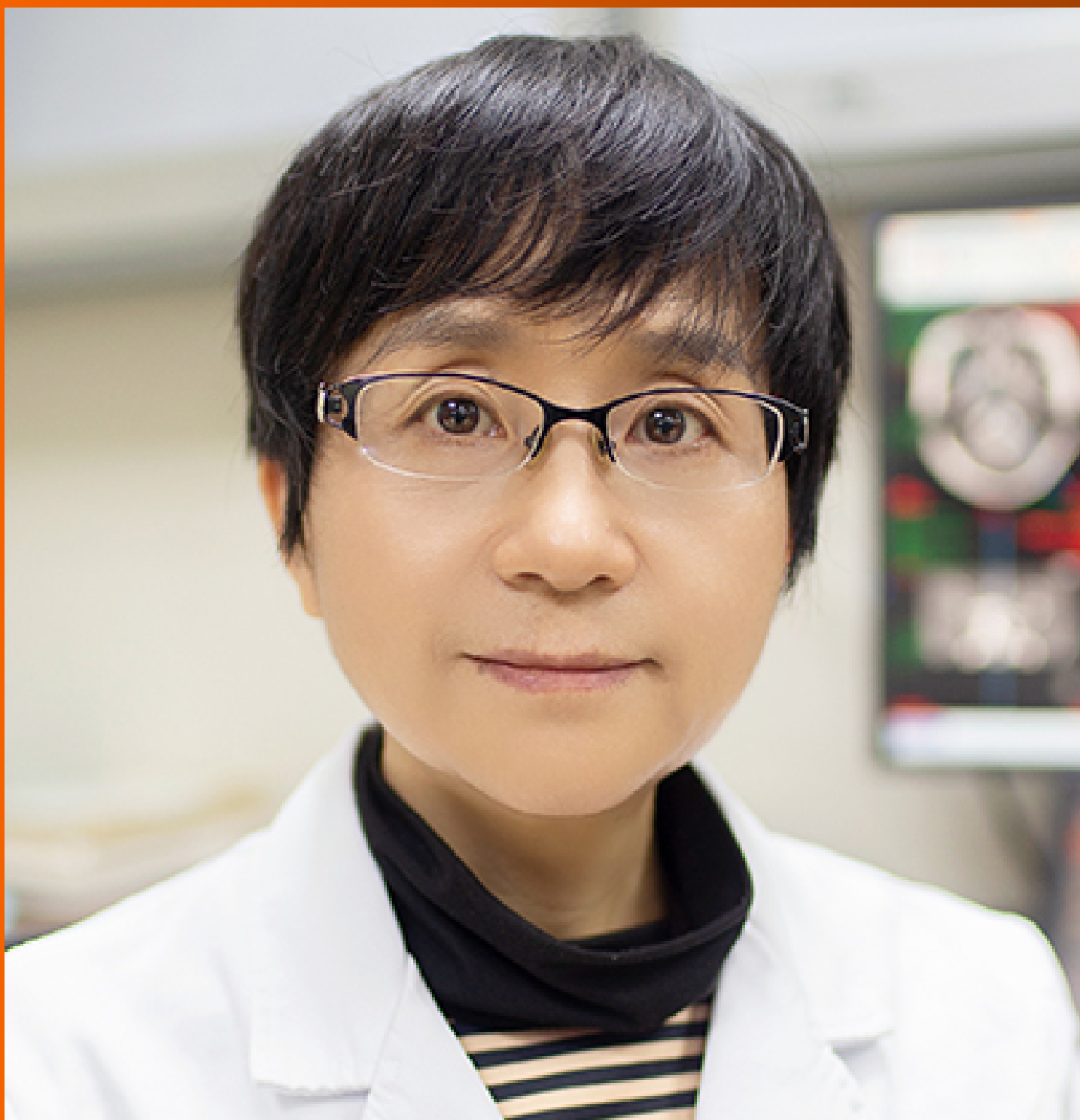


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Radiotherapy as an immune checkpoint blockade combination strategy for hepatocellular carcinoma

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Abstract

In the immune oncology era, the clinical efficacy of immune checkpoint inhibitors (ICIs) against most solid cancers is well known. In hepatocellular carcinoma, the recent success of combination therapy with targeting agents has accelerated the search for novel combination strategies. Radiotherapy (RT), an attractive modality, can be combined with ICIs, which act as strong modulators of the tumor immune microenvironment. Herein, we discuss immune modulation caused by radiation and the current trials of RT-ICI combination treatment as well as future perspectives.

Key Words: Hepatocellular carcinoma; Immune checkpoint inhibitor; Radiotherapy; Immune modulation; Tumor microenvironment; Immune oncology

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Core Tip: Immune modulatory effect of radiation is highlighted as a combination strategy with immune checkpoint inhibitors. This strategy has been actively adopted in most solid cancers. Although it is in relatively early stage for hepatocellular carcinoma, accumulated evidence drives clinical trials on testing its efficacy. Still, there remain several challenges to overcome for the best oncologic outcome.

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INTRODUCTION

As immune checkpoint inhibitors (ICIs) have demonstrated promising clinical outcomes, cancer immunotherapy has shifted the paradigm in cancer therapy. ICIs have shown efficacy against various types of cancers such as malignant melanoma and non-small cell lung cancer^[1-3]. For hepatocellular carcinoma (HCC), ICI monotherapy has not been successful, with a response rate of no more than 20%, which suggests the need for a combination strategy. The recent IMbrave150 trial demonstrated superior progression-free survival (PFS) and better overall survival (OS) with combination treatment using atezolizumab [an anti-programmed death ligand-1 (PD-L1) agent] and bevacizumab (an anti-vascular endothelial growth factor-A agent) compared to those with sorafenib in HCC patients^[4]. The IMbrave150 trial showed the potential of ICIs in combination with a tumor microenvironment (TME)-modulating agent for the treatment of HCC. Identification of the optimal combination treatment using ICIs as a novel therapy is gaining extensive attention.

Radiotherapy (RT), one of the major cancer treatments, promotes localized tumor cell killing and induces immune modulation in the TME^[5,6]. Increasing evidence has demonstrated that radiation reinforces tumor-related immunity^[7,8]. RT exerts synergistic effects with ICIs by increasing lymphocyte infiltration into tumors, inducing immunogenic cell death, and enhancing the performance of antigen-presenting cells (APCs)^[9]. Herein, we discuss immune modulation by radiation, the rationale for RT-ICI combination treatment in preclinical settings, and future approaches to overcome the hurdles in combination therapy for HCC.

CHALLENGES IN CURRENT ICIs

Although ICIs show promising treatment outcomes, challenges remain in their application. One recent study reported that the tumor immune cell composition plays a key role in the response to immunotherapy^[10-12]. Although the initial T-cell population mainly comprised effective “transitional” cells, a substantial number of infiltrating CD8 T-cells transformed gradually into dysfunctional T-cells. CD8 T-cells with cytotoxic functions were rare among intratumoral immune cells, while dysfunctional T-cells were the major immune cells in tumors. Furthermore, the proportion of dysfunctional T-cells was associated with tumor proliferation. These findings suggest that ICIs alone might be insufficient for achieving an adequate clinical response.

The infiltrating dysfunctional T cells by immunosuppressive mechanisms in TME is one of the reasons for failed ICI^[13,14]. The exhausted T cells can explain the lack of response in ICI. To elevate the efficacy of ICI response, converting the dysfunctional T cell into functional T cell is important. The reinvigorating exhausted T cell is expected to improve the outcome of ICI. The successful reinvigoration of T cell function would recover the antitumor activity^[15].

Currently, the reinvigoration of T-cells appears to be a key outcome in immune oncologic therapy. Huang *et al*^[16] reported that the reinvigoration of T-cells is closely related to tumor burden, and this association was also correlated with the clinical response to ICIs^[16-18]. The authors reported that the ratio of T-cell reinvigoration to the tumor burden was the key predictive factor of the clinical response to ICIs, which explains the heterogeneous and unsustainable clinical benefit in patients^[16-18]. Therefore, reducing the tumor burden before administering ICIs seems important for improving clinical outcomes. In this regard, RT may be effective in reducing the tumor burden^[19]. In addition, RT has been known for its modulation effect on the immune TME.

IMMUNE MODULATION EFFECT OF RADIATION

Besides cell killing, RT induces an immune-mediated antitumor response. Its effect in terms of immune modulation is summarized in [Table 1](#). First, RT induces antigen release and immunogenic cell death. Radiation upregulates the expression of major histocompatibility complex (MHC) class I, thus enhancing the immune response and efficacy of ICIs^[20,21]. Naturally, MHC expression is downregulated in tumors to allow immune evasion. Expression of MHC class I enables CD8 T-cells to recognize tumor cells and trigger a major cell-mediated cytotoxic response. Enhanced antigen presentation with upregulated MHC class I expression is one mechanism by which

Table 1 Four key steps of a radiation-induced immune response

Major steps	Ref.
Induction of antigen release and immunogenic cell death	[20-22]
Induction of antigen-presenting cell maturation and antigen presentation	[23,24]
Induction of T-cell recruitment and infiltration	[21,29-32]
Induction of tumor cell sensitization to immune-mediated cell death	[27,28,33]

radiation induces immune-mediated cell death^[20]. Radiation promotes the expression of not only MHC class I in tumor cells but also damage-associated molecular patterns, such as HMGB1, and the release of phagocytotic signals, such as calreticulin^[20,22].

Second, RT mediates the release of tumor antigens, which leads to the activation and transfer of dendritic cells to draining lymph nodes, resulting in tumor-specific T-cell activation and proliferation. After RT, antigens are released from dying tumor cells, and antigens are taken up by APCs such as macrophages, dendritic cells, and B-cells. Antigen uptake by APCs is an important step in priming adaptive immunity. Dendritic cells are activated after antigen uptake, and the activated dendritic cells migrate to lymph nodes. In tumor-draining lymph nodes, dendritic cells present antigens to either T-cells or B-cells^[23]. HMGB1, a radiation-induced damage-associated molecular pattern, enhances dendritic cell maturation^[24].

Several studies have demonstrated that RT increases the number of tumor-infiltrating lymphocytes (TILs), indicating that RT aids in overcoming the physical barriers of the tumor, which facilitates a substantial response by the adaptive immune system^[25-28]. Two mechanisms have been proposed to explain the increased number of TILs after RT^[21,29-31]. One mechanism involves the modification of the vascular endothelium, enabling the extravasation of immune cells. The expression of E-selectin and intercellular adhesion molecule (ICAM)-1, one of the cell adhesion molecules on the vascular endothelium, has been shown to increase after RT^[32]. These molecules help the leukocytes migrate from vessels, which is a key step in enhancing the immune response against the tumor. Another mechanism involves the promotion of the expression of chemokines, increasing immune cell migration and invasion. Radiation increases the expression of CXCL16, the ligand for CXCR6^[31]. CD8 T-cells expressing CXCR6 are recruited toward tumor cells as radiation exposure increases the expression of CXCL16. In summary, radiation promotes the migration of TILs into the TME, ultimately generating an immunogenic environment.

Lastly, RT induces the sensitization of tumor cells to immune-mediated cell death. As previously described, radiation increases MHC class I expression, together with the immunogenic release of damage-associated molecular patterns and phagocytotic signals. This mechanism induces immune-mediated cell death^[28]. Along with the enhanced expression of MHC class I and HMGB1, radiation exposure induces FAS expression. FAS is a cell surface molecule that induces programmed cell death. FAS expression is upregulated in human tumor cell lines after radiation^[33]. Upregulated FAS expression on tumor cells enhanced binding to nearby immune cells expressing the FAS ligand^[27,33]. Radiation-induced upregulation of FAS expression is one of the important mechanisms by which the immune system can trigger tumor cell death. Taken together, RT can change the immunogenicity of tumors from low to high through these key mechanisms. The mechanisms that occurred when combining the ICI and radiation are summarized in **Figure 1**.

These immune-modifying mechanisms were also observed in a murine HCC model^[34]. MHC class I expression was upregulated after RT in the HCC model. The expression level of MHC class I was significantly higher in the RT group than in the control group. Concordant with the expression of MHC class I, upregulated expression of HMGB1 and ICAM-1 was observed after RT. The upregulated expression of HMGB1 is expected to lead to dendritic cell maturation, and increased ICAM-1 expression is thought to induce leukocyte outflow. These molecules, induced by radiation, alter the TME to an immunogenic environment in HCC.

COMBINATION OF RADIATION WITH ICIS

The notion of combination treatment is now generally accepted with respect to the clinical application of ICIs. It is known that multiple co-stimulatory and inhibitory

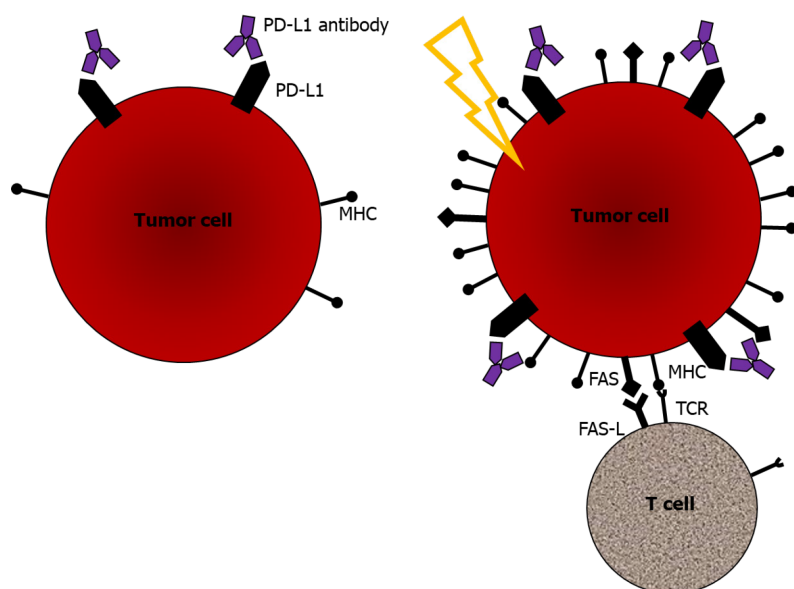


Figure 1 Combination of immune checkpoint inhibitor and radiation enhances immune-mediated cell death. PD-L1: Programmed cell death ligand 1; MHC: Major histocompatibility complex; TCR: T cell receptor.

signals regulate T-cell activation^[35,36]. These co-stimulatory and inhibitory signals play an important role in immune resistance. ICIs, which block these inhibitory signals, eliminate immune resistance mechanisms. Interestingly, these co-stimulatory and inhibitory signals are modulated by radiation^[29,37]. Based on these findings, the combination of RT and ICIs is thought to have a synergistic effect, and some preclinical data support its use against HCC.

Our group demonstrated that RT induced PD-L1 expression in tumor cells and showed the potential antitumor effect of anti-PD-L1 agents against HCC^[38]. The expression of PD-L1 is induced maximally between 24 and 48 h after RT. RT with up to 10 Gy was administered, and PD-L1 expression was upregulated in a dose-dependent manner. The antitumor effect was also examined for the anti-PD-L1 agent-RT combination *in vivo*. Tumor growth suppression and survival improvement were significantly superior in the combination group than in the anti-PD-L1 agent alone or RT alone group. Furthermore, the combination of an anti-PD-L1 agent and RT significantly increased cytotoxicity and the proliferation of CD8 T-cells compared to RT alone or the anti-PD-L1 agent alone.

T-cell immunoglobulin and mucin-domain-containing molecule-3 (TIM3) is an inhibitory molecule present on T-cells. TIM3-expressing T-cells showed dysfunction or “exhaustion”^[39]. It has been reported that TIM-3 expression is higher in HCC patients than in those with other liver diseases, such as chronic hepatitis and liver cirrhosis^[40]. TIM-3-positive T-cells showed high expression in HCC cells, in contrast to that in normal cells present in adjacent tissues^[41]. Although TIM-3 blockade can modulate the immune response *via* several cell types^[42-44], there are limited studies regarding the effect of anti-TIM3 agents in HCC patients. RT upregulated TIM-3 expression in HCC cell lines, and the combination of an anti-TIM-3 agent and radiation promoted cytotoxicity and the proliferation of CD8 T-cells^[45]. Furthermore, the combination of an anti-TIM-3 agent and radiation significantly suppressed tumor growth compared to radiation or anti-TIM-3 agent alone. Concordant with the results of tumor growth, the combination group demonstrated a significant improvement in survival.

Despite these promising preclinical data regarding the combination of RT and ICIs against HCC, clinical studies are severely limited. One study investigated the clinical implications of PD-L1 levels in patients with HCC undergoing RT^[46]. The level of soluble PD-L1 (sPD-L1) was quantified in patients who underwent RT for HCC. The initial sPD-L1 level was significantly associated with tumor aggressiveness (tumor size and stage). A high initial sPD-L1 level was related to poorer OS than a low initial sPD-L1 level. The sPD-L1 levels increased significantly after both conventional RT and stereotactic body RT (SBRT), but the pattern of sPD-L1 change was different depending on the dose scheme. The sPD-L1 level increased immediately after RT but decreased at 1 mo after conventional RT, while a continuous increase was observed in those undergoing SBRT. In the SBRT group, the median sPD-L1 level at 1 mo increased

to approximately 3-times the initial sPD-L1 level. Therefore, the combination of ICIs and RT may be a promising treatment in patients with HCC, and efficacy might be better with SBRT. This notion needs clinical validation to evaluate the efficacy of combined treatment with RT and ICIs for HCC. Several prospective trials registered at www.ClinicalTrials.gov are ongoing to investigate the combination of ICIs and RT (Table 2).

CHALLENGES WITH THE COMBINATION OF RADIATION AND ICIS

Radiation fractionation

There is no established dose or fractionation regimen that optimizes the therapeutic effect of RT plus ICIs. It is clear that the immunologic response differs depending on the RT dose as *per* fractionation. With conventional fractionation, RT promotes the recovery of tumor vessels *via* the migration of immune cells through the endothelium^[47] and induction of M1-type macrophages^[47,48]. These actions have a positive effect on immunity. With hypofractionation, treatment-related lymphopenia occurs less frequently^[49], and Tregs are activated, shifting the balance of T-cells toward the immunosuppressive state^[50,51]. Additionally, preclinical data have shown that hypofractionation regimens favor an antitumor response and induce a strong lymphoid response^[52,53].

In contrast, a high fractional dose led to a different immune response. As *per* preclinical data, fractional doses higher than 12 Gy induce the production of 3' repair exonuclease 1 (TREX1), which degrades cytosolic DNA after RT^[54]. Consequently, TREX1 inactivates the cyclic guanosine monophosphate-adenosine monophosphate synthase (cGAS)–stimulator of interferon genes (STING) pathway. With conventional fractionation, the cytosolic DNA after radiation binds to cGAS and activates STING^[55,56]. Consequently, cGAS and STING induce the production of type I interferon and activate an antitumor immune response^[57,58]. As a fractional dose of more than 12 Gy induces TREX1, the fractional dose of more than 12 Gy results in the inhibition of antitumor immune responses. Furthermore, doses greater than 10 Gy *per* fraction enhance vascular damage, leading to less effective T-cell recruitment because of reduced vascularity^[59]. The different types of radiation-induced immune modulation by different fractionation scheme of radiation are summarized in Figure 2. For an optimal combination of RT and ICIs, it is important to gain an understanding of the immune response depending on different fractionations to improve therapy efficacy and administer personalized medicine^[19].

Treatment sequence

The optimal timing of administering ICIs in combination with RT has not yet been defined. To determine the optimal timing of RT and ICI treatment, several preclinical studies have been performed. One report showed that administering ICIs 7 d after RT was less effective in enhancing OS than administering ICIs concurrently with RT^[37]. In the PACIFIC trial, durvalumab started within 14 d of completing RT resulted in better PFS than durvalumab started after 14 d^[2]. A recent study showed that OS was longer in patients who received ICIs concurrently with RT^[60]. Among the patients who received concurrent treatment, induction immunotherapy administered more than 30 d before RT led to longer OS than that of administered within 30 d before RT. Scheduling of RT and immunotherapy must be considered with caution in the context of clinical trials.

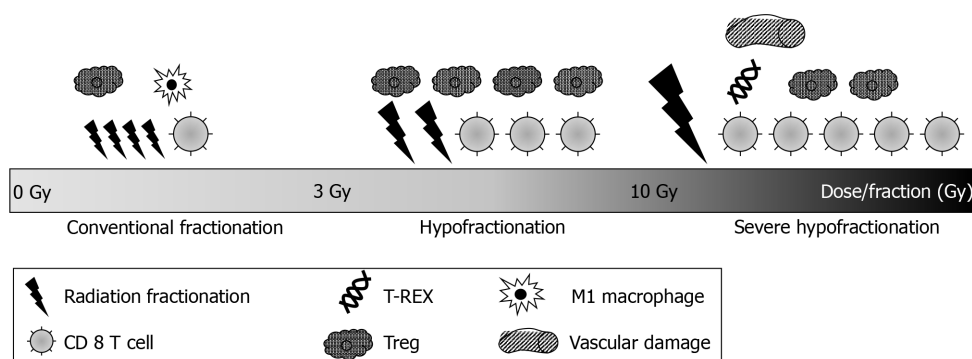
CONCLUSION

ICIs have emerged as a promising therapy for various malignancies including HCC. T-cell reinvigoration by activating dysfunctional T-cells into cytotoxic T-cells is a key factor in the novel therapeutic effect of ICIs. However, ICI monotherapy has some limitations in circumstances such as T-cell dysfunction and high tumor burden. Meanwhile, RT has been shown to cause high immunogenicity in tumors through various mechanisms of immune modulation. The combination of ICIs and RT is being studied as a promising treatment for HCC to take advantage of the synergistic effect. Further studies are necessary to determine the appropriate treatment regimen for achieving optimal clinical benefit.

Table 2 Ongoing clinical trials investigating the combination of radiotherapy and immune checkpoint inhibitors against hepatocellular carcinoma

NCT number	Institution	Disease	Estimated enrollment	Phase	Primary endpoint	Intervention
NCT04167293	China (Sun Yat-sen University Cancer Center)	HCC with portal vein invasion	116	II/III	6-mo PFS	SBRT + sintilimab <i>vs</i> SBRT
NCT03817736	Hong Kong (Queen Mary Hospital)	HCC	33	II	Number of patients eligible for curative surgical interventions	TACE/SBRT + ICI
NCT03203304	United States (University of Chicago)	Unresectable HCC	50	I	Number of participants with adverse events	Nivolumab + SBRT <i>vs</i> nivolumab and ipilimumab + SBRT
NCT04611165	South Korea (NCC)	HCC with major vascular invasion	50	II	PFS	Nivolumab + EBRT
NCT03482102	United States (MGH)	Locally advanced/unresectable or metastatic HCC or biliary tract cancer	70	II	ORR	Tremelimumab + durvalumab + RT
NCT03316872	Canada (UHN)	HCC progression after sorafenib	30	II	ORR	Pembrolizumab + SBRT
NCT04547452	China (West China Hospital)	Metastatic HCC	84	II	PFS	SBRT + sintilimab <i>vs</i> sintilimab
NCT04193696	China (Guangxi Medical University)	Advanced HCC	39	II	ORR	RT+ anti-PD-1 agent

HCC: Hepatocellular carcinoma; PFS: Progression-free survival; SBRT: Stereotactic body radiation therapy; TACE: Transcatheter arterial chemoembolization; ICI: Immune checkpoint inhibitor; NCC: National Cancer Center; EBRT: External beam radiotherapy; MGH: Massachusetts General Hospital; ORR: Overall response rate; RT: Radiotherapy; UHN: University Health Network; PD-L1: Programmed cell death ligand 1.

**Figure 2 Types of radiation-induced immune modulation by different fractionation scheme of radiation.**

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