Review Article

Role of radiotherapy and its contribution to immunotherapy in hepatocellular carcinoma

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Abstract: Hepatocellular carcinoma (HCC) is a major contributor to cancer-related deaths, with the incidence of HCC increasing in regions of the world with a high incidence of hepatitis B and C. The therapeutic landscape for HCC management has substantially transformed over recent years, shifting towards a multimodal treatment paradigm. This approach provides a range of medical and surgical interventions aimed at managing the disease effectively. Radiotherapy (RT) has surfaced as a critical player in the preoperative management of inoperable HCC, demonstrating potential in downstaging the disease and achieving disease stability. This advantage may potentially be attributed to the abscopal effect, where localized radiation leads to the regression of metastatic cancer outside of the irradiated site through upregulation of the immune system. The advent of recent technological breakthroughs has paved the way for innovative approaches, notably the integration of immunotherapy and RT. This strategy is emerging as a promising avenue for managing HCC. Preliminary findings from the fusion of RT and immunotherapy are encouraging, with ongoing trials keenly evaluating the optimal parameters for therapy administration, such as timing, dosage, and sequence. The development of combined treatments involving immune checkpoint inhibitors (ICIs) has opened new avenues for advanced HCC treatment. Several immunotherapeutic agents with RT are concurrently being explored for their potential contributions to HCC management.

Keywords: Hepatocellular carcinoma (HCC); abscopal effect; radiotherapy (RT); immune check point inhibitors; immunotherapy

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Introduction

Overview of hepatocellular carcinoma (HCC) incidence and risk factors

HCC is a major contributor to global cancer-related deaths (1,2). The incidence of HCC is increasing in many regions of the world, particularly in areas with a high incidence of hepatitis B and C (3). HCC has a male predominance with a two-fold higher incidence in males than females and a higher prevalence in East Asian countries relative to European countries (4). The incidence and mortality of HCC in the United States are undergoing a shift, with

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a transition from predominantly affecting Asians/Pacific Islanders to affecting African American and Hispanic communities (5). This change is likely attributed to the effective implementation of hepatitis B virus (HBV) control measures, including vaccination and antiviral therapy, as HBV is the primary cause of HCC in Asian populations (6,7). Other major risk factors for HCC, besides chronic viral hepatitis, include cirrhosis, nonalcoholic steatohepatitis associated with metabolic syndrome, alcohol abuse, tobacco consumption, and aflatoxin B1 (2,8,9).

Current treatments for advanced HCC

The Barcelona Clinic Liver Cancer (BCLC) staging system utilizes the patient's liver function, tumor characteristics, and performance status to guide treatment decisions (10-12) (*Table 1*). The majority of patients present with BCLC B or later stages which are not amenable for curative intent therapies such as resection, ablation or transplantation. In fact, local treatments such as transarterial chemoembolization (TACE) only serve a minority of patients in the BCLC B stage with well-defined nodules, preserved portal flow without portal hypertension, and selective access to tumor-feeding arteries (13-15). TACE has often served as a bridge to transplantation, but many patients cannot ultimately receive transplantation due to either the progression of the disease or the determination of liver function (16-18).

The 2022 BCLC updated guidelines have been revised to offer guidance on first- and second-line systemic therapies for patients with advanced-stage HCC (BCLC C) (10,19). The atezolizumab/bevacizumab [programmed death ligand-1 (PD-L1)/anti-vascular endothelial growth factor (VEGF)] combination is currently regarded as the standard of care for HCC patients with BCLC C or any patients not amendable for or have progressed after curative or local therapies. A combination of tremelimumab and durvalumab has been shown to be more effective than sorafenib and is another first-line treatment option (20). Both regimens significantly improve overall survival (OS) in the first-line setting (20-23).

Limitations of current systemic therapies in HCC

It is now well-accepted that immunotherapy offers the best potential for optimal outcomes in advanced HCC. Such regimens were only studied in patients with Eastern Cooperative Oncology Group Performance Status (ECOG PS) status at least 1 or better and in patients with a preserved liver function such as Child-Pugh Class (CPC) A (20,21,23). Unfortunately, many patients with HCC are diagnosed with either ECOG PS status of 2 or CPC B (24-26), leaving many patients without adequate therapeutic options (24,27-29).

The rationale of radiotherapy (RT) utilization in HCC

Although the updated 2022 BCLC guidelines did not incorporate RT in the modified treatment algorithm for HCC, RT has recently emerged as a potential therapy (30-35). Liver tumors exhibit moderate sensitivity to radiation (36). The sensitivities of tissues to radiation are determined by their cellular states of differentiation, division, and potential to divide. The hematopoietic system, reproductive system, gastrointestinal lining, and skin are more radiosensitive than solid organs such as the kidney, lungs, and liver. Muscles and nerves are less radiosensitive than the liver (37).

RT is a localized treatment that utilizes ionizing radiation to induce direct and indirect DNA double-strand breaks (38). Ionizing radiation damages tumor cells by causing direct damage to their DNA, particularly double-strand DNA breaks (39,40). Irradiating water within the cytoplasm of tumor cells can lead to the formation of reactive oxygen species. This ionization results in indirect unrepairable double-strand DNA breaks that disrupt tumor function (41).

The abscopal effect in RT

An advantage of localized irradiation is the abscopal effect (42). The abscopal effect refers to the phenomenon where local RT leads to the regression of metastatic cancer at a distance outside the irradiated site, mediated by the activation of the immune system (43-46). In this phenomenon, RT can induce immunogenic cell death in irradiated tumor cells, which leads to the release of neoantigens into the tumor microenvironment (47,48). Neoantigens predominantly represent novel tumor-specific antigens that arise from mutations within neoplastic cells, resulting in their exclusive expression in the malignant cellular population (49,50).

These neoantigens are taken up by antigen-presenting cells and processed to become mature dendritic cells (DCs). These mature DCs then migrate to the tumor-draining lymph nodes. The neoantigens are presented to T cells, a process mediated by the major histocompatibility complex

Table 1 BCLC staging incorporating tumor burden, liver function, and patient physical status

Classification component	BCLC stage				
	0	A	B	C	D
Tumor burden	Single ≤2 cm	Single or ≤3 nodules each ≤3 cm	Multinodular	Portal invasion and/or extrahepatic spread	Any tumor burden
Liver function (CPC)	A	A or B	A or B	A or B	C
PS (ECOG scale)	0	0	0	1 or 2	3 or 4

The tumor burden encompasses the number, size, portal and extrahepatic spread. Liver function is based on the CPC, which measures the severity of liver disease according to ascites, serum concentration of bilirubin, serum concentration of albumin, prothrombin time, and degree of encephalopathy. CPC A is a well-compensated disease, CPC B indicates significant functional compromise, and CPC C represents a decompensated disease state. The PS is based on the ECOG scale. PS 0 is where one is fully active and can carry on all pre-disease performance without restrictions. PS 1 is where a patient is restricted in heavy physical work but can perform work of a light or sedentary nature. PS 2 is where the patient is ambulatory and capable of self-care but cannot carry out any work activities. This patient is confined to the bed less than 50% of the time. PS 3 is where the patient can only have limited self-care and is confined to bed or chair more than 50% of the time. PS 4 is where a patient is completely disabled and cannot carry out self-care. The patient is confined to the bed or chair 100% of the time. BCLC, Barcelona Clinic Liver Cancer; CPC, Child-Pugh Class; PS, Performance Status; ECOG, Eastern Cooperative Oncology Group.

(MHC) pathway and other co-stimulatory signals, such as CD80 and CD28. The T cells differentiate into cytotoxic T lymphocytes, which can recognize and eliminate tumor cells as they recirculate within the body (42,51-53) (*Figure 1*). This is particularly relevant when combined with immunotherapy such as cytotoxic T-lymphocyte-associated protein 4 (CTLA 4) antibody that energizes cytotoxic T cells. The beneficial effects on cytotoxic T cells by the abscopal effect can be important when combined with programmed death-1 (PD-1) inhibitors, as cytotoxic T cells and the PD-1 pathway have been shown to be synergistic in HCC treatment. This has been illustrated by the significant OS benefits of combining CTLA 4 antibody and PD-1 inhibitor (54,55).

Despite a growing number of trials and cases reporting the abscopal effect of RT alone, the overall occurrence rate has been observed to be relatively low (56-58). Since the introduction of immune checkpoint inhibitors (ICIs) in oncology, interest in the abscopal effects of radiation has increased dramatically. It presents the idea of possible potentiation of abscopal effects in patients receiving RT and ICIs, particularly in cancers where RT has a limited role, whereas immunotherapy is beneficial. The low rate of abscopal effect can be attributed to the insufficient ability of RT alone to overcome the immunoresistance of malignant tumors (56-59). Combining immunotherapy with RT can enhance the systemic anti-tumor response of RT, possibly due to the reduction of immune tolerance toward tumors by immunotherapy (56,57). This combination has been a subject of intense interest as it is thought to amplify the anti-tumor immune response and increase the likelihood of an abscopal effect (47,60,61). Moreover, the release of neoantigens by RT presents increased areas for PD-1 inhibitors to target. It helps overcome immune exhaustion experienced by patients on long-term immunotherapy and resensitizes tumors to the effects of immunotherapy (47,56).

Translational research has explored the potentiation of immunotherapy by RT. In a study investigating the antitumor effect of a combination of immune checkpoint blockade and RT, the authors found that *in vitro* radiation application upregulated PD-L1 protein expression in HCC murine and human cell lines (62). *In vivo* radiation exposure also upregulated PD-L1 expression in a dose-dependent manner in murine HCC tumor tissue. Investigation into the signaling pathways responsible for radiation-induced upregulation of PD-L1 suggests that radiation initially induces the production of IFN-γ, which then signals downstream expression of STAT3, ultimately increasing PD-L1 expression in HCC tumor cells. Mice receiving a combination of anti-PD-L1 treatment and radiation demonstrated significantly suppressed tumor growth and increased survival rate compared to those receiving anti-PD-L1 or radiation alone. These findings support the reasoning that radiation increases the susceptibility of tumor cells to anti-PD-L1 treatment by increasing induction of PD-L1.

It is also important to note that enhanced PD-L1 expression can promote T cell exhaustion and subsequent dysfunction through the upregulation of inhibitory

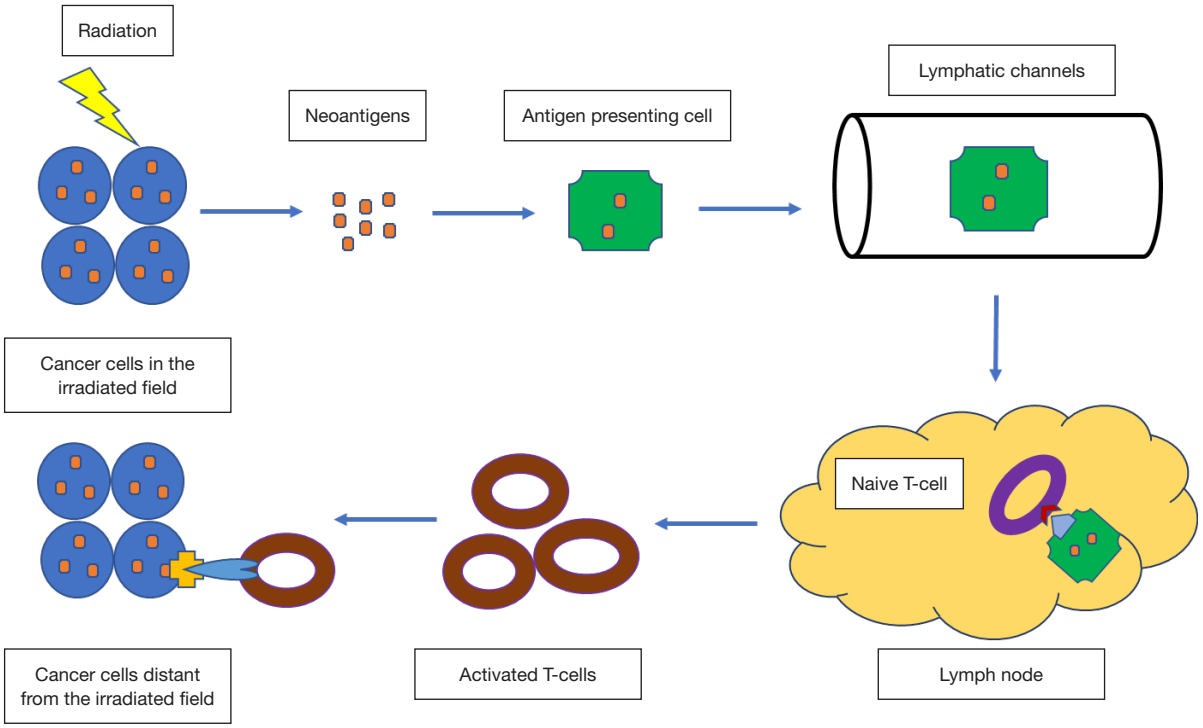

Figure 1 The abscopal effect. Radiotherapy can lead to immunogenic cell death in irradiated cancer cells, leading to the release of neoantigens. The neoantigens (orange) are taken up by the APCs (green). These APCs process the neoantigens and migrate through lymphatic channels to lymph nodes (yellow). In the lymph nodes, the APC presents the neoantigen to naive T-cells (purple) via the major histocompatibility complex and other stimulatory signals. Subsequently, these T-cells become activated and proliferate. The activated T cells (brown) leave the lymph nodes and migrate to distant sites. They execute their anti-tumor function by killing abscopal cancer cells distant from the irradiated field. APCs, antigen-presenting cells.

receptors such as PD-1 and CTLA-4. The authors found that combination treatment not only increased the percentage of CD8 T cells but also increased IFN-γ CD8 T cells, CD107a CD8 T cells, and Ki67 CD8 T cells, indicating an increased effector cell cytotoxicity and proliferation, when compared to those treated with monotherapy (62).

Therapeutic benefits of RT in HCC

RT is an emerging option for treating HCC across all BCLC stages (31). Historically, the use of external beam radiotherapy (EBRT) has been restricted in managing HCC due to technical limitations and fear of hepatic toxicities (63). Recent technological advancements have ensured the precise delivery of high doses of radiation to the liver for HCC while minimizing damage to normal tissue (38,64,65). In addition to EBRT for the treatment of HCC, other forms of RT include stereotactic body radiotherapy (SBRT), including CyberKnife (66,67), selective internal radiation therapy (SIRT) (68), carbon iron radiation therapy (CIRT) (69), and proton beam therapy (PBT) (70-76) (*Table 2*).

EBRT and SBRT are both viable radiation therapy options for the management of HCC. However, they possess distinct characteristics, benefits, and limitations. EBRT is a conventional therapy that delivers radiation to the tumor site over multiple sessions. It uses a broad radiation beam that passes through healthy tissue to reach the HCC tumor (77). In contrast, SBRT is a more advanced and targeted form of RT that delivers high doses of radiation to the tumor in fewer sessions (78). SBRT is more precise than EBRT, as it accurately targets the HCC tumor while sparing adjacent healthy tissue (78,79). This allows higher radiation doses to be administered over fewer treatment sessions, resulting in better tumor control and potentially fewer side effects (66,67,79). EBRT typically requires daily treatment sessions over several weeks, while SBRT involves fewer sessions (usually between 1 and 5) (77-79).

Table 2 Advantages and disadvantages of various RTs for the treatment of HCC

Treatment method	Description	Delivery method	Main advantages	Main disadvantages
EBRT (72)	A traditional form of radiation therapy that uses external beams of radiation to treat cancer	External beam directed at the tumor, with intensity modulated to spare healthy tissue	Can treat a larger area and is not limited by the size or shape of the tumor	Requires many treatments over several weeks. More exposure of healthy tissue to radiation, which can lead to side effects
SBRT (73)	A radiation therapy that delivers very high doses of radiation to a small, precise area of the body	External beam targeted precisely to the tumor	Can treat smaller, well-defined tumors. Fewer treatments needed than traditional radiation. Minimizes exposure to healthy tissue	May not be suitable for larger or less well-defined tumors. Can have side effects such as fatigue, skin changes, and other symptoms depending on the location of the treatment
CyberKnife (66,67)	A type of SBRT. It uses a robotic arm to deliver highly focused beams of radiation	External beam targeted precisely to the tumor, capable of adjusting to patient movement	Offers real-time tracking and adjustment for patient movement, making it highly precise. Can treat tumors in challenging or risky areas	Limited by the size of the tumor and can be more costly. Requires sophisticated equipment and experienced clinicians
SIRT (68,74)	A form of internal radiation therapy where radioactive microspheres are injected into the blood vessels that feed the tumor	Internal, via catheter directly into blood vessels feeding the tumor	Delivers radiation directly to the tumor, sparing healthy liver tissue. Can be used in patients with larger or multifocal liver disease	Risk of radiation exposure to non-targeted tissues and can be more costly. More invasive procedure. Requires a specialized interventional radiology team
CIRT (69,75)	A type of particle therapy that uses carbon ions to treat cancer	External beam directed at the tumor	Carbon ions are heavier and have a higher LET, leading to more precise targeting and potential for greater tumor kill	Limited availability as it requires specialized equipment and can be more costly. More research is needed to fully understand the long-term effects and comparative effectiveness
PBT (70,76)	A type of radiation therapy that uses protons to treat cancer	External beam directed at the tumor	Protons stop at the tumor site, reducing exposure of healthy tissue beyond the tumor. Can be more precise than traditional radiation	Requires specialized equipment and can be more costly. More research is needed to fully understand the long-term effects and comparative effectiveness

RT, radiotherapy; HCC, hepatocellular carcinoma; EBRT, external beam radiation therapy; SBRT, stereotactic body radiation therapy; SIRT, selective internal radiation therapy; CIRT, carbon ion radiation therapy; LET, linear energy transfer; PBT, proton beam therapy.

The use of EBRT as a localized therapeutic approach for advanced HCCs has expanded, particularly in the form of three-dimensional conformal RT (77). The general description, advantages and disadvantages of each form of RT are covered in *Table 2*.

RT monotherapy in early-stage HCC (BCLC A)

EBRT is utilized for primary HCC with diverse objectives, including ablation of HCC, consolidation of other local treatments, linking to liver transplantation, and treating recalcitrant disease (80-82). SBRT administers targeted, high-dose external radiation to the tumor site while minimizing radiation-induced damage to the adjacent liver parenchyma (31).

A retrospective trial demonstrated that after propensity score matching, the 2-year freedom from local progression rates was 74.9% for the SBRT group and 64.9% for the radiofrequency ablation (RFA) group. This study indicated that SBRT seems to be a promising alternative treatment option for HCC, mainly when RFA is not feasible due to tumor location or size (83). A retrospective analysis and

large-scale metanalysis suggested the superiority of SBRT over RFA in local control (LC) for HCC (84-86).

In a randomized phase III-controlled trial comparing PBT to RFA in the treatment of recurrent HCC (size <3 cm, number ≤2), PBT demonstrated non-inferiority to RFA in terms of 2-year local progression-free survival (LPFS) rates, with 94.8% for PBT and 83.9% for RFA (87). The intention-to-treat analysis also showed comparable LPFS rates between the two treatment arms. The progression-free survival (PFS) and OS rates were not significantly different between the two arms.

In a recent study, PBT was utilized as a primary treatment modality in HCC patients, who either could not undergo other localized therapies or opted against them (88). Notably, the use of PBT led to encouraging outcomes, presenting a 5-year freedom from local progression (FFLP) rate of 94.5% and a 5-year OS rate of 76.7% in patients classified as BCLC 0/A/B, where the majority were stage A (92.3%). A comparable study evaluated the same treatment modality, PBT, in a cohort of treatment-naive HCC patients. They documented a 5-year FFLP and OS rates of 94% and 69%, respectively, in BCLC 0/A patients (n=30) (89). The studies affirm the promising potential of PBT as a viable treatment option for HCC patients for BCLC 0/A.

A comparison study was conducted to evaluate the efficacy of CIRT versus TACE in the treatment of single HCC (90). The study included 31 patients who received CIRT and 23 patients who received TACE. After propensity score matching, 17 matched pairs of patients from each treatment group were analyzed. The median follow-up durations after CIRT and TACE were 43 and 32 months, respectively. The 3-year OS, local control, and PFS rates in the CIRT group were significantly higher than those in the TACE group, with rates of 88% *vs.* 58% (P<0.05), 80% *vs.* 26% (P<0.01), and 51% *vs.* 15% (P<0.05), respectively (90). These results suggest that CIRT may be a more effective treatment option for single HCC than TACE.

RT for intermediate stage HCC (BCLC B)

In a retrospective analysis, when compared to TACE, SBRT was linked to better tumor control for primary therapy (91% *vs.* 23% at 2 years) (91). Moreover, in a prospective study, SBRT was found to be on par with other treatments for bridging to transplantation (92).

In a study looking at treatment-naive HCC patients with PBT, patients categorized as BCLC B (n=34) had 5-year FFLP and OS rates, 87% and 66% respectively that were slightly lower than those seen with BCLC 0/A (89).

SIRT and transarterial radioembolization (TARE) for intermediate-stage HCC (BCLC B)

SIRT, also known as radioembolization, delivers tiny radioactive particles called microspheres directly to the tumor through a catheter, which are then lodged in the tumor's blood vessels, where they deliver targeted radiation to the cancer cells (93). The microspheres used in SIRT are usually made of a radioactive isotope called yttrium-90 (^{90}Y), which has a short half-life and therefore delivers high doses of radiation to the tumor while minimizing exposure to surrounding healthy tissues (94). This results in less damage to healthy liver tissue and fewer side effects compared to traditional RT (94).

The use of SIRT may have future benefits that are not entirely seen at the moment. In a multi-site, prospective trial comparing sorafenib alone and a combination of sorafenib and SIRT with ^{90}Y microspheres in patients with advanced HCC (BCLC A/B/C, and CPC A to B7), it found median OS was 11.4 months with sorafenib and 12.1 months with sorafenib and SIRT. This study concluded that including SIRT alongside sorafenib did not lead to a notable enhancement in OS when compared to using sorafenib alone (94).

Evidence supporting the effectiveness of radiation therapy in the form of TARE is progressively accumulating. The fundamental concept underlying TARE infusion involves administering high-dose ionizing radiation directly into the tumor bed via the hepatic artery, leading to continuous radiation exposure as ^{90}Y decays over time (31). TARE has gained traction as a frequently employed locoregional therapy for HCC (95,96). In the early and intermediate stages of HCC, TARE segmentectomy is a promising technique that exhibits a positive risk profile and presents favorable radiology-pathology outcomes for HCC that is ≤5 cm (97).

RT for late-stage HCC

LC and OS with RT (Table 3)

RT has been shown to achieve moderate LC in patients with unresectable HCC (105-107). LC rates following SBRT for HCC range from 68% to 95% at 2 to 3 years after treatment (71,98-103). In a phase II, single-site, prospective trial of 50 patients who progressed after TACE for inoperable HCC (41 with CPC A, 6 with CPC B7, and

Table 3 Radiation therapy for late-stage HCC

Trial	Type of study	Prospective *vs.* retrospective	Radiotherapy	Local control rate at 2 years	Overall survival rate at 2 years
Kang *et al.* (98)	Single-site	Prospective	SBRT	94.6%	68.7%
Andolino *et al.* (99)	Single site	Prospective	SBRT	90%	48%
Kwon *et al.* (71)	Single-site	Prospective	SBRT	67.5%	77.3%
Huang *et al.* (100)	Single-site	Prospective, matched-pair	SBRT	75%	72.6%
Bujold *et al.* (101)	Single-site	Prospective	SBRT	87% at 1 year	55% at 1 year
Sanuke *et al.* (102)	Single-site	Retrospective	SBRT	91% at 3 years	70% at 3 years
Jang *et al.* (103)	Single-site	Prospective	SBRT	87%	63%
Yoon *et al.* (104)	Single-site	Prospective	EBRT + TACE	None reported	55.4% at 48 weeks or roughly 28% at 2 years

HCC, hepatocellular carcinoma; SBRT, stereotactic body radiotherapy; EBRT, external beam radiotherapy; TACE, transarterial chemoembolization.

5 with portal vein tumor thrombosis), SBRT achieved an LC rate of 94.6% and OS rate of 68.7% after 2 years (98).

In another single-institution, prospective trial of 60 HCC patients that included 36 CPC A and 24 CPC B, all of the tumors (1 to 3 for each patient) had a maximal diameter of ≤6 cm, SBRT achieved 2-year LC rate of 90% and a 2-year OS rate of 48% (99). A single-site, prospective study using CyberKnife SBRT in 42 HCC patients. Three patients were eligible for local ablation or surgical resection, who had CPC A (38) and B (4) all had a tumor volume ≤100 cc. This study demonstrated LC rates of 72.0% and 67.5% at 1 and 2 years, respectively. OS rates were 92.9% and 77.3% at 1 and 2 years, respectively (71).

A study examined 36 unresectable HCC patients treated with CyberKnife SBRT matched for ECOG PS and CPC with 138 historical control who received other systemic therapies such as thalidomide, sorafenib, TACE, and liver transplantation or no treatments. This analysis showed that patients undergoing CyberKnife had better 2-year OS rates of 72.6% as compared to that of 42.1% in the historical group. Moreover, the SBRT-treated group had an in-field control rate of 75% after 2 years (100).

In a prospective sequential phase I/II trial, 102 HCC patients unsuitable for RFA, TACE, surgery, or alcohol ablation were treated with SBRT (24–55 Gy) in 6 fractions. Patients had ECOG performance score ≤2, CPC A, and at least 700 mL of non-HCC liver. These patients achieved an LC rate of 87% and an OS rate of 55% at 1 year (101).

In a separate retrospective study, where patients with HCC (CPC A and B) were treated with SBRT (40 Gy for CPC A and 35 Gy for PC in 5 fractions), the overall 3-year LC rate and OS rate were 91% and 70%, respectively. No statistical differences in LC or OS were seen between the SBRT dose levels (102). In contrast, a prospective study selected 108 HCC patients with incomplete responses to TACE who were unsuitable for local ablation or surgery. SBRT in these patients showed 2-year LC and OS rates of 87% and 63%, respectively. This investigation also revealed a positive correlation between RT dose and LC, with a similar dose response in OS when utilizing SBRT for HCC treatment. This study also suggested that enhanced LC outcomes may potentially lead to survival advantages for individuals diagnosed with HCC (103).

An open-label randomized trial demonstrated that EBRT with TACE for advanced HCC (with portal vein invasion) was well-tolerated and improved PFS and OS compared to sorafenib treatment (104). The trial explored the combination of EBRT with TACE *vs.* sorafenib in treatment naive HCC patients with macrovascular invasion. Ninety patients were randomized in a 1:1 fashion. The primary endpoint of the trial was 12-week PFS rate. In this head-to-head comparison, the PFS rate was significantly higher in the TACE-EBRT group (86.7% *vs.* 34.4%, P<0.001). Higher rates of radiologic response were also seen in the TACE-EBRT group when compared to sorafenib (33.3% *vs.* 2.2%) at the 24-week mark. Modified progression free survival (mPFS) and OS were 31 and 55 weeks for TACE-EBRT group and 11.7 and 43 weeks for sorafenib. Notably, patients with macrovascular invasion, a prognostic predictor of poor OS, were evaluated in this trial (104). The trial

allowed for treatment crossover and were evaluated with intention-to-treat analysis. The superior mPFS of the TACE-EBRT group can make a case for treating patients initially with this combination prior to starting treatment with sorafenib. One limitation of the study is that the majority of the patients (85%) had hepatitis B associated HCC, and the results cannot be extrapolated to the general HCC population.

The recent results from the National Surgical Adjuvant Breast and Bowel Project (NSABP), the Radiation Therapy Oncology Group (RTOG), and the Gynecologic Oncology Group (GOG)/Radiation Therapy Oncology Group 1112 further indicate the role of combination strategies for treating HCC (108). The combination of sorafenib with SBRT *vs.* then standard-of-care sorafenib was evaluated in treatment naive advanced HCC patients. Trial accrual was closed early with new therapies approved for first line use in advanced HCC. Patients treated with SBRT + sorafenib had improved OS of 15.8 months (90% CI, 11.4–19.2) *vs.* 12.3 months (90% CI, 10.6–14.3) with sorafenib alone [hazard ratio (HR), 0.77; 90% CI, 0.59–1.01; 1-sided P=0.55]. Notably, 75% and 73% of patients in the SBRT/sorafenib and sorafenib monotherapy arms had macrovascular invasions, respectively. Also, the SBRT with sorafenib combination achieved a higher mPFS of 9.2 months (95% CI, 7.5–11.9) *vs.* 5.5 months (95% CI, 3.4–6.3) in those treated with sorafenib alone (HR, 0.55; 95% CI, 0.40–0.75; P=0.0001) (108). The improved PFS and OS might indicate future role of combination strategies involving RT with newly approved IO strategies in management of HCC (*Table 3*).

Symptom palliation with RT

The requirement for palliative care has been raised in cases of metastatic HCC, and advancements in technology have resulted in higher utilization of palliative RT (109). This approach is commonly pursued when no more effective systemic therapy exists. Initial studies on whole-liver RT at doses between 20–30 Gy for patients with mainly liver metastases demonstrated symptom palliation benefits for 49–95% of patients with minimal adverse effects (110-118). Most of these studies employed outdated radiation techniques, extended fractionation schedules, or concurrent radiosensitizers that are no longer commonly used in clinical practice (110). In one of the largest prospective studies of pain amelioration, patients with liver metastases were administered 21 Gy in 7 fractions to the whole liver and were randomized to misonidazole or placebo. This study found that patients with radiation and misonidazole had a response rate of improved abdominal pain of 87% compared to that of 74% in patients with radiation alone. The median response time was 13 weeks (117).

A prospective trial that studied 41 patients with liver metastases using 8 Gy in a single fraction to the whole liver showed improved average index symptom intensity in 48% of patients 1 month following RT. Still, benefits were observed only in patients with pain and abdominal discomfort. Treatment was well-tolerated, with only one patient developing grade 3 toxicity (119).

A similar result was seen in another single-site prospective study of 52 patients who received a single fraction (8 Gy) of palliative RT for abdominal discomfort due to unresectable HCC. More than 50% (51.9%) of patients experienced an improvement in their index symptoms after 1 month, with a median response duration of 89 days. The treatment was well tolerated, with only 3.8% of patients developing grade 3 gastrointestinal toxicities (110).

Not surprisingly, this is in line with another multi-center, phase III prospective study that shows that for patients with end-stage HCC or liver metastases, single-fraction radiation therapy (8 Gy) results in pain relief (worst pain) for the majority of patients and a potential improvement in survival (120).

RT and immunotherapy for intermediate stage in HCC (BCLC B)

With the emergence of ICIs, treatment options for advanced HCC have expanded beyond tyrosine kinase inhibitors (TKIs), such as sorafenib and lenvatinib, to include atezolizumab and bevacizumab based on the IMBRAVE150 study, and the STRIDE regimen based on HIMALAYA study (108,121-123).

There is growing interest in combining RT with immunotherapy in managing HCC. The immunomodulatory effects of RT have been well studied (124). RT enhances the infiltration of cytotoxic T cells within the tumor microenvironment. A robust and durable immune response can be obtained in combination with ICIs, which can potentially reverse the RT-mediated exhaustion pathways. Innate and adaptive immunity can also be activated when immuno-oncology (IO) is combined with low-dose RT, and a robust anti-tumor response can be obtained (125).

As mentioned before, RT can induce immunogenic cell death, release tumor antigens, and modulate the tumor

microenvironment, while immunotherapy can enhance immune responses against cancer cells in HCC. The optimal dose, fractionation, and sequence of these treatment modalities are still being explored. The selection of dose and fractionation depends on various factors, including tumor size, location, and liver function. In general, lower doses of radiation (hypofractionation) are thought to be more immunogenic, potentially enhancing the immune response (126,127). However, higher doses (conventional fractionation) may also have immunomodulatory effects (127,128). The optimal approach may involve a balance between tumor control and immune activation, which requires further investigation in clinical trials specific to HCC.

Early results from several prospective trials evaluating RT and IO are discussed here. A phase II single-arm prospective study, sequential transarterial chemoembolization (TACE) and SBRT followed by IO as conversion therapy for patients with locally advanced HCC unsuitable for curative therapy (START-FIT), was conducted (129,130). The trial's purpose was to evaluate the role of a combined modality approach for unresectable local HCC and make it amenable to curative treatment. Critical eligibility criteria included patients with HCC ≥5 cm, tumor nodules ≤3, and CPC A5-B7 liver function. Tumors with distant metastasis, main portal vein (VP4) invasion, or inferior vena cava (VV3) invasion were excluded. All enrolled patients underwent TACE on day 1, followed by 5 fractions of SBRT (27.5–40 Gy) on day 28. This treatment was followed by Avelumab (10 mg/kg) over 2 weeks. The study would be stopped if patients were deemed evaluable for surgery or had grade 3 or higher adverse events that required withdrawal or progression of the disease.

Thirty-three patients were enrolled in the study, with 32/33 male patients enrolled. The median sum of the diameter of the lesion(s) was 15.1 cm (range, 5.3–31.1 cm), 21 (63.6%) had macrovascular invasion (13 hepatic vein, 3 branched portal vein, 5 both) and 24 (73%) had hepatitis B. Most patients (21/33) patients were also BCLC C. After a median follow-up of 17.2 months (range, 3.5–31.6 months), 3 (9.1%) patients had tumor downstage with curative surgery done. Of the 33 patients, 18 were deemed amenable to curative treatment. Fourteen had a complete response (CR), and four had a partial response. Eight of the fifteen patients considered not amenable to curative therapy had a progression of the disease, and there was one grade 5 adverse event. The objective response rate (ORR) was 62.5% (95% CI, 45.3–77.1%), of whom 15 had a CR (43.8%), and 6 had a partial response (18.7%). The median OS and PFS were 30.3 months (95% CI: 22.7– not reached) and 20.7 months (95% CI: 14.6–26.8), respectively. The median time to progression was 21.4 months (95% CI: 16.4–26.4).

Eleven patients (33%) experienced ≥ grade 3 treatment-related adverse events, commonly transient increases in alanine transaminase (ALT)/aspartate aminotransferase (AST) (n=5, 15%) and bilirubin (n=2, 6%) levels after TACE. All patients recovered with conservative management (129). Five patients (15.2%) developed ≥ grade 3 immune-related adverse events (irAEs), primarily hepatitis and dermatitis. Two patients had irAEs which led to discontinuation of avelumab. However, 55% (18/33) of patients were amenable to curative treatment, with 12% undergoing curative treatment and 42% having radiographic CR without surgery, with an OS rate of 92% (129). These results warrant further exploration of a multimodality approach for successfully treating locally advanced unresectable HCC. The effectiveness of LC achieved through TACE and SBRT is further compounded by the addition of immunotherapy.

RT and immunotherapy for late-stage HCC (BCLC C)

First line therapy

A single-site retrospective case series reported impressive results on five patients (ECPG PS 0–2) with unresectable CPC A and B HCC with SBRT followed by anti-PD1 antibodies (nivolumab or pembrolizumab). All five patients responded to treatment, with two complete and three partial responses. Three patients had underlying hepatitis B, and 4 of them had BCLC C disease. The median tumor size was 9.8 cm (8.5–16.1 cm), with two patients having tumor vascular thrombosis and 1 having extrahepatic disease. No patients progressed on treatment during a median follow-up of 14.9 months (8.6–19 months). The combination also helped downstage the tumor, making it amendable to RFA, as reported in 1 partial responder. One patient had grade ≥3 toxicities (pneumonitis and skin reaction). No patient had grade >3 hepatotoxicity (131). The effective local tumor control obtained through a combination of SBRT with PD-1 inhibitors warranted further exploration of this combination in future, more extensive prospective studies.

Another phase I trial was conducted, which evaluated SBRT (40 Gy in 5 fractions) followed by either ipilimumab/nivolumab or nivolumab alone. This trial is the first prospective study assessing the role of immunotherapy with SBRT in advanced or unresectable HCC. The trial was closed early due to slow accrual. Fourteen patients were

enrolled, with thirteen evaluable. Six patients were allocated to the nivolumab arm, whereas the remaining eight were assigned to the ipilimumab/nivolumab arm. Most patients were male (11/13), and the median age was 67 years (63-71). All patients had CPC A classification, and the most common etiology of cirrhosis was hepatitis C (50%), followed by alcohol use (36%). Two patients received prior systemic therapy with TKIs. Four enrolled patients had extrahepatic disease, and four patients had tumor thrombus. All patients underwent liver SBRT, delivering 40 Gy in 5 fractions (132). The primary endpoint of the study was dose-limiting toxicity (DLT). Two patients had DLT, with one each observed in the ipilimumab/nivolumab arm and nivolumab alone arm within 6 months of SBRT. There were no grade 4 or 5 toxicities. Grade 3 adverse events occurred in 8 patients, 3 in the nivolumab alone arm and 5 in the ipilimumab/nivolumab arm. These included AST/ALT elevations, lipase elevations, thrombocytopenia, hyponatremia, fatigue, and generalized muscle weakness. Grade 3 hepatotoxicity events were AST/ALT elevations and occurred in 4 (30.8%) of 13 patients, 1 (16.7%) of 6 patients, and 3 (42.9%) of 7 patients in the respective cohorts (132).

Additionally, after a median follow-up of 42.1 months, the ORR was 57% (4 of 7 patients; 90% CI, 23–87%) in the ipilimumab/nivolumab arm compared to 0% (0 of 6 patients; 90% CI, 0–39%) in the nivolumab alone arm. All four patients had a partial response to treatment. The study reported the following: median PFS of 11.6 months (90% CI, 4.5 to not reached) versus 2.7 months (90% CI, 1.3–4.7), and median OS of 41.6 months (90% CI, 4.5 to not reached) versus 4.7 months (90% CI, 2.0–16.2). In addition, the ipilimumab/nivolumab arm showed more grade 3 hepatotoxicity (4 *vs.* 1 patient in the nivolumab arm) (132). The small sample size of 14 patients split into two arms is a key limitation of this study. Still, it offers safety and efficacy data on the potential efficacy of this combination of RT and ipilimumab/nivolumab. Further studies should be done to explore the role of this combination.

Second line therapy

Camrelizumab, in combination with SBRT, in a phase IIA trial, was also studied to evaluate the potential efficacy and toxicity of the combination in patients with advanced HCC who had progressed on prior systemic therapy. SBRT with administered with 30–50 Gy over 10 fractions (133,134). Camrelizumab 200 mg was given intravenously every 3 weeks since the first day of RT until disease progression or intolerable toxicity. Seventeen patients were enrolled in the study (median age 54 years; range, 32–69 years). Fifteen (88%) patients were male. Fourteen (82%) were ECOG 0. All patients had CPC A and mainly had BCLC C (16/17). Thirteen patients had a history of hepatitis B. Extrahepatic metastases were present in 11 patients (65%). Fifteen patients previously had >2 lines of prior therapy. The ORR was 47%. The best response assessed by RECIST 1.1 was a partial response (8 patients). Four patients had grade 3 irAEs, including elevated LFTs (n=1), decreased hemoglobin (n=1), reduced platelet count (n=1), and decreased neutrophil count (n=1). All grade 3 irAEs were mitigated with proper treatment. No treatment-related deaths occurred during the study (133). This study's high ORR of 47% in the 2nd line setting of HCC highlighted the vital role of combined SBRT and PD-1 blockade approach in managing HCC.

Ongoing clinical studies for RT with PD-1 and PD-L1 inhibitors in HCCs (*Table 4*)

An open-label, multi-center study currently aims to assess the efficacy and safety of combining pembrolizumab and ^{90}Y radioembolization in patients with high-risk HCC who are not eligible for liver transplantation or surgical resection and have a well-compensated liver function. The treatment protocol involves administering pembrolizumab 200 mg intravenously every 3 weeks, along with ^{90}Y radioembolization performed 1 week after the initial pembrolizumab dose. In cases of bilobar disease, a second ^{90}Y radioembolization will be conducted no later than 4 weeks following the first procedure, targeting the contralateral hepatic lobe (*Table 4*) (140).

Two phase I trials (NCT05488522 and NCT05096715) are currently evaluating the role of concurrent SBRT with atezolizumab, a PD-L1 inhibitor, and bevacizumab with SBRT for patients with advanced HCC deemed not amenable to curative treatment (135,141). The primary endpoint of the study is to establish dose-limiting toxicity. Secondary endpoints are OS, PFS, ORR, and toxicity rates. Trials evaluating other ICIs such as durvalumab (NCT04913480) and pembrolizumab (NCT03316872) with SBRT are also currently underway (138,142) (*Table 4*).

Conclusions

The management of HCC has seen a remarkable evolution over the years. A combined modality approach has become

Table 4 Trials using a combined RT and immunotherapeutic approach for the management of HCC

Trial phase	NCT number	HCC patient population	Treatment arms	SBRT dose	Primary endpoint	Secondary endpoints
IB	NCT05096715 (135)	Unresectable	Atezolizumab + bevacizumab + SBRT (1–3 days of C1), followed by atezolizumab + bevacizumab	20 Gy	DLT	PFS, OS, in-field RR, out of field RR, and change in CP score
I	NCT05488522 (136)	Unresectable	Atezolizumab + bevacizumab + SBRT	17 Gy (max 3 fractions) of SBRT at 4-week intervals	DLT	ORR, OS, PFS
I	NCT03203304 (completed; terminated early because of poor enrollment) (132)	Unresectable	SBRT + nivolumab +/– ipilimumab	40 Gy in 5 fractions	DLT	ORR, OS, PFS, AE rate, LC
II	NCT04913480 (137)	Unresectable	SBRT + durvalumab	27.5–50 Gy/5 fractions	PFS	OS, ORR, LC, LFR, AE rate, change in PD-L1 before and after RT
II	NCT03316872 (138)	Advanced disease after progression on sorafenib	SBRT + pembrolizumab	5 fractions	ORR	PFS, OS, RR in non-irradiated tumors
II	NCT03817736 (129) unresectable hepatocellular carcinoma (START-FIT)	Locally advanced disease for downstaging	SBRT + TACE + Avelumab	27.5–40.0 Gy/5 fractions	No patients downstaged for curative resection	OS, PFS, TTP
II	NCT03857815 (139)	Recurrent or oligometastatic disease	SBRT + sintilimab	54 Gy (48–60 Gy)/ 6 fractions	PFS	ORR, OS, AE

RT, radiotherapy; HCC, hepatocellular carcinoma; SBRT, stereotactic body radiotherapy; DLT, dose-limiting toxicity; PFS, progression-free survival; OS, overall survival; RR, response rate; CP, Child-Pugh; ORR, overall response rate; AE, adverse event; LC, local control, LFR, liver failure-free, PD-L1, programmed death-ligand 1; TACE, transarterial chemoembolization; TTP, time to progression.

increasingly common, with several treatment strategies available to treat the disease medically and surgically. RT has shown a role in downstaging unresectable HCC and potentially achieving disease control. Based on recent technological advances, the combination of immunotherapy and RT has emerged as a promising approach for the treatment of unresectable HCC. The combination approach of RT and immunotherapy has shown promising results, with several trials evaluating the optimal timing, dose, and sequence of these therapies. In addition, combination therapies involving ICIs have emerged as potential treatment options for advanced HCC, with several immunotherapeutic agents also in development for their potential role in treating HCC. Future studies would include well-designed clinical trials using RT and IO combinations such as PD-1 inhibitor + CTLA 4 antibody, PD-1 inhibitor combined with lymphocyte activation gene 3 (LAG 3) inhibitor, or PD-1 inhibitor + VEGF inhibitor.

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Footnote

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